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A History of Psycho-Neuro-Endocrine Immune Interactions in Rheumatic Diseases

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Abstract
Background: All active scientists stand on the shoulders of giants and many other more anonymous scientists, and this is not different in our field of psycho-neuro-endocrine immunology in rheumatic diseases. Too often, the modern world of publishing forgets about the collective enterprise of scientists. Some journals advise the authors to present only literature from the last decade, and it has become a natural attitude of many scientists to present only the latest publications. In order to work against this general unempirical behavior, neuroimmunomodulation devotes the 30th anniversary issue to the history of medical science in psycho-neuro-endocrine immunology. ***Summary:*** Keywords were derived from the psycho-neuro-endocrine immunology research field very well known to the authors (R.H.S. has collected a list of keywords since 1994). We screened PubMed, the Cochran Library of Medicine, Embase, Scopus database, and the ORCID database to find relevant historical literature. The Snowballing procedure helped find related work. According to the historical appearance of discoveries in the field, the order of presentation follows the subsequent scheme: (1) the sensory nervous system, (2) the sympathetic nervous system, (3) the vagus nerve, (4) steroid hormones (glucocorticoids, androgens, progesterone, estrogens, and the vitamin D hormone), (5) afferent pathways involved in fatigue, anxiety, insomnia, and depression (includes pathophysiology), and (6) evolutionary medicine and energy regulation – an umbrella theory. ***Key Messages:*** A brief history on psycho-neuro-endocrine immunology cannot address all relevant aspects of the field. The authors are aware of this shortcoming. The reader must see this review as a viewpoint through the biased eyes of the authors. Nevertheless, the text gives an overview of the history in psycho-neuro-endocrine immunology of rheumatic diseases.

Introduction

Neuroendocrine immunology describes the influence of neuronal pathways with neurotransmitters or endocrine glands with hormones on immune functions. Originally, this portrays the efferent influence of the brain on immune cells making use of connecting factors

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Table 1. Role of neuronal innervation for the development of RA and other inflammatory diseases

Situation	Modulation of disease symptoms	Reference
Poliomyelitis paralysis	RA only on the non-paralyzed side	[1]
Hemiplegia	RA only on the non-paralyzed side	[2–14]
Hemiplegia	RA vasculitis only on the non-paralyzed side	[15]
Hemiplegia	Gouty arthritis only on the non-paralyzed side	[16]
Hemiplegia	Skin changes in pSS only on the non-paralyzed side	[17]
Hemiplegia	Psoriatic arthritis only on the non-paralyzed side	[18]
Sensory denervation	Respective finger is spared from psoriatic arthritis	[19]
Brachial plexus lesion	Shoulder inflammation in a PMR patient only on intact side	[20]
Hemiplegia	DTH skin lesions more marked on the non-paralyzed side	[21]
Hemiplegia	Hemochromatosis arthritis only on the non-paralyzed side	[22]
Surgical removal of the first 5 sympathetic ganglia from top	Complete removal of vasospastic disease of finger and left hand and of osteoarthritis of left hand (impressive photo)	[23]

DTH, delayed-type hypersensitivity; PMR, polymyalgia rheumatica; pSS, progressive systemic sclerosis; RA, rheumatoid arthritis.

(neurotransmitters, especially steroid hormones). Nowadays, the bidirectional aspect of the communication between the brain and the immune system is described with the expression psycho-neuro-endocrine immunology, which also reflects the strong influence of the immune system on brain function (with psychological/psychiatric, neuronal and endocrine consequences). Using this description, we briefly summarize the historical development in the field of rheumatology.

Historically, neuronal pathways with the sensory nervous system and the autonomic nervous system (sympathetic; parasympathetic: N. Vagus) were described before hormonal pathways came on stage, which led to the sequence of presentation in this article.

Efferent Pathways from the Brain to the Immune System

Hemiplegia and Chronic Inflammation

With a look on clinical cases, the concept of neuronal regulation of inflammation is confirmed by reports of patients with hemiplegia and chronic inflammatory diseases, where the paralytic side is protected from inflammation. Cases have been reported in whom hemiplegia manifested long after outbreak of chronic inflammatory rheumatic disease or long before, leading to protection independent of the time point of disease onset. Table 1 demonstrates the respective historical literature. The natural experiment of hemiplegia clearly demonstrates the importance of the nervous system in chronic inflammatory rheumatic diseases.

Neuronal Pathways – The Sensory Nervous System

Neurogenic Inflammation and Sensory Neurotransmitters

Since 2000 years (Celsus and Galen), clinicians recognize redness, warmth, swelling, pain, and altered function as immediate cardinal signs of inflammation. Neurogenic vasodilatation reported in 1876 by Stricker and 1901 by Bayliss [24, 25]; the inflammatory axon reflex with reddening skin observed in the 1910s by Bruce and by Breslauer [26–28]; the flare response reported by Lewis around 1930 with erythema, hyperalgesia, and edema [29]; rediscovery of the antidromic vasodilatory flare response and dorsal root reflex by Chapman [30]; and Kelly's and Jancsó's more extended concept of neurogenic inflammation in the 1950 an 1960s [31, 32] were all expressions of the same principle: the proinflammatory influence of sensory nociceptive nerve fibers on acute inflammation and on above-mentioned cardinal clinical signs.

In these early years of scientific inquiry, the focus was mainly on the vasodilatory aspect of inflammation and plasma extravasation that leads to redness, warmth, swelling, pain, and altered function. With the discovery of substance P in 1931 by Ulf von Euler [33] and the later correct allocation to sensory nerve fibers by Lembeck in

1953 and, particularly, by Otskua and Konishi in 1976 [34, 35], the important immunomodulating role of substance P was found, e.g., in experimental arthritis in 1984 by Levine et al. [36]. The discovery of substance P is nicely demonstrated elsewhere [37]. Neurotransmitters of the sensory nervous system and propagation of inflammatory activation of neurons/microglia in the spinal cord are relevant for symmetrical joint symptoms [38, 39].

Neurotransmitters/neuropeptides from sensory nerve fibers like substance P are proinflammatory [40], and upon activation of the sensory nerve fiber substance P is released into the vicinity of the nerve ending (an efferent function of sensory nerve fibers). This is the mode how the sensory nerve fiber can have a proinflammatory effect in the periphery.

Other neuropeptides of afferent sensory nerve fibers and their receptors were discovered like calcitonin gene-regulated peptide (CGRP) in 1982 [41], galanin, glutamate, and others. While substance P is often described as a prototype proinflammatory neuropeptide [40], CGRP might have opposing anti-inflammatory but also vasodilatory activities [42]. Thus, depending on the local amount of released substance P relative to CGRP, the tissue might undergo a proinflammatory or anti-inflammatory reaction (in any case a vasodilatory reaction with more immune cell evasion).

In synovial tissue of patients with rheumatoid arthritis (RA), our group demonstrated a preponderance of substance P-positive nerve fibers over CGRP-positive nerve fibers [43]. This would render sensory nerve fibers proinflammatory by a direct action of substance P on immune cells, which supports the earlier concept of neurogenic inflammation (vasodilation, plasma extravasation, broad immune cell activation).

Sensitization, Hypersensitivity, and Early Adverse Experiences

Another phenomenon in many inflammatory diseases is sensitization of the sensory nervous system (nociceptive pathways) because of peripheral, spinal, and more central sensitization [44]. The brain controls the input arriving through afferent sensory nerve fibers by descending pathways, which has been first described by Sherrington in 1915 [45] and later by Melzack and Wall in 1965 [46–48]. Missing control or altered control of this input through sensory nerve fibers and upregulation of local inflammatory pathways (microglia) can lead to sensitization of nociceptive pathways leading, e.g., to hyperalgesia [49].

In parallel, nociceptive fibers can be activated/sensitized to release more neuropeptides into the vicinity of the peripheral nerve terminal [50, 51], which is an efferent function of otherwise afferent nerves. Thus, a hyperactive pain system can have a proinflammatory role by releasing substance P and other neurotransmitters locally. This is particularly true when sensory nerve fibers start to sprout under inflammatory conditions as demonstrated in RA [52, 53].

Cytokines play an important role for sensitization in arthritic joints and the spinal cord as recognized in the 1990s [54–59]. While the role of mitogen-activated protein kinases for sensitization is known for a while [56, 60], recently, therapy with Janus kinase inhibitors also showed the stimulating role of Janus kinase-signal transducer and activator of transcription pathways for sensitization [61]. Importantly, autoantibodies can directly induce hypersensitivity in mice [62, 63]. More central sensitization might be observed through functional magnetic resonance imaging techniques and anti-TNF therapy rapidly ameliorates central nervous system (CNS) sensitization [64].

The term hypersensitivity is used in pain science, neurology (headache), dental medicine (dentine hypersensitivity, temporomandibular disorder), gastroenterology (irritable bowel syndrome), dermatology (itch, lipohyperplasia dolorosa), urology (interstitial cystitis, pelvic pain), psychiatry (autism spectrum disorders), and other medical disciplines. In rheumatology, the word "hypersensitivity" was typically linked to the hypersensitive immune system such as in adverse reactions versus medication, anaphylaxis, contact dermatitis, allergy, or other acute immune reactions. Maybe the presence of the notion of "immune hypersensitivity" slowed down the uptake of the expression "sensory hypersensitivity" in rheumatology. Nevertheless, rheumatologists have treated patients with sensory hypersensitivity for a long time.

Already in 1904, William Gowers coined the expression fibrositis [65], which was correctly renamed into fibromyalgia by Yunus et al. [66] in 1981 because the disease was not inflammatory at all [67]. The primary form of fibromyalgia is characterized by diffuse musculoskeletal aches, pains or stiffness and accompanied by several other symptoms such as tiredness, anxiety, sleep problems, headache, irritable bowel syndrome, and numbness as originally described in the paper of Yunus et al. [66]. Hypersensitivity characterizes primary and secondary fibromyalgia (primary = without any other disease; secondary = with another disease, e.g., systemic lupus erythematosus [SLE]). Again, autoantibodies might play a role in fibromyalgia hypersensitivity that has recently been put forward [68].

The idea of "primary hypersensitivity" of nociceptive pathways led to a third form of pain description next to

nociceptive pain (arises from actual or threatened damage to nonneural tissue and is due to the activation of nociceptors) and neuropathic pain (caused by a lesion or disease of the somatosensory nervous system). The new form of pain was called nociplastic pain [69, 70], and it is characterized by "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" [69]. This form of pain has much to do with altered function of pain-related sensory pathways in the periphery and brain.

An important origin for nociplastic pain is early traumatic experiences in childhood or adolescence sometimes reexperienced in adulthood (double hit). It was Freud and Breuer already in 1895, in their much-criticized book on hysteria (German title: *Studien über Hysterie*), to link earlier experiences in childhood and adolescence with chronic pain in adulthood. The subject of early trauma and later chronic pain has been resumed in the 1950s by George Engel, who described among many affected individuals a patient with chronic painful states and arthritis after childhood abuse/neglect [71].

The first study in rheumatology was carried out in the early 1990s on patients with fibromyalgia [72], a disease with marked sensory hypersensitivity (see above). The authors from McGill University in Montreal found a strong interrelation between childhood trauma and later chronic pain in these patients [72].

A recent book summarized clinical and pathophysiological consequences of early traumatic events including pain, sleep disorders, fatigue, psychiatric diseases, chronic inflammation, and others using more than 1,100 references including historical literature [73]. This book also summarizes the links between early traumatic experience, chronic immune activation, and autoimmunity, an association first described in the year 1978 in the juvenile form of arthritis [74] and in 2004 in the adult form of arthritis [75]. Since these first papers were published, many more similar reports in different rheumatic diseases confirmed this strong interrelationship (see literature in ref. [73]).

Neuronal Pathways – The Sympathetic Nervous System

From the Sympathetic Nervous System to Sympathetic Neuroimmunomodulation

Already Galen, 2000 years ago, described the sympathetic trunk in contrast to the vagus nerve and, in addition, he found the superior and inferior cervical ganglia, the semilunar (celiac) ganglia, and the rami communicantes [76]. Jean Riolan in the early 17th century reported that these nerve fibers have their origin in the spinal cord and not in the vagus nerve, which was the general belief since Galen [76]. Willis in 1664 showed the great mesenteric plexus radiating like a sun (solar plexus), and he gave a much better description of the anatomy of the autonomic nervous system [76].

While the term "sympathetic" already existed since Galen described simultaneity of functional change in one organ and "sympathetically" in another organ (particularly, during disease such as in "sympathetic ophthalmia"), the expression "sympathetic" was not allocated to the above-described nervous system or the sympathetic trunk until the appearance of J. B. Winslow, who worked in Paris in the early 18th century. Before Winslow, the nervous structure made up of the sympathetic trunk was called "nervus intercostalis," and Windslow renamed it into "la grande sympathique" to designate it as the major source of sympathetic outflow [76].

Xavier Bichat in 1800 introduced a physiological and anatomical separation of two nervous systems: organic life (autonomic nervous) versus animal life (somatomotor). He recognized that the sympathetic trunk is a chain of "little brains" (=ganglia) [77]. Friedrich Henle, Benedict Stilling, Claude Bernard, and Charles-Edouard Brown-Séquard discovered regulation of the vessel diameter through sympathetic nerve fibers [77].

Claude Bernard first demonstrated higher centers of the sympathetic nervous system (SNS) in his famous puncturing experiment of the hypothalamus leading to glycosuria, which was blocked by cutting splenic/mesenteric nerves [77]. The first to distinguish SNS and parasympathetic nervous system was Langely in 1921 [78], who also coined the expression "autonomic nervous system." Excellent reviews and books demonstrate more history on the SNS [76–80].

The first hormone described was adrenaline as recently depicted [81]. While different groups discovered adrenaline at the transition from the 19th to the 20th century [82–84], Ulf von Euler found the key neurotransmitter of sympathetic nerve fibers much later in 1940 in the Karolinska Institute [85, 86]. Noradrenaline is the key neurotransmitter in sympathetic nerve fibers because adrenaline – the "hormone" – does not predominate in these nerve terminals. Importantly, von Euler also described the presence of noradrenaline in lymphoid tissue like the spleen [85, 87], which was confirmed for little amounts of administered radioactive adrenaline by later studies by Axelrod et al. [88]. However, at that time, scientists thought that sympathetic regulation in the spleen serves solely vasoregulation and

perhaps storage of red blood cells – and nothing else. The term sympathetic neuroimmunomodulation was not born.

The link of the SNS to the immune system was prepared by work of Tohru Ishigami in 1919 by his experiments of adrenaline-regulated opsonization of tubercle bacilli [89]; by Metalnikov and Chlorine by conditioning the immune response in 1926 [90] (now known to be partially related to the SNS [91]); by Andor Szentivanyi studying the role of beta-adrenergic receptors in anaphylactic reaction in the late 1950s [92, 93]; by Draskoci and Jankovic [94] describing thymus involution and suppression of immune responses after systemic reserpine in 1964; by Charles Reed and his team studying the suppressive effect of adrenaline on vaccination response in 1968 (Abstract: [95]); and by Macmanus and Whitfield [96] showing the stimulating effect of cyclic AMP on thymocyte mitogenic responses.

However, the breakthrough work was carried out around the year 1970 because two groups demonstrated the influence of adrenergic agonists and antagonists on phytohemagglutinin (PHA)-stimulated transformation of human lymphocytes [97–99]. This is the start of mechanistic sympathetic neuroimmunomodulation. Hadden et al. wrote [98]:

> "The demonstration *in vitro* that PHA-stimulated lymphocytes are capable of adrenergic receptor response may be relevant to *in vivo* immunologic reactivity to antigenic stimulation. Lymphoid tissue contains a high concentration of norepinephrine, presumably related to autonomic innervation, and the sympathetic nervous system (alpha-adrenergic influence) may modify lymphocyte function *in vivo*. Knowledge of the mechanism of action of the catecholamines on lymphocytes and its importance to immunologic reactivity is required before *in vivo* relationships and events can be understood."

The findings were corroborated by many studies in the 1970s that described specific adrenoceptors on the membranes of leukocytes/lymphocytes and sympathetic influence on immune function [100–110]. A further key to crack open the enigma of sympathetic neuroimmunomodulation was the staining of sympathetic nerve fibers by chemical techniques such as with formalin (fixing and staining) known already in the 1950s/early 1960s [111, 112] and early 1970s using the sucrose-glyoxylic acid method [113]. Using these techniques – not specific for noradrenaline – sympathetic staining of lymphoid organs was fairly possible for the first time [114–118].

Another step forward was the discovery of tyrosine hydroxylase, the rate-limiting enzyme for adrenaline/noradrenaline biosynthesis [119]. This enzyme also exists in sympathetic nerve fibers and sympathetic denervation reduces the activity of this enzyme in the nerve ending [120]. Tyrosine hydroxylase is transported along the sympathetic axon outside the vesicles/granules [121] using a slow transport system with a velocity of 1–3 mm/day [122].

These findings allowed for specific staining of sympathetic nerve fibers at a time point when respective antibodies/antiserum against tyrosine hydroxylase were first reported in the middle of the 1970s [123, 124]. Both techniques – chemical and immunological – together with the understanding of a crosstalk between immune cells and sympathetic nerve fibers led to clear evidence of anatomical contact sites between nerve fibers and immune cells in lymphoid organs studied by David Felten and his group [125–129], which was also supported for peptidergic innervation [130, 131].

While (1) noradrenaline exists in sympathetic nerve endings in the spleen, (2) since anatomical contact sites between sympathetic nerve fibers and splenic immune cells were demonstrated, (3) given that release of noradrenaline can be stimulated from splenic nerve terminals, and (4) because adrenergic receptors on immune cells were well known, our group added to this evidence of a real neuroimmune synapse by showing functional crosstalk between nerve ending and immune cell (reviewed in [132]). Using microsuperfusion chambers loaded with intact splenic tissue, we showed that the action of electrically released endogenous noradrenaline modulates macrophage cytokine secretion in the spleen, which can be inhibited by competitive neurotransmitter antagonists at intact anatomical locations (reviewed in [132]). In the model of collagen type II arthritis (CIA), the technique demonstrated that an α-adrenergic influence on immune function comes to the fore, which has a general proinflammatory character [133]. All information showed that in the spleen, a functional neuroimmune synapse exists (Table 2). Now, the time was ripe for the study of the SNS in situations with chronic inflammatory diseases/experimental rheumatology.

From Sympathetic Neuroimmunomodulation to Its Role in Chronic Inflammation

In the absence of better therapeutic options, necessity is the mother of invention. In the 1950s, some groups experimented with epinephrine injections in patients with arthritis in order to stimulate the adrenal cortex (i.e., glucocorticoids) but the anti-inflammatory success of this hormone therapy in low doses was marginal compared to glucocorticoids per se [143]. Others tested therapeutic removal of sympathetic lumbar ganglia in patients with RA and osteoarthritis in order to treat

Table 2. Neuroimmune synapse meets the criteria for chemically mediated neurotransmission

Criteria for chemically mediated neurotransmission	Literature
There is an anatomical connection between sympathetic nerve fibers and splenic immune cells	[128]
The neurotransmitter is synthesized in the postganglionic nerve and stored in the nerve terminal	[134, 135]
The neurotransmitter is released into the vicinity of the nerve terminal	[136, 137]
Target immune cell receptors bind and recognize the neurotransmitter	[138, 139]
The action of electrically released endogenous neurotransmitters is inhibited by competitive antagonists at intact anatomical locations	[140–142]

painful states in hip and knee joints [23, 144], but this heroic treatment did not stand the test of time.

In the 1970s, Dick et al. [145] found a decreased α-adrenergic vasoconstrictor tone during ^{133}Xenon perfusion of the knee joint in patients with RA as compared to controls and osteoarthritis. This indicated that inflammation impedes the normal α-adrenergic vasoconstrictor tone – a typical vasodilatory response during inflammation in different tissues. This phenomenon was observed by several other groups and, thus, stood the test of time (e.g. [146–148]).

The first authors that markedly added to the knowledge of the sympathetic influence on experimental arthritis were the group around Jon Levine and Allan Basbaum in San Francisco after they had published their seminal paper on proinflammatory substance P effects in arthritis [36, 149]. Although their clinical paper on guanethidine therapy in RA has never been repeated in larger groups of patients [150], it shows the conviction towards the proinflammatory effect of the SNS. A publication of the same group in the year 1988 stated that the SNS exerts its proinflammatory effects on adjuvant arthritis through the β2-adrenergic receptor while α1/2-adrenergic pathways were not influential [151]. The same group later corrected this statement because an α2-adrenergic suppressive effect on adjuvant arthritis was observed [152]. In the late 1990s, the San Francisco group switched to other possible mediating factors like bradykinin and the vagus nerve.

At approximately the same time, the Rochester group around David Felten, Dianne Lorton, and Denise Bellinger started studies on adjuvant arthritis showing that denervation of the sympathetic influence at local lymph nodes enhanced severity of arthritic changes. They summarized their findings as follows [153]: "*These modulatory effects are distinctly different from the effects of sympathetic nerve fibers in the joints themselves* (AU: considering the data of Levine et al.)." This was corroborated by the same group in 1996 and 1999 [154, 155].

From the studies of Levine et al. [36, 149] and Lorton et al. [153–155], one recognizes two important locations of influence: (1) the local influence in the synovial tissue (β2-adrenergic effects support inflammation in the form of vasodilation and plasma extravasation) versus (2) the local influence in draining lymph nodes and spleen (β2-adrenergic effects inhibit inflammation/specific immune responses).

The increasing understanding of the immune system that started with the discovery of cellular surface markers on immune cells (typing of cells) and secreted products such as cytokines (typing of cells) and chemokines in the 1980s changed the understanding of pathophysiology in different experimental models of arthritis. While the earlier applied injections of capsaicin, zymosan, kaolin, Freund adjuvant, carrageenan and others locally into the joint only reflected a very acute inflammatory response with plasma extravasation and local stimulation of innate immune and bystander mechanisms (= a real acute neurogenic inflammation), the auto-antigenic induction of experimental arthritis with bovine collagen type II, methylated bovine serum albumin and other antigens demonstrated the full spectrum of innate and adaptive immune reactions locally and in distant lymphoid organs. The parallel understanding that neurotransmitters of the SNS influence innate and adaptive pathways in very distinct and sometimes opposing ways depending on location and timing, led to a more complex picture of sympathetic neuroimmunomodulation in arthritis. More and more, it became the affair of trained immunologists.

Our group added to this complexity by demonstrating anti- and proinflammatory effects of 6-hydroxydopamine-induced sympathectomy in the CIA model depending on the time point of drug application during the development of chronic arthritis [156, 157]. An early sympathectomy (before onset of CIA and until approximately day 20) always protected the animals from arthritis; however, later sympathectomy on day 55 in the mouse model aggravated CIA.

The differential effect of early and late sympathectomy is probably due to the appearance of catecholamine-producing local cells in the later phases of the disease. While early sympathectomy destroys the proinflammatory neuronal influence on CIA development, late sympathectomy destroys anti-inflammatory catecholamine-producing cells beneficial in CIA [158–160]. Today, we recognize a multitude of influencing roles of the SNS on chronic inflammation/chronic immune activation through a variety of different pathways (summarized in Table 3). In the following text, some arguments of Table 3 are shown in a historical perspective.

Loss of Sympathetic Nerve Fibers in Inflamed Tissue

The local influence of sympathetic neurotransmitters will change when sympathetic nerve fibers are reduced in inflamed tissue because it changes local neurotransmitter concentrations. Noradrenaline at low concentrations binds to α-adrenoceptors, at high concentrations it binds to, both, α- and β-adrenoceptors (it is a question of affinity). In the early 1990s, two groups independently showed the loss of sympathetic nerve fibers in synovial tissue of patients with RA using qualitative methods of immunostaining in a small number of RA patients [167, 168].

In extensive quantitative immunofluorescent studies on a great number of RA patients, we corroborated the loss of sympathetic nerve fibers in synovial tissue of RA and other inflammatory diseases [52, 166, 169–173]. In experimental models of arthritis, others demonstrated a significant loss of sympathetic nerve fibers of splenic regions distant to the entry point (hilus of the spleen) [174]. At the entry point, the density is even higher as if the nerve fibers accumulate there after retraction, which was confirmed by others near the lymph nodes [175, 176].

The loss of sympathetic nerve fibers with lower concentrations of noradrenaline was discussed as an evolutionarily positively selected process to create "zones of permitted inflammation" [162]. Low concentrations of noradrenaline would only activate α-adrenergic but not β2-adrenergic receptors, which is a proinflammatory signal helpful in wound healing and local infection [162].

Notwithstanding the general finding of lower sympathetic nerve fiber density in inflamed tissue, some authors have demonstrated increased innervation toward distinct sites in the tissue. Increased innervation in synovial tissue appeared in experimental arthritis models in the proximity of cartilage [177, 178] and around arterial walls in synovial tissue of RA patients and arthritic animals [179, 180]. The meaning of uneven distribution of sympathetic innervation in inflamed joints is not yet known, but it might be due to different species, timing of sample collection, specific regions in inflamed tissue and divergent methods of quantification. It might also occur as a controlled process in areas where a high sympathetic influence through β2-adrenoceptors serves a particular function (cartilage: support of cartilage degradation to release energy-rich fuels [181]; around vessels: support of β-adrenergically mediated vasodilation instead of α-adrenergically stimulated vasoconstriction to favor immune cell extravasation).

Loss of β-Adrenergic Receptors and Change of β2-Adrenergic Signaling Pathways

The important function of β-adrenergic receptors for inflammation, mainly the β2-adrenergic receptor, goes back to asthma/anaphylaxis research in the 1960s by Andor Szentivanyi [182], but still today, the β2-adrenergic receptor is given a main role in asthma [183]. In asthma research, the loss of adequate β2-adrenergic signaling remains a challenge because cofactors like inflammatory cytokines, growth factors, respiratory viruses, and certain allergens can disturb the function of the receptor [184]. The first indication of β2-adrenergic receptor dysfunction in asthma goes back into the 1980s [185] and, e.g., TNF plays an important role because it can inhibit β-adrenergically stimulated adenylyl cyclase activity in cultured airway smooth muscle cells [186].

Since the β2-adrenergic receptor has an important anti-inflammatory function in macrophages when acutely challenged with lipopolysaccharide [187], a similar loss in anti-inflammatory capacities of the β2-adrenergic receptor in asthma can lead to deficits in anti-inflammatory sympathetic neuroimmunomodulation, which was confirmed in an animal model of arthritis [188].

Stimulated by asthma research, Christoph Baerwald and his student Matthias Wahle investigated this phenomenon carefully, and they found clear evidence for decreased function of the β-adrenergic receptor in leukocytes from RA patients [189–193]. This was the first evidence that this phenomenon exists in RA similar than in asthma patients and also known for the β1-adrenoceptor in the heart as demonstrated in aged people [194].

Not many studies worked on β-adrenergic receptor signaling in inflamed tissue of patients with rheumatic diseases such as RA. One study demonstrated an obvious decrease of G protein-coupled receptor kinase 2 (GRK2) but not of GRK 5 in material from RA patients [195]. The disease of adjuvant-induced arthritis led to a decrease of

Table 3. Factors that determine the pro- or anti-inflammatory effect of the SNS [161–163]

Factors involved
The immune stimulus and the associated immune response to a particular disease is important. After all, not all types of diseases are always associated with the same immune reaction under the same disease name. For example, there are at least two types of rheumatoid arthritis, one started by B cells (rituximab leads to remission) and the other by T cells (T helper type 1 or T helper type 17, abatacept leads to remission). The result is always joint inflammation. Since sympathetic neurotransmitters have different effects on these different cell types, it can sometimes lead to stimulation and sometimes to inhibition. Nothing is fixed because the relevant cell type can change over the course of a disease. This is not only the case in RA but also with other autoimmune diseases
Migration of immune cells in the early phase of inflammation is promoted by the sympathetic nervous system. The sympathetic nervous system promotes migration and egress of leukocytes from secondary lymphoid organs affecting the development of arthritis [164]
The systemic energy provided is important for immune reactions. The sympathetic nervous system provides energy-rich substrates such as glucose and free fatty acids to the activated immune system [165]
The additional cell types involved in addition to the immune cells are important because they react differently to sympathetic neurotransmitters (e.g., vascular endothelial or smooth muscle cell vs. epithelial cell.)
Switching on and off the sympathetic nervous system in relation to the triggering of the chronic immune reaction is important (vaccination/immunization). In the acute phase, the sympathetic nervous system is proinflammatory, and in the chronic phase, it can be anti-inflammatory (catecholamine-producing cells) [160]
The possible function of other neurotransmitters of the sympathetic nerve ending, such as neuropeptide Y, which has its own effect on immune cells and other cells. With long-term stimulation of the sympathetic nerve fiber, the nerve ending becomes depleted of neuropeptide Y, and then this influence is lost. This can be the case, for example, during a strong sympathetic response. This reduces the effect via β-adrenergic receptors (co-transmission is lost)
Glucocorticoids and catecholamines support each other's role in inhibiting the immune process at high concentrations. Sympathetic neurotransmitters have stronger anti-inflammatory effects when glucocorticoids are simultaneously present [166]. The cooperation of the two hormones/neurotransmitters is important
The concentration and type of sympathetic neurotransmitter (low concentrations act via α-adrenergic receptors that is often proinflammatory, and high concentrations act via β-adrenergic receptors that is often anti-inflammatory)
The variability of the presence of sympathetic nerve fibers in the tissue (low density, effect via proinflammatory α-adrenergic receptors; high density, effect via β-adrenergic receptors) (see subchapter)
The variability of the presence of adrenergic receptors on the surface of involved cells, especially immune cells (i.e., whether there are many or few α- or β-adrenergic receptors) (see subchapter)
The variability of signal transduction from the adrenergic receptor into the respective cell. This can vary greatly, leading to anti- and proinflammatory effects (see subchapter)

GRK2, GRK3, and GRK6 in splenocytes and mesenteric lymph node cells [196]. This differential regulation of the GRKs leads to activation of the noncanonical β-adrenoceptor signaling pathways with proinflammatory effects through mitogen-activated protein kinases [197].

In 2013, Lorton and Bellinger showed defects in β2-adrenergic receptor signaling with reduced cyclic AMP induction in splenocytes of adjuvant arthritic rats [198]. In 2015, we corroborated the idea/the finding of a malfunctioning β2-adrenergic receptor in mixed synovial cells of patients with RA by observing a GαS-to-Gαi signaling switch [199]. Inhibitors of GRK2 might reverse this switch [200]. All these studies, clearly point to defects of the canonical β2-adrenergic receptor signaling, leading to proinflammatory consequences. Thus, loss of sympathetic nerve fibers plus changes in β2-adrenergic signaling are strong proinflammatory signals.

High Sympathetic Activity in Inflammation

In the early 1980s, Sato et al. [201] demonstrated the first mechanistic link between inflammation and a heightened sympathetic activity to the heart. These authors studied the influence of pain on the activity of the sympathetic inferior cardiac nerve. They observed a clear increase of the firing rate of these sympathetic nerve fibers upon stimulating pain in joints, skin, and muscles. When the authors acutely provoked joint inflammation by injection of kaolin and carrageenan, the firing rate markedly

rose and this surmounted the normal pain response [201, 202]. Others corroborated the inflammation-induced increase in sympathetic activity in the adjuvant arthritis model [203]. Pain and inflammation stimulate the SNS because under both conditions the body requires high amounts of energy-rich fuels [204].

Today, we observe a high sympathetic activity in different chronic inflammatory diseases [205–213]. This circumstance certainly adds to the increased frequency of cardiovascular diseases in patients with chronic inflammation [214–216]. A higher sympathetic activity is also related to energy provision to the immune system [165], water retention, and volume overload in patients with rheumatic diseases [217, 218].

Neuronal Pathways – The Vagus Nerve

For the first time, Galen described the vagus nerve [77]. The role of the vagus nerve as a possible inhibitor of the SNS was demonstrated in 1846 by arresting the heartbeat after electrical vagus nerve stimulation (Ernst Heinrich Weber and Eduard Weber from Leipzig, cited in [77]). Pflüger, Bidder, and the Webers showed the influence of the vagus nerve on the intestine [77].

Chemical neurotransmission of neuronal impulses was studied by Dixon in 1907 (muscarine effects), Lehmann found choline in 1907, and Loewi found acetylcholine as the vagus neurotransmitter in 1921 [77]. Furthermore, John Langely [78] distinguished sympathetic and parasympathetic nervous system and created the expression "autonomic nervous system." Langley recognized the antagonism between sympathetic and parasympathetic systems.

While the role of the SNS in neuroimmunomodulation has been studied for more than a century [219], investigation of the vagus nerve as a significant factor of neuroimmunomodulation appeared late in the 20th century. Some groups recognized the proinflammatory effects of vagus manipulation or electrical vagus nerve stimulation for neurogenic inflammation in the rat trachea [220–226]. Mediastinal vagotomy inhibits neurogenic inflammation in the rat bronchial tree [221, 227]. In the field of pulmonary research, the phenomenon of vagally induced neurogenic inflammation is widely known (we can call it textbook knowledge).

At the beginning of the 1990s, two groups independently discovered vagus-mediated sickness behavior including hyperthermia stimulated by injection of proinflammatory substances into the peritoneal cavity [228–230]. A possible crosstalk of vagus nerve fibers and mast cells was demonstrated in intestinal mucosa [130, 231].

A first indication of a vagally mediated inhibition of inflammation was shown in the model of colitis with trinitrobezenesulfonic acid in rats, and the authors concluded that vagal nerve fibers have a protective role [232], later supported by others [233]. This was challenged by others in the dextran sodium sulfate colitis because the SNS – not the vagus nerve – had the major anti-inflammatory role [170, 234, 235].

Kevin Tracey's group then produced several publications at the beginning of the 2000s that showed the anti-inflammatory influence of electrical vagus nerve stimulation on systemic inflammation, particularly TNF secretion, which was mediated through the alpha7 nicotinergic acetylcholine receptor (α7nAChR) [236–239]. Interestingly, the spleen is an important relay station relevant for these vagally mediated effects [240, 241].

According to Tracey's group, sympathetic nerve fibers to the spleen should be responsible for anti-inflammatory vagal effects mediated in the spleen through acetylcholine-producing cells [242], but others criticized this unilateral interpretation because of the fundamental role of sympathetic nerve fibers to the spleen and the absence of cholinergic nerve fibers [243–246]. In addition, data in humans with vagus nerve stimulation or vagotomy did not fit to the concept of vagal anti-inflammation in the early years of inquiry [247–252], which might depend on the fact that investigated subjects did not suffer from a chronic inflammatory disease. Subsequent studies in patients with chronic inflammatory diseases provided a new picture (next paragraphs).

After several reviews of Kevin Tracey and his group, many researchers of chronic inflammation took up the idea of the anti-inflammatory vagus nerve influence. The theory also entered the field of rheumatic diseases. Soon, it was shown that an agonist to the α7nAChR had anti-inflammatory influence in synovial cells of patients with RA and in the CIA model [253–256]. In addition, vagus nerve stimulation in the rat CIA model showed some anti-inflammatory activities [257], supported in zymosan arthritis in rats through vagal and central nervous pathways that activate (!) the SNS [258, 259]. This opened the question whether, or not, the vagus stimulation exerts anti-inflammatory effects through retrograde central processing and augmentation of downstream sympathetic influences. This question is still unanswered.

With vagus nerve stimulation in humans, researchers obtained mixed results with positive anti-inflammatory effects in Crohn's disease, RA, and psoriatic arthritis [260–265] but negative results in other studies in rheumatic diseases, which might depend on stimulation techniques [266, 267]. All studies in patients were carried

out in an uncontrolled fashion, which still inhibit the authors of this review from drawing firm conclusions due to well-known placebo effects.

Hormonal Pathways

Although many different hormones have been studied in rheumatic diseases, this brief history can only cover the most important ones. We focus on glucocorticoids, androgens, progesterone, estrogens, and the Vitamin D hormone.

Glucocorticoids

Philip Showalter Hench (1896–1965) was an American rheumatologist. Together with his colleague Edward C Kendall and the Swiss chemist Tadeus Reichstein, he was awarded the Nobel Prize for Medicine in the year 1950 for the discoveries on glucocorticoid hormones and their favorable effects in RA.

Already in the late 1920s, Hench observed the favorable effects of jaundice in a patient with RA. At the time, this was a great surprise because RA remission was a medical curiosity. Between 1929 and 1934, he collected data of 16 patients with RA who developed jaundice that ameliorated the crippling disease [268]. Today, we know that in the bile, some biliary acids with the typical steroid hormone structure can have anti-inflammatory activities [269]. However, many therapeutic approaches with bile or compounds thereof – Hench expected to discover the healing "substance X" in the bile – were not successful.

At the same time, he observed the ameliorating effect of pregnancy in women with RA, and he speculated on a "*common denominator substance X*" favorable in jaundice and pregnancy [270]. He wrote: "*It does not seem illogical to suppose that the agents responsible for both these phenomena are closely related, perhaps identical, and if the agent is a chemical substance, it would appear that it is neither bilirubin nor a strictly female sex hormone.*"

During the hunt for "substance X," Philip Hench also recognized that other inflammatory diseases like psoriasis arthritis, asthma, hay fever, Addison's disease, and even migraine were sometimes relieved during pregnancy and/or jaundice. "*Substance X was unspecific and bisexual.*"

In the early 1940s, he started a collaboration with Edward Kendall "*in a laboratory* (at Mayo Clinic) *a few yards away.*" Edward Kendall and colleagues – biochemists – already isolated several adrenal steroid hormones in the late 1930s [271], but administration of them to humans lasted years because the substances were difficult to isolate from extracts. In the year 1948, in a collaboration of Edward Kendall and the American company of Merck and Co., Inc., enough compound E (cortisone) was available to treat a woman "*badly crippled with RA*" [272]. More patients followed with highly favorable results because the biologically inactive cortisone is reactivated to active cortisol.

The similar effects of adrenocorticotropic hormone were linked to the adrenocorticotropic hormone-induced secretion of adrenal glucocorticoids. This was the breakthrough! In Switzerland, concurrently, Tadeus Reichstein also discovered the different adrenal hormones.

Today, we well know that therapeutic glucocorticoids ameliorate inflammation in autoimmune diseases and other inflammatory diseases [273]. The anti-inflammatory effects of glucocorticoids stood the test of time. However, we also know that glucocorticoids must be administered at low doses up to a maximum of 5 mg prednisolone per day to induce a sufficient effect [274] and to prevent severe side effects [275–277]. Administration according to circadian rhythms with a nightly increase of low-dose glucocorticoids at 2:00 a.m. has shown several beneficial effects [278–280].

Although low doses of glucocorticoids below 5 mg prednisolone/day seem to be relatively safe, the subject is still strongly debated due to adverse events [281]. In a world of biological and targeted synthetic disease-modifying antirheumatic drugs, rheumatologists try to avoid the use of glucocorticoids over longer periods. The consensus accepted by almost all rheumatologists is to use the lowest dose for the shortest time possible to deliver the required benefit [281].

The known inadequate secretion of the hypothalamic-pituitary-adrenal axis in patients with chronic inflammatory diseases has been extensively described earlier [282, 283]. This discrepancy of lowered glucocorticoid availability and action on one side and increased inflammation on the other side has been called "disproportion principle" [284].

Androgens

Testosterone and other androgens were discovered in the early 1930s by two groups from the Netherlands [285] and Germany [286]. For the work on the discovery of sex hormones, Adolf Butenandt and Leopold Ruzicka received the Nobel Prize in the year 1939.

The first study on 17-ketosteroids (e.g., androstenedione, dehydroepiandrosterone [DHEA]) in ankylosing spondylitis and RA dates back to the year 1947 [287]. However, the authors of this early report did not see marked differences in urine concentrations of 17-ketosteroids compared to controls. Already 3 years later, however, in 1950, the lower excretion of 17-ketosteroids was demonstrated in RA

patients [288], which was confirmed in many later investigations in the 1980s [289–293].

After the impressive success of therapy with glucocorticoids by Hench and colleagues [272] (see above), some researchers used other steroid hormones like testosterone in the treatment of RA [143, 294, 295]. In the study by Ishmael et al. [294] in patients with RA, it was reported that intramuscular testosterone propionate led to decided improvement in 65% of patients within 24 h, but this was challenged by Guest et al. [143]. Several little uncontrolled therapy studies with testosterone were reported between 1950 and 1970, but results were mixed. Later, animal studies using androgens showed favorable effects in different animal models of SLE and arthritis [296–300].

In 1991, in an open-labeled study on testosterone undecanoate in male patients with RA, one of us (M.C.) demonstrated the anti-inflammatory effects as a significant reduction in IgM rheumatoid factor concentration, lower number of affected joints and decreased daily intake of NSAIDs [301]. In a double-blind placebo-controlled study in RA patients, the group of Bijlsma et al. [302] showed that testosterone had several beneficial effects [303]. Similarly, in SLE, androgens such as DHEA were tested with some positive effects on disease activity and bone quality [304–308], which was recently systematically summarized [309]. These studies stimulated some rheumatologists until this day to use androgens such as DHEA in an off-label therapy.

Already in the 1950s, conversion studies with precursor androgens were reported in vivo in an RA patient and guinea pigs and in vitro in perfused liver [310]. Since androgens can give rise to estrogen production by the aromatase complex, the question of conversion of androgens to other hormones was important. Using original synovial material from RA patients, it was demonstrated that androgens are increasingly converted to estrogens in patients with RA [311]. Nevertheless, some androgens like androstenedione and testosterone even inhibited androgen-to-estrogen conversion in mixed RA synovial cells and stimulated the production of more potent 5α-reduced androgens [312]. Thus, testosterone may still be an interesting treatment option in patients with RA with generally low levels of this hormone, particularly in men. Several anti-autoimmune effects of androgens on diverse immune cells were recently summarized [313]. Androgen and estrogen receptors were discovered in synovial tissue and cells of RA patients in the early 1990s [314, 315], later confirmed by others [316].

The important role of proinflammatory cytokines in inhibiting androgen production was confirmed during biological disease-modifying therapy because, e.g., tocilizumab (inhibits IL-6 receptor) increased serum levels of the potent precursor androstenedione, also observed relative to cortisol and 17-hydroxyprogesterone [317], and anti-TNF therapy increased the precursor DHEA sulfate [318]. The loss of systemic androgens in chronic inflammatory diseases was interpreted as a mechanism of energy distribution to an activated immune system by the breakdown of glycogenic amino acids in skeletal muscles with the consequence of sarcopenia [165].

Progesterone

Similarly stimulated by Hench's publication in 1949, progesterone was used in several very small studies in RA around 1950, but this therapy was not successful [319–321]. Guest et al. [143] used the progesterone precursor pregnenolone and in combinations with testosterone showed some beneficial effects in open studies. A group from Chile, in the 1980s, reported on some beneficial effects of intra-articular progesterone injections in RA patients [322].

In studies in experimental arthritis, progesterone alone had no effect on the clinical course of the disease [323–325]. When progesterone was given together with 17β-estradiol, the favorable effect was stronger than with the estrogen alone [324], which was challenged by others [325]. In an inflammation-induced cartilage degradation model, progesterone treatment had no beneficial effects in vivo, but it blocked IL-1-induced cartilage degradation in vitro [326]. Others confirmed the beneficial effect of progesterone in a model of destructive cartilage invasion by activated synovial fibroblasts in vitro [327], which serve as an RA model.

Progesterone treatment showed positive effects in the lupus model of New Zealand rats [328]. The favorable anti-inflammatory role of progesterone in vitro has been reviewed [329].

Estrogens – The Women-to-Men Preponderance in Chronic Inflammation

Due to the strong women-to-men preponderance in many chronic inflammatory diseases, estrogens were in the focus from the start of their discovery in the 1930s with the assumption that they could have rheumatic disease-stimulating effects. From the late 1940s – after the publication on glucocorticoids by Hench et al. [272] – some groups treated patients with chronic inflammatory diseases using estrogens. Most studies were carried out in small numbers of patients without randomization or placebo control. Some even tried to treat SLE with strong estrogens like diethylstilbestrol [330], a

substance that was banned in the USA in 1971 due to severe side effects. Soon, it was clear that estrogens are not an adequate therapy for chronic rheumatic diseases.

The discussions on unfavorable effects of oral contraceptives in chronic inflammatory rheumatic diseases started in the 1960s, particularly in the direction of SLE. It was summarized in a publication by Chapel and Burns in 1971 [331]. They recommended to prevent treating SLE women with oral contraceptives. This was the situation with the early generation of oral contraceptives where estrogen and progesterone doses were relatively high. Particularly, thromboembolic events were in the focus of considerations. Case reports in this direction appeared all the time during the late 1960s until 1980.

The first studies on the risk of increased susceptibility to chronic rheumatic diseases in normal women taking oral contraceptives appeared at around the same time [332]. The authors concluded that "*results obtained fail to demonstrate that normal women using oral contraceptives are at a greater risk of developing rheumatic symptoms or serological changes than a similar group of non-users*." After many studies into this subject [333–335], today, we know that in SLE, no influence of oral contraceptives exists in mild disease, whereas a higher risk of flares and complications are present in patients with antiphospholipid antibodies or preceding thrombosis. In RA, modern oral contraceptives might even be protective, and they certainly do not exacerbate the disease (summarized in [313]).

In 1977, Kunkel's group in New York established an interesting link between estrogens and autoimmune diseases because they related the estrogen excess and androgen deficit in Klinefelter's syndrome to the susceptibility of SLE [336]. Later reports confirmed this association in SLE and other diseases [337–339]. Somewhat later Bob Lahita of the same group found high urinary 16α-hydroxylated estrogens [340], which have strong immunostimulating and proliferative effects later confirmed by others [341, 342]. The role of sex hormones in SLE was reviewed for the first time in 1981 [298].

In the same period, early studies in New Zealand lupus mice found an influence of sex hormones on disease outcome, and estrogen antagonists and androgens were demonstrated to be favorable in this model [297, 343]. However, estrogen antagonist therapy with tamoxifen failed in SLE patients in 1984 [344]. In models of RA like the CIA model, however, estrogen therapy had beneficial effects because incidence and severity of the disease were suppressed presented by Rikard Holmdahl and Hans Carlsten from Sweden [324, 345, 346].

The success of estrogens in RA models prompted the first therapy with modern estrogens in a small group of RA patients carried out by Hans Bijlsma's group [302]. The authors reported some beneficial effects, which were later challenged by other investigators [347]. However, the beneficial influence of estrogens on bone density was confirmed in RA patients [348].

More and more discussions appeared around the use of hormone replacement therapy in postmenopausal women. After a multitude of epidemiological studies carried out between 1990 and 2020, we can summarize that the risk of developing SLE is somewhat increased and that there is a higher incidence of mild to moderate flares in SLE. In RA patients, hormone replacement therapy is protective (summarized in [313]).

At around 1990, the clear difference of sex hormone influence in diseases such as SLE (estrogens aggravate) in contrast to RA (estrogens can suppress) was state of the art. However, within the same diseased animal, estrogens sometimes exacerbated and sometimes ameliorated typical manifestations of autoimmunity [349]. The dichotomous effect was a mainstay of scientific discovery because it explained the diverse effects of sex hormones within the same animal/disease/patient.

While some author groups spoke for the beneficial effects of estrogens in RA/experimental arthritis others argued strongly against it. We recall a NeuroEndocrine Immune Study Group meeting at the beginning of the 2000s of the American College of Rheumatology during which the two groups were present. Understanding the dichotomous effects of estrogens on different basic immune functions can help explain the contrasting situation [350]. In the years between 1980 and 2005, many stimulating effects of estrogens on B-cell function were discovered (e.g., antibody production by a Japanese group in the early 1980s [351]). During the same years, many inhibitory effects of estrogens on T cell and macrophage function were similarly reported (summarized in [350]).

Today, we know that one and the same disease like RA can be triggered by a prevailing influence of B cells (rituximab leads to remission) or – in contrast in another patient – by a prevailing influence of T cells (abatacept leads to remission). Even within an animal model two contrasting estrogen-sensitive pathophysiologies can exist [349]. This is similar to many chronic inflammatory diseases where either rituximab or abatacept leads to remission. From a clinical standpoint, whether the B cell or the T cell is dominant does not play a role because the disease has very similar clinical manifestations. Thus, the old B-cell and T-cell schools of disease pathophysiology were both correct, and who was correct simply depended

on the prevailing immune mechanism in the affected patient.

It was hypothesized that B-cell diseases and T-cell diseases exist under the same clinically observable entity (summarized in [350]). If this is the case, estrogens with their stimulating effect on B cells would exacerbate B-cell diseases, whereas it is opposite for the T-cell disease/macrophage disease. The theory includes the following standpoint: when diseases during reproductive years are more frequent in women than men, they are estrogen-stimulated B-cell diseases. While this theory can unify the opposite standpoints, it has not yet led to a clinical characterization of subgroups of hormone-dominant immune pathophysiologies that can be used to treat patients.

In general, women are more affected by these diseases than men. We called it the women-to-men preponderance [352]. Why does it happen in the first place? Estrogens serve a fantastic immune supporting role, which is relevant during the reproductive years, during which women are at a higher risk to develop infectious diseases than men are (during cohabitation, pregnancy, postpartum, breastfeeding). At the expense of a higher risk of autoimmune diseases, estrogens protect women during episodes with a higher danger of infections.

Vitamin D Hormone

Rickets, the English disease, or scientifically correctly rachitis is a condition of weak or even soft bones appearing in young children leading, e.g., to bowed legs, stunted growth, bone pain, and other skeletal abnormalities. In an article of 2018, it is described that rickets was a widespread phenomenon 2000 years ago in Roman times [353]. Francis Glisson (1597–1677) described the condition in much detail using strong expression like "*. . . the whole bony system . . . flexible like wax that is rather liquid, so that the flabby and toneless legs scarcely sustain the weight of the superimposed body, so that the tibiae yield to the weight of the fabric pressing down on them from above and become bent. . .*" [354].

Usually, we link the problem of rickets to Victorian England because it was widespread at that time. Thus, it is not surprising that English scientists were strong in this special field of inquiry. In 1906, F. Gowland Hopkins postulated a dietary factor highly important to overcome rickets [355]. In 1919, Edward Mellanby produced a model of rachitis by feeding young dogs with a low-fat diet, and he diagnosed the disease radiologically. In addition, he successfully treated the condition with cod-liver oil [356], which was later confirmed by Harriette Chick and colleagues in rachitic children at the University Kinderklinik in Vienna [357].

McCollum et al. [358] at Johns Hopkins University, Baltimore, took a great step toward discovering the mediator of these effects. They found that there exists a fourth substance next to the already known vitamin A, B, and C, in fat preparations or cod-liver oil, which they called vitamin D (the fourth letter in the alphabet). In the next years, seminal papers of Hess/Weinstock, Steenbock, Windaus/Hess, and Rosenheim/Webster more and more drew nearer to the molecular structure of vitamin D [359–363]. All teams in London, Göttingen, and New York worked together "*according to a friendly arrangement*" [364]. Finally, the structure of the important provitamin was discovered simultaneously by Windaus/Hess in Göttingen/New York and Rosenheim/Webster in London [362, 365].

To summarize the discovery of vitamin D, it remains surprising that only Adolf Windaus received the Nobel Prize in Chemistry in 1928 "*for the services rendered through his research into the constitution of the sterols and their connection with the vitamins*" declared on the official site of the Nobel Prize homepage (https://www.nobelprize.org/prizes/chemistry/1928/summary/). A share of the prize between Windaus, Hess, and Rosenheim would have been more appropriate when the subject of the price would have been vitamin D alone.

In the late 1960s and early 1970s, the first evidence appeared indicative of a vitamin D receptor (VDR) [366–368]. The receptor had a generalized tissue distribution beyond the classical target organs of the intestine (calcium uptake), bone (calcium incorporation), and kidneys (calcium reabsorption) [369]. In 1983, a 1,25-dihydroxyvitamin D3 receptor macromolecule was detected in peripheral mononuclear leukocytes and T and B lymphocytes from normal humans [370]. The gene for the VDR has been discovered in the later 1980s [371, 372]. Interestingly, over the past 3 decades Haussler, Pike and colleagues have demonstrated that 1,25-(OH)2 vitamin D3 works through a VDR-mediated mechanism that involves many coactivators and repressors or directly interact with and regulate hundreds of genes in the entire body (partly by epigenetic mechanisms) [373].

Clinical and translational studies finally showed the major effects of vitamin D3 that include bone metabolism, protection against bacterial and viral infections and immune system modulation [374, 375]. Late at the beginning of the XXI century, several findings indicated a complex interplay between viral infections and vitamin D, including the induction of an antiviral state, functional immunoregulatory features, interaction with cellular and

viral factors, induction of autophagy and apoptosis, and genetic and epigenetic alterations [376]. The most recent evidences for the antiviral effects of vitamin D were shown from 2020 onwards in the context of the SARS-Cov-2 infection (COVID-19) and the effects of low vitamin D serum levels on COVID-19 severity [377].

Another set of extra-endocrine effects exerted by vitamin D3 concerned its immunoregulatory activities, first shown in 1981 with vitamin D-induced in vitro differentiation of mouse myeloid leukemia cells and vitamin D3 metabolism-dependent phagocytic functions of macrophages [378, 379]. In 1984, the combination of the presence of the VDR in human T lymphocytes and the effect of vitamin D3 (1,25-dihydroxyvitamin D3) in inhibiting the growth-promoting interleukin-2 produced by human T lymphocytes activated in vitro represented the first evidence of vitamin D3 as an immunoregulatory hormone [380].

As for the role of vitamin D in rheumatology, until November 2023 almost 6,000 publications (PubMed) have investigated it, reporting progressive achievements in basic and clinical research regarding the role of vitamin D3 in immune-mediated and autoimmune pathological conditions [381, 382]. From a practical point of view, data have confirmed that keeping serum 25(OH)D concentrations above 50 ng/mL (125 nmol/L) all year long reduces the risk for community outbreaks of infections, sepsis, and autoimmune disorders [383].

Afferent Pathways from the Immune System to the Brain

The Clinical Problem

Several autoimmune disease can directly affect the CNS such as multiple sclerosis, Guillain-Barré syndrome, neuromyelitis optica, autoimmune hypophysitis, and some others. A peripheral immune cell is usually the stimulator of the local autoimmune problem in the brain. Other autoimmune disease such as neuropsychiatric SLE can severely affect the CNS through brain-reactive autoantibodies and CNS vasculitis leading even to overt psychosis [384]. These diseases/phenomena are not included in our presentation.

Although separation of organic CNS diseases based on central immune reactions of aggressive peripheral immune cells in contrast to "functional disorders" based on peripheral inflammation is difficult, we focused here on the latter bystander disease sequelae like fatigue, anxiety, insomnia, and depression. The observation of fatigue, anxiety, insomnia, and depression in patients with chronic inflammatory diseases goes back into the 1930s and even before (summarized in [385, 386]). In the 1960s and 1970s, smaller studies correctly identified anxiety and depression in patients with RA [387–391] or SLE [386]. However, clinicians did not know the epidemiologic dimension of these sequelae for many years.

This markedly changed with the introduction of health scoring systems that also included questions towards anxiety and depression like the "Arthritis Impact Measurement Scales (AIMS)" in 1980 [392, 393], the "Stanford Health Assessment Questionnaire Functional Disability Index (HAQ)" [394], or the "short-form health survey (SF-36)" [395]. From 1990 onwards, with the use of scoring systems, many epidemiological studies clearly confirmed the frequent presence of fatigue, anxiety, insomnia, and depression [396–402]. Anxiety, insomnia, and depression were linked to disease activity and pain [403–405].

Similarly, fatigue was not a clinical manifestation that would have been recognized until the middle of the 1980s [406–408]. Neurasthenia as it was called in much earlier times – from the 19th century onwards – had a strong negative connotation (e.g., [409]). Many rheumatologists recognized fatigue in the context of fibromyalgia, a disease that was not palpable for the typical physician in the 1980s/1990s or before. Modern systematic reviews and meta-analyses demonstrated a prevalence for fatigue in chronic rheumatic diseases in the range of 40–60% (healthy population 9–20%) and a prevalence for depression in the range of 10–20% (healthy population: 2–4%). Nowadays, the clinical problem is obvious.

Pathophysiology

Benjamin Hart was the first to have described sickness behavior in animals [410, 411]. Key characteristics are lethargy, sleepiness and depression, anorexia and less thirst, weight loss, reduced grooming and bodily activity, and he recognized that "*it is a highly organized behavioral strategy … at times critical to the survival of an individual*" [411]. He also mentions that the sickness response saves energy for making fever and installing an adequate immune reaction. He hypothesized that IL-1 is the essential central and peripheral cytokine in these very acute responses [411].

IL-1 was the cytokine of interest in finding an important sensory role of afferent vagus nerve fibers in 1994. Two groups independently discovered vagus-mediated sickness behavior including fever responses elicited by injection of proinflammatory substances into the peritoneal cavity [228–230, 412]. The group of Robert Dantzer and Rosemarie Bluthé focused on IL-1 in their

mechanistic studies of sickness behavior [413, 414]. The endogenous IL-1 receptor antagonist blocked IL-1 mediated effects in the CNS [415] (10,437). IL-1 also disturbed sexual behavior in rats injected with IL-1, and this disturbance was aggravated by parallel administration of TNF [416]. This latter phenomenon clearly points to the redundancy of cytokines in stimulating sickness behavior.

At the beginning of the 2000s, the link between cytokines and depression was more and more established. One study in human subjects was groundbreaking because the group of Andy Miller from Atlanta, GA, USA, showed that interferon alpha therapy in 40 melanoma patients led to severe depression, particularly, in those patients on parallel placebo therapy in contrast to parallel paroxetine [417]. The interferons entered the stage of sickness behavior.

In rheumatology, anti-TNF therapy was just approved for the treatment of patients with RA [418]. In 2004, in RA patients, the reduction of fatigue by anti-TNF strategies was first described in a progress report [419], and this was supported by a report on IL-1 receptor antagonist (anakinra) [420, 421]. The first clear indication of a highly beneficial effect on fatigue of biologic disease-modifying antirheumatic therapy was given in a study in psoriasis patients in 2006 [422] and in RA in the same year [423]. Soon other similar studies followed to confirm these favorable effects in other chronic inflammatory diseases.

We recently summarized the pathophysiologic underpinnings of cytokine-induced fatigue making use of many basic research studies (historical literature in this reference [424]). Robert Dantzer, in a review article of 2008, described the pathways from high inflammatory load to fatigue, anxiety, and finally major depression as a continuum with the end result of "*decompensation of the mechanisms that regulate sickness behavior*" [425]. Here, decompensation means breakdown of physiological mechanisms, unfortunately, leading to pathology. Recall that sickness behavior is an evolutionary positively selected physiological strategy of the body to preserve energy stores for the activated immune system [165]. An important aspect in decompensation might be adverse life events experienced in childhood and adolescence as described above [73].

Evolutionary Medicine and Energy Regulation – An Umbrella Theory

Evolutionary medicine is a relatively new approach in psycho-neuro-endocrine immunology in rheumatic diseases that started in the later 2000s. This is not totally correct because aspects like sickness behavior (see above) have been seen through the lens of evolutionary medicine already in the late 1980s [411].

Combining evolutionary medicine with bodily energy regulation, however, results in a strong umbrella theory that can teach us much about the clinical manifestations of chronic inflammatory diseases [165, 204, 426–432]. The model will not be repeated here in detail due to space constraints. In short, the theory says that physiological responses of the immune system and the brain – the two dominant selfish organ systems – were positively selected during evolution for transient, non-life-eliminating inflammatory episodes like infection or wound healing. In chronic inflammatory diseases, our body uses the same basically physiological responses for a too long time.

Suffice it to say that disease sequelae like fatigue, anxiety, depression, insomnia, anorexia, malnutrition, volume overload due to increased water retention, cachexia, cachectic obesity, insulin resistance and hyperinsulinemia, dyslipidemia, inadequate secretion of cortisol relative to inflammation, loss of androgens and higher conversion of androgens to estrogens, hypogonadism, local adipose tissue in inflamed regions, high sympathetic activity, hypertension, loss of local sympathetic nerve fibers, decreased parasympathetic activity, sprouting of sensory nerve fibers and sensory sensitization, inflammation-related anemia, and inflammation-related osteopenia can be explained using the theory. Considering evolved energy trade-offs helps us understand how an energy imbalance can lead to these disease sequelae [165, 204, 426–432].

Some Thoughts at the End

A brief history on psycho-neuro-endocrine immunology in the field of rheumatology unfortunately cannot address all relevant aspects of one specific field, and the authors are very aware of this shortcoming. Therefore, the reader must see this review as a viewpoint through the biased eyes of the authors. We apologize that we missed several publications that have paved the way to psycho-neuro-endocrine immunology of rheumatic diseases. In addition, including publications for an article like this one must necessarily stop at a certain time point, which in our situation is somewhere around the late 2000 years (but some papers were also included from the 2010s). We know that important articles have appeared thereafter.

For example, former critics now recognize dysfunction of the hypothalamic-pituitary adrenal axis as a relatively normal thing in patients with RA (the disproportion

principle was explained in subchapter 3.5 Hormonal Pathways – Glucocorticoids). They base the new understanding on the hyporesponsiveness of the adrenal gland and on tissue glucocorticoid resistance [433]. Adrenal androgen deficiency became a well-known fact in clinical medicine, and many clinicians treat their patients with androgens off-label when serum levels of testosterone are low (but big studies do not exist). We have not reported on prolactin whose proinflammatory role for chronic inflammatory diseases was described early [434]. Similarly, no report was given on the role of vasoactive intestinal peptide, an important neuropeptide with anti-inflammatory activities [435, 436].

The hypogonadal situation in men and women with decreased ovarian reserve was not part of our presentation, although many studies since 2010 demonstrated this phenomenon. Investigations on thyroid abnormalities are still in a state of infancy although the low T3 syndrome is often present in our patients. Natriuretic hormones were not discussed, although we know that serum levels are often elevated indicating sympathetic activity, cardiac involvement, or volume overload due to water retention. We omitted mentioning the role of corticotropin-releasing hormone, melatonin, and α-MSH in chronic inflammation.

Finally, the literature on fatigue, anxiety, depression, and insomnia became innumerable since the year 2010. Most of it has not been reported here because the general pathophysiologic ideas were known before. Importantly, with the focus on fatigue, clinicians started to understand the broad ideas of psycho-neuro-endocrine immunology that entered practical rheumatology today.

When we look into the future, we still wish to see more therapies, which emanate from the field of psycho-neuro-endocrine immunology. The pharmaceutical companies addressed some of the ideas, but developments into this direction are still scarce.

Conflict of Interest Statement

The authors declare that they do not have any conflicts of interest related to the contents of the work.

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References

1 Glick EN. Asymmetrical rheumatoid arthritis after poliomyelitis. Br Med J. 1967;3(5556):26–8. https://doi.org/10.1136/bmj.3.5556.26
2 Jacqueline F. A case of evolutive polyarthritis with localisation controlateral to a hemiplegia. Rev Rhum Mal Osteoartic. 1953;20:323–4.
3 Thompson M, Bywaters EGL. Unilateral rheumatoid arthritis following hemiplegia. Ann Rheum Dis. 1962;21(4):370–7. https://doi.org/10.1136/ard.21.4.370
4 Bland JH, Eddy WM. Hemiplegia and rheumatoid hemiarthritis. Arthritis Rheum. 1968;11(1):72–80. https://doi.org/10.1002/art.1780110110
5 Garwolinska H. Effect of hemiplegia on the course of rheumatoid arthritis. Reumatologia. 1972;10(3):259–61.
6 Velayos EE, Cohen BS. The effect of stroke on well-established rheumatoid arthritis. Md State Med J. 1972;21(3):38–42.
7 Yaghmai I, Rooholamini SM, Faunce HF. Unilateral rheumatoid arthritis: protective effect of neurologic deficits. AJR Am J Roentgenol. 1977;128(2):299–301. https://doi.org/10.2214/ajr.128.2.299
8 Smith RD. Effect of hemiparesis on rheumatoid arthritis. Arthritis Rheum. 1979;22(12):1419–20. https://doi.org/10.1002/art.1780221225
9 Carcassi A, Boschi S, Tundo G, Macri P. Unilateral rheumatoid arthritis. Minerva Med. 1981;72(15):951–6.
10 Ueno Y, Sawada K, Imura H. Protective effect of neural lesion on rheumatoid arthritis. Arthritis Rheum. 1983;26(1):118. https://doi.org/10.1002/art.1780260124
11 Hamilton S. Unilateral rheumatoid arthritis in hemiplegia. J Can Assoc Radiol. 1983;34(1):49–50.
12 Nakamura K, Akizuki M, Kimura A, Chino N. A case of polyarthritis developed on the non-paralytic side in a hemiplegic patient. Ryumachi. 1994;34(3):656–61.
13 Lapadula G, Iannone F, Zuccaro C, Covelli M, Grattagliano V, Pipitone V. Recovery of erosive rheumatoid arthritis after human immunodeficiency virus-1 infection and hemiplegia. J Rheumatol. 1997;24(4):747–51.
14 Keyszer G, Langer T, Kornhuber M, Taute B, Horneff G. Neurovascular mechanisms as a possible cause of remission of rheumatoid arthritis in hemiparetic limbs. Ann Rheum Dis. 2004;63(10):1349–51. https://doi.org/10.1136/ard.2003.016410
15 Dolan AL. Asymmetric rheumatoid vasculitis in a hemiplegic patient. Ann Rheum Dis. 1995;54(6):532. https://doi.org/10.1136/ard.54.6.532
16 Glynn JJ, Clayton ML. Sparing effect of hemiplegia on tophaceous gout. Ann Rheum Dis. 1976;35(6):534–5. https://doi.org/10.1136/ard.35.6.534
17 Sethi S, Sequeira W. Sparing effect of hemiplegia on scleroderma. Ann Rheum Dis. 1990;49(12):999–1000. https://doi.org/10.1136/ard.49.12.999
18 Veale D, Farrell M, Fitzgerald O. Mechanism of joint sparing in a patient with unilateral psoriatic arthritis and a longstanding hemiplegia. Br J Rheumatol. 1993;32(5):413–6. https://doi.org/10.1093/rheumatology/32.5.413
19 Kane D, Lockhart JC, Balint PV, Mann C, Ferrell WR, McInnes IB. Protective effect of sensory denervation in inflammatory arthritis (evidence of regulatory neuro-immune pathways in the arthritic joint). Ann Rheum Dis. 2005;64(2):325–7. https://doi.org/10.1136/ard.2004.022277

20 Bordin G, Atzeni F, Bettazzi L, Beyene NB, Carrabba M, Sarzi-Puttini P. Unilateral polymyalgia rheumatica with controlateral sympathetic dystrophy syndrome. A case of asymmetrical involvement due to pre-existing peripheral palsy. Rheumatology. 2006;45(12):1578–80. https://doi.org/10.1093/rheumatology/kel334
21 Tarkowski E, Naver H, Wallin BG, Blomstrand C, Tarkowski A. Lateralization of T-lymphocyte responses in patients with stroke. Effect of sympathetic dysfunction? Stroke. 1995;26(1):57–62. https://doi.org/10.1161/01.str.26.1.57
22 Lee JC, Salonen DC, Inman RD. Unilateral hemochromatosis arthropathy on a neurogenic basis. J Rheumatol. 1997;24(12):2476–8.
23 Lilly GD. Effect of sympathectomy on development of chronic osteoarthritis: case report. Ann Surg. 1966;163(6):856–8. https://doi.org/10.1097/00000658-196606000-00006
24 Stricker S. Untersuchungen über die Gefäßwurzel des Ischiadicus. Ber Akad Wiss Wien. 1876;3:173–85.
25 Bayliss WM. On the origin from the spinal cord of the vaso-dilator fibres of the hind-limb, and on the nature of these fibres. J Physiol. 1901;26(3–4):173–209. https://doi.org/10.1113/jphysiol.1901.sp000831
26 Bruce AN. Über die Beziehung der sensiblen Nervenendigungen zum Entzündungsvorgang. Arch Exp Pathol Pharmakol. 1910;63:424–33.
27 Bruce AN. Vasodilator axon-reflexes. Q J Exp Physiol. 1913;6(4):339–54. https://doi.org/10.1113/expphysiol.1913.sp000144
28 Breslauer F. Die Pathogenese des trophischen Gewebeschadens nach der Nervenverletzung. Chir Deut Z. 1919;150(1–2):50–81. https://doi.org/10.1007/bf02796922
29 Lewis T. Experiments relating to cutaneous hyperalgesia and its spread through somatic nerves. Clin Sci. 1936;2:373–423.
30 Chapman LF, Ramos A, Goodell H, Wolff HG. Neurokinin - a polypeptide formed during neuronal activity in man. Observations on the axon reflex and antidromic dorsal root stimulation. Trans Am Neurol Assoc. 1960;85:42–5.
31 Kelly M. The neurogenic factor in rheumatic inflammation. Med J Aust. 1951;1(24):859–64. https://doi.org/10.5694/j.1326-5377.1951.tb88497.x
32 Jancso N, Jancso-Gabor A, Szolcsanyi J. Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment with capsaicin. Br J Pharmacol Chemother. 1967;31(1):138–51. https://doi.org/10.1111/j.1476-5381.1967.tb01984.x
33 V Euler US, Gaddum JH. An unidentified depressor substance in certain tissue extracts. J Physiol. 1931;72(1):74–87. https://doi.org/10.1113/jphysiol.1931.sp002763
34 Lembeck F. Central transmission of afferent impulses. III. Incidence and significance of the substance P in the dorsal roots of the spinal cord. Naunyn Schmiedebergs Arch Exp Pathol Pharmakol. 1953;219(3):197–213.
35 Otsuka M, Konishi S. Release of substance P-like immunoreactivity from isolated spinal cord of newborn rat. Nature. 1976;264(5581):83–4. https://doi.org/10.1038/264083a0
36 Levine JD, Clark R, Devor M, Helms C, Moskowitz MA, Basbaum AI. Intraneuronal substance P contributes to the severity of experimental arthritis. Science. 1984;226(4674):547–9. https://doi.org/10.1126/science.6208609
37 Harrison S, Geppetti P. Substance p. Int J Biochem Cell Biol. 2001;33(6):555–76. https://doi.org/10.1016/s1357-2725(01)00031-0
38 Kidd BL, Mapp PI, Gibson SJ, Polak JM, O'Higgins F, Buckland-Wright JC, et al. A neurogenic mechanism for symmetrical arthritis. Lancet. 1989;2(8672):1128–30. https://doi.org/10.1016/s0140-6736(89)91491-8
39 Mapp PI, Terenghi G, Walsh DA, Chen ST, Cruwys SC, Garrett N, et al. Monoarthritis in the rat knee induces bilateral and time-dependent changes in substance P and calcitonin gene-related peptide immunoreactivity in the spinal cord. Neuroscience. 1993;57(4):1091–6. https://doi.org/10.1016/0306-4522(93)90051-g
40 Suvas S. Role of substance P neuropeptide in inflammation, wound healing, and tissue homeostasis. J Immunol. 2017;199(5):1543–52. https://doi.org/10.4049/jimmunol.1601751
41 Amara SG, Jonas V, Rosenfeld MG, Ong ES, Evans RM. Alternative RNA processing in calcitonin gene expression generates mRNAs encoding different polypeptide products. Nature. 1982;298(5871):240–4. https://doi.org/10.1038/298240a0
42 Holzmann B. Modulation of immune responses by the neuropeptide CGRP. Amino acids. 2013;45:1–7. https://doi.org/10.1007/s00726-011-1161-2
43 Dirmeier M, Capellino S, Schubert T, Angele P, Anders S, Straub RH. Lower density of synovial nerve fibres positive for calcitonin gene-related peptide relative to substance P in rheumatoid arthritis but not in osteoarthritis. Rheumatology. 2008;47(1):36–40. https://doi.org/10.1093/rheumatology/kem301
44 Meeus M, Vervisch S, De Clerck LS, Moorkens G, Hans G, Nijs J. Central sensitization in patients with rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum. 2012;41(4):556–67. https://doi.org/10.1016/j.semarthrit.2011.08.001
45 Sherrington CS, Sowton SC. Observations on reflex responses to single break-shocks. J Physiol. 1915;49(5):331–48. https://doi.org/10.1113/jphysiol.1915.sp001713
46 Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971–9. https://doi.org/10.1126/science.150.3699.971
47 Brown AG. Effects of descending impulses on transmission through the spinocervical tract. J Physiol. 1971;219(1):103–25. https://doi.org/10.1113/jphysiol.1971.sp009652
48 WillisWD Jr. Anatomy and physiology of descending control of nociceptive responses of dorsal horn neurons: comprehensive review. Prog Brain Res. 1988;77:1–29. https://doi.org/10.1016/s0079-6123(08)62776-4
49 Schaible HG, König C, Ebersberger A. Spinal pain processing in arthritis: neuron and glia (inter)actions. J Neurochem. 2023. https://doi.org/10.1111/jnc.15742
50 Sluka KA, Westlund KN. An experimental arthritis model in rats: the effects of NMDA and non-NMDA antagonists on aspartate and glutamate release in the dorsal horn. Neurosci Lett. 1993;149(1):99–102. https://doi.org/10.1016/0304-3940(93)90357-q
51 Rees H, Sluka KA, Westlund KN, Willis WD. Do dorsal root reflexes augment peripheral inflammation? Neuroreport. 1994;5(7):821–4. https://doi.org/10.1097/00001756-199403000-00021
52 Weidler C, Holzer C, Harbuz M, Hofbauer R, Angele P, Schölmerich J, et al. Low density of sympathetic nerve fibres and increased density of brain derived neurotrophic factor positive cells in RA synovium. Ann Rheum Dis. 2005;64(1):13–20. https://doi.org/10.1136/ard.2003.016154
53 Ossyssek B, Anders S, Grifka J, Straub RH. Surgical synovectomy decreases density of sensory nerve fibers in synovial tissue of non-inflamed controls and rheumatoid arthritis patients. J Orthop Res. 2011;29(2):297–302. https://doi.org/10.1002/jor.21233
54 Bao L, Zhu Y, Elhassan AM, Wu Q, Xiao B, Zhu J, et al. Adjuvant-induced arthritis: IL-1 beta, IL-6 and TNF-alpha are up-regulated in the spinal cord. Neuroreport. 2001;12(18):3905–8. https://doi.org/10.1097/00001756-200112210-00010
55 Watkins LR, Maier SF. Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. Physiol Rev. 2002;82(4):981–1011. https://doi.org/10.1152/physrev.00011.2002
56 Boyle DL, Jones TL, Hammaker D, Svensson CI, Rosengren S, Albani S, et al. Regulation of peripheral inflammation by spinal p38 MAP kinase in rats. PLoS Med. 2006;3(9):e338. https://doi.org/10.1371/journal.pmed.0030338
57 Boettger MK, Weber K, Grossmann D, Gajda M, Bauer R, Bar KJ, et al. Spinal tumor necrosis factor alpha neutralization reduces peripheral inflammation and hyperalgesia and suppresses autonomic responses in experimental arthritis: a role for spinal tumor necrosis factor alpha during induction and maintenance of peripheral inflammation. Arthritis Rheum. 2010;62(5):1308–18. https://doi.org/10.1002/art.27380
58 Schaible HG. Nociceptive neurons detect cytokines in arthritis. Arthritis Res Ther. 2014;16(5):470. https://doi.org/10.1186/s13075-014-0470-8

59 Cao Y, Fan D, Yin Y. Pain mechanism in rheumatoid arthritis: from cytokines to central sensitization. Mediators Inflamm. 2020;2020:2076328. https://doi.org/10.1155/2020/2076328
60 Svensson CI, Hua XY, Protter AA, Powell HC, Yaksh TL. Spinal p38 MAP kinase is necessary for NMDA-induced spinal PGE(2) release and thermal hyperalgesia. Neuroreport. 2003;14(8):1153–7. https://doi.org/10.1097/00001756-200306110-00010
61 Sarzi-Puttini P, Zen M, Arru F, Giorgi V, Choy EA. Reprint of "Residual pain in rheumatoid arthritis: is it a real problem?" Autoimmun Rev. 2024;23(1):103516. https://doi.org/10.1016/j.autrev.2024.103516
62 Bas DB, Su J, Sandor K, Agalave NM, Lundberg J, Codeluppi S, et al. Collagen antibody-induced arthritis evokes persistent pain with spinal glial involvement and transient prostaglandin dependency. Arthritis Rheum. 2012;64(12):3886–96. https://doi.org/10.1002/art.37686
63 Dawes JM, Weir GA, Middleton SJ, Patel R, Chisholm KI, Pettingill P, et al. Immune or genetic-mediated disruption of CASPR2 causes pain hypersensitivity due to enhanced primary afferent excitability. Neuron. 2018;97(4):806–22.e10. https://doi.org/10.1016/j.neuron.2018.01.033
64 Hess A, Axmann R, Rech J, Finzel S, Heindl C, Kreitz S, et al. Blockade of TNF-α rapidly inhibits pain responses in the central nervous system. Proc Natl Acad Sci U S A. 2011;108(9):3731–6. https://doi.org/10.1073/pnas.1011774108
65 Gowers WR. A lecture on lumbago: its lessons and analogues: delivered at the national hospital for the paralysed and epileptic. Br Med J. 1904;1(2246):117–21. https://doi.org/10.1136/bmj.1.2246.117
66 Yunus M, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. Semin Arthritis Rheum. 1981;11(1):151–71. https://doi.org/10.1016/0049-0172(81)90096-2
67 Wallace DJ. The fibromyalgia syndrome. Ann Med. 1997;29(1):9–21. https://doi.org/10.3109/07853899708998739
68 Goebel A, Krock E, Gentry C, Israel MR, Jurczak A, Urbina CM, et al. Passive transfer of fibromyalgia symptoms from patients to mice. J Clin Invest. 2021;131(13):e144201. https://doi.org/10.1172/JCI144201
69 Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice ASC, et al. Do we need a third mechanistic descriptor for chronic pain states? Pain. 2016;157(7):1382–6. https://doi.org/10.1097/j.pain.0000000000000507
70 Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet. 2021;397(10289):2098–110. https://doi.org/10.1016/S0140-6736(21)00392-5
71 Engel GL. Psychogenic pain and pain-prone patient. Am J Med. 1959;26(6):899–918. https://doi.org/10.1016/0002-9343(59)90212-8
72 Boisset-Pioro MH, Esdaile JM, Fitzcharles MA. Sexual and physical abuse in women with fibromyalgia syndrome. Arthritis Rheum. 1995;38(2):235–41. https://doi.org/10.1002/art.1780380212
73 Straub RH. Early trauma as the origin of chronic inflammation - a psychoneuroimmunological perspective. Heidelberg: Springer; 2023.
74 Henoch MJ, Batson JW, Baum J. Psychosocial factors in juvenile rheumatoid arthritis. Arthritis Rheum. 1978;21(2):229–33. https://doi.org/10.1002/art.1780210209
75 Kopec JA, Sayre EC. Traumatic experiences in childhood and the risk of arthritis: a prospective cohort study. Can J Public Health. 2004;95:361–5. https://doi.org/10.1007/BF03405147
76 Oakes PC, Fisahn C, Iwanaga J, DiLorenzo D, Oskouian RJ, Tubbs RS. A history of the autonomic nervous system: part I: from Galen to Bichat. Childs Nerv Syst. 2016;32(12):2303–8. https://doi.org/10.1007/s00381-016-3246-4
77 Ackerknecht EH. The history of the discovery of the vegatative (autonomic) nervous system. Med Hist. 1974;18:1–8. https://doi.org/10.1017/s0025727300019189
78 Langely JN. The autonomic nervous system. Cambridge: W. Heffer and Sons, Ltd; 1921.
79 White JC, Smithwick RH, Simeone FA The autonomic nervous system; anatomy, physiology, and surgical application. London: Macmillan Surgical Monographs; 1952.
80 Oakes PC, Fisahn C, Iwanaga J, DiLorenzo D, Oskouian RJ, Tubbs RS. A history of the autonomic nervous system: part II: from Reil to the modern era. Childs Nerv Syst. 2016;32(12):2309–15. https://doi.org/10.1007/s00381-016-3247-3
81 Rao Y. The first hormone: adrenaline. Trends Endocrinol Metab. 2019;30(6):331–4. https://doi.org/10.1016/j.tem.2019.03.005
82 Oliver G, Schäfer EA. The physiological effects of extracts of the suprarenal capsules. J Physiol. 1895;18(3):230–76. https://doi.org/10.1113/jphysiol.1895.sp000564
83 Abel J. On epinephrine, the active constituent of the suprarenal capsule and its compounds. Proc Am Physiol Soc. 1898(3–4):3–5.
84 Takamine J. Adrenalin, the active principle of the suprarenal glands, and its mode of preparation. Am J Pharm. 1901;73:523–31.
85 Von Euler US. A substance with sympathin E properties in spleen extracts. Nature. 1946;157:369. https://doi.org/10.1038/157369b0
86 Von Euler US. Sympathin in adrenergic nerve fibres. J Physiol. 1946;105:26.
87 Von Euler US, Purkhold A. Effect of sympathetic denervation on the noradrenaline and adrenaline content of the spleen, kidney, and salivary glands in the sheep. Acta Physiol Scand. 1951;24(2–3):212–7. https://doi.org/10.1111/j.1748-1716.1951.tb00839.x
88 Axelrod J, Weil-Malherbe H, Tomchick R. The physiological disposition of H3-epinephrine and its metabolite metanephrine. J Pharmacol Exp Ther. 1959;127:251–6.
89 Ishigami T. The influence of psychic acts on the progress of pulmonary tuberculosis. Am Rev Tuberc. 1919;2:470–84.
90 Metalnikov S, Chorine V. Role des reflexes conditionnels dans l'immunite. Ann Inst Pasteur. 1926;40:893–900.
91 Exton MS, von Hörsten S, Schult M, Vöge J, Strubel T, Donath S, et al. Behaviorally conditioned immunosuppression using cyclosporine A: central nervous system reduces IL-2 production via splenic innervation. J Neuroimmunol. 1998;88(1–2):182–91. https://doi.org/10.1016/s0165-5728(98)00122-2
92 Szentivanyi A, Filipp G. Anaphylaxis and the nervous system. II. Ann Allergy. 1958;16(2):143–51.
93 Szentivanyi A, Szekely J. Anaphylaxis and the nervous system. IV. Ann Allergy. 1958;16(4):389–92.
94 Draskoci M, Jankovic BD. Involution of the thymus and suppression of immune responses in rats treated with reserpine. Nature. 1964;202:408–9. https://doi.org/10.1038/202408a0
95 Benner MH, Enta T, Lockey S Jr, Makino S, Reed CE. The immunosuppressive effect of epinephrine and the adjuvant effect of beta-adrenergic blockade. J Allergy. 1968;41.
96 Macmanus JP, Whitfield JF. Stimulation of DNA synthesis and mitotic activity of thymic lymphocytes by cyclic adenosine 3'5'-monophosphate. Exp Cell Res. 1969;58(1):188–91. https://doi.org/10.1016/0014-4827(69)90135-9
97 Smith JW, Steiner AL, Newberry WM Jr, Parker CW. Cyclic nucleotide inhibition of lymphocyte transformation. Clin Res. 1969;17:549. (abstract).
98 Hadden JW, Hadden EM, Middleton E Jr. Lymphocyte blast transformation. I. Demonstration of adrenergic receptors in human peripheral lymphocytes. Cell Immunol. 1970;1(6):583–95. https://doi.org/10.1016/0008-8749(70)90024-9
99 Hadden JW, Hadden EM, Middleton E Jr, Good RA. Lymphocyte blast transformation. II. The mechanism of action of alpha adrenergic receptor effects. Int Arch Allergy Appl Immunol. 1971;40(4–5):526–39.
100 Bourne HR, Melmon KL. Adenyl cyclase in human leukocytes: evidence for activation by separate beta adrenergic and prostaglandin receptors. J Pharmacol Exp Ther. 1971;178:1–7.
101 Sokol WN, Beall GN. Leukocytic epinephrine receptors of normal and asthmatic individuals. J Allergy Clin Immunol. 1975;55(5):310–24. https://doi.org/10.1016/0091-6749(75)90003-2

102 Coffey RG, Hadden EM, Hadden JW. Norepinephrine stimulation of lymphocyte ATPase by an alpha adrenergic receptor mechanism. Endocr Res Commun. 1975;2:179–98. https://doi.org/10.1080/07435807509053848

103 Grieco MH, Siegel I, Goel Z. Modulation of human T lymphocyte rosette formation by autonomic agonists and cyclic nucleotides. J Allergy Clin Immunol. 1976;58(1 PT. 2):149–59. https://doi.org/10.1016/0091-6749(76)90150-0

104 Williams LT, Snyderman R, Lefkowitz RJ. Identification of beta-adrenergic receptors in human lymphocytes by (-) (3H) alprenolol binding. J Clin Invest. 1976;57(1):149–55. https://doi.org/10.1172/JCI108254

105 Conolly ME, Greenacre JK. The beta-adrenoceptor of the human lymphocyte and human lung parenchyma. Br J Pharmacol. 1977;59(1):17–23. https://doi.org/10.1111/j.1476-5381.1977.tb06971.x

106 Dunne JV, Peters CJ, Moore TL, Vaughan JH. Differential effects of propranolol on lymphocyte rosette formation and response to plant mitogens. Arthritis Rheum. 1978;21(7):767–73. https://doi.org/10.1002/art.1780210705

107 Besedovsky HO, del Rey A, Sorkin E, Da Prada M, Keller HH. Immunoregulation mediated by the sympathetic nervous system. Cell Immunol. 1979;48(2):346–55. https://doi.org/10.1016/0008-8749(79)90129-1

108 del Rey A, Besedovsky HO, Sorkin E, Da Prada M, Arrenbrecht S. Immunoregulation mediated by the sympathetic nervous system, II. Cell Immunol. 1981;63(2):329–34. https://doi.org/10.1016/0008-8749(81)90012-5

109 del Rey A, Besedovsky HO, Sorkin E, Da Prada M, Bondiolotti GP. Sympathetic immunoregulation: difference between high- and low-responder animals. Am J Physiol. 1982;242(1):R30–3. https://doi.org/10.1152/ajpregu.1982.242.1.R30

110 Besedovsky H, del Rey A, Sorkin E, Da Prada M, Burri R, Honegger C. The immune response evokes changes in brain noradrenergic neurons. Science. 1983;221(4610):564–6. https://doi.org/10.1126/science.6867729

111 Falck B, Torp A. A fluorescence method for histochemical demonstration of noradrenalin in the adrenal medulla. Med Exp Int J Exp Med. 1961;5(6):429–32. https://doi.org/10.1159/000135115

112 Hillarp NA, Hökfelt B. Evidence of adrenaline and noradrenaline in separate adrenal medullary cells. Acta Physiol Scand. 1953;30(1):55–68. https://doi.org/10.1111/j.1748-1716.1954.tb01074.x

113 Lindvall O, Björklund A, Hökfelt T, Ljungdahl A. Application of the glyoxylic acid method to vibratome sections for the improved visualization of central catecholamine neurons. Histochemie. 1973;35(1):31–8. https://doi.org/10.1007/BF00303662

114 Dahlstroem AB, Zetterstroem BE. Noradrenaline stores in nerve terminals of the spleen: changes during hemorrhagic shock. Science. 1965;147(3665):1583–5. https://doi.org/10.1126/science.147.3665.1583

115 Hamberger B, Malmfors T, Stjärne L. Noradrenaline uptake and fluorescence histochemistry in bovine splenic nerves. Acta Physiol Scand. 1971;82(1):107–14. https://doi.org/10.1111/j.1748-1716.1971.tb04947.x

116 Sergeeva VE. Histotopography of catecholamines in the mammalian thymus. Bull Exp Biol Med. 1974;77(4):456–8. https://doi.org/10.1007/BF00798115

117 Giron LT Jr, Crutcher KA, Davis JN. Lymph nodes: a possible site for sympathetic neuronal regulation of immune responses. Ann Neurol. 1980;8:520–5. https://doi.org/10.1002/ana.410080509

118 Felten DL, Overhage JM, Felten SY, Schmedtje JF. Noradrenergic sympathetic innervation of lymphoid tissue in the rabbit appendix: further evidence for a link between the nervous and immune systems. Brain Res Bull. 1981;7(5):595–612. https://doi.org/10.1016/0361-9230(81)90010-1

119 Nagatsu T, Levitt M, Udenfriend S. Tyrosine hydroxylase. J Biol Chem. 1964;239(9):2910–7. https://doi.org/10.1016/s0021-9258(18)93832-9

120 Axelrod J, Kopin IJ. The uptake, storage, release and metabolism of noradrenaline in sympathetic nerves. Prog Brain Res. 1969;31:21–32. https://doi.org/10.1016/S0079-6123(08)63224-0

121 Laduron P, Belpaire F. Evidence for an extragranular localization of tyrosine hydroxylase. Nature. 1968;217(5134):1155–6. https://doi.org/10.1038/2171155a0

122 Kopin IJ, Silberstein SD. Axons of sympathetic neurons; transport of enzymes in vivo and properties of axonal sprouts in vitro. Pharmacol Rev. 1972;24(2):245–54.

123 Joh TH, Geghman C, Reis D. Immunochemical demonstration of increased accumulation of tyrosine hydroxylase protein in sympathetic ganglia and adrenal medulla elicited by reserpine. Proc Natl Acad Sci U S A. 1973;70(10):2767–71. https://doi.org/10.1073/pnas.70.10.2767

124 Pickel VM, Joh TH, Field PM, Becker CG, Reis DJ. Cellular localization of tyrosine hydroxylase by immunohistochemistry. J Histochem Cytochem. 1975;23:1–12. https://doi.org/10.1177/23.1.234988

125 Jesseph JM, Felten DL. Noradrenergic innervation of the Gut-Associated Lymphoid Tissues (GALT) in the rabbit [abstract]. Anat Rec. 1984;208:81A–A.

126 Felten DL, Felten SY, Carlson SL, Olschowka JA, Livnat S. Noradrenergic and peptidergic innervation of lymphoid tissue. J Immunol. 1985;135(2):755s–65s. https://doi.org/10.4049/jimmunol.135.2.755

127 Felten DL, Felten SY, Bellinger DL, Carlson SL, Ackerman KD, Madden KS, et al. Noradrenergic sympathetic neural interactions with the immune system: structure and function. Immunol Rev. 1987;100:225–60. https://doi.org/10.1111/j.1600-065x.1987.tb00534.x

128 Felten SY, Olschowka J. Noradrenergic sympathetic innervation of the spleen: II. Tyrosine Hydroxylase (TH)-positive nerve terminals form synapticlike contacts on lymphocytes in the splenic white pulp. J Neurosci Res. 1987;18(1):37–48. https://doi.org/10.1002/jnr.490180108

129 Lorton D, Hewitt D, Bellinger DL, Felten SY, Felten DL. Noradrenergic reinnervation of the rat spleen following chemical sympathectomy with 6-hydroxydopamine: pattern and time course of reinnervation. Brain Behav Immun. 1990;4(3):198–222. https://doi.org/10.1016/0889-1591(90)90023-j

130 Stead RH, Tomioka M, Quinonez G, Simon GT, Felten SY, Bienenstock J. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. Proc Natl Acad Sci U S A. 1987;84:2975–9. https://doi.org/10.1073/pnas.84.9.2975

131 Weihe E, Nohr D, Michel S, Muller S, Zentel HJ, Fink T, et al. Molecular anatomy of the neuro-immune connection. Int J Neurosci. 1991;59(1–3):1–23. https://doi.org/10.3109/00207459108985446

132 Straub RH. Complexity of the bi-directional neuroimmune junction in the spleen. Trends Pharmacol Sci. 2004;25(12):640–6. https://doi.org/10.1016/j.tips.2004.10.007

133 Straub RH, Dufner B, Rauch L. Proinflammatory α-adrenergic neuronal regulation of splenic IFN-γ, IL-6, and TGF-β of mice from day 15 onwards in arthritis. Neuroimmunomodulation. 2020;27(1):58–68. https://doi.org/10.1159/000508109

134 von Euler US, Hillarp NA. Evidence for the presence of noradrenaline in submicroscopic structures of adrenergic axons. Nature. 1956;177(4497):44–5. https://doi.org/10.1038/177044b0

135 Lundberg JM, Rudehill A, Sollevi A, Fried G, Wallin G. Co-release of neuropeptide Y and noradrenaline from pig spleen in vivo: importance of subcellular storage, nerve impulse frequency and pattern, feedback regulation and resupply by axonal transport. Neuroscience. 1989;28(2):475–86. https://doi.org/10.1016/0306-4522(89)90193-0

136 Bognar IT, Albrecht SA, Farasaty M, Schmitt E, Seidel G, Fuder H. Effects of human recombinant interleukins on stimulation-evoked noradrenaline overflow from the rat perfused spleen. Naunyn Schmiedebergs Arch Pharmacol. 1994;349(5):497–502. https://doi.org/10.1007/BF00169139

137 Straub RH, Lang B, Falk W, Schölmerich J, Singer EA. In vitro superfusion method for the investigation of nerve-immune cell interaction in murine spleen. J Neuroimmunol. 1995;61(1):53–60. https://doi.org/10.1016/0165-5728(95)00073-b

138 Carr DJ. Neuroendocrine peptide receptors on cells of the immune system. Chem Immunol. 1992;52:84–105. https://doi.org/10.1159/000319386
139 Sanders VM, Kasprowicz DJ, Kohm AP, Swanson MA. Neurotransmitter receptors on lymphocytes and other lymphoid cells. In: Ader R, Felten DL, Cohen N, editors. Psychneuroimmunology. San Diego: Academic Press; 2001. p. 161–96.
140 Straub RH, Dorner M, Riedel J, Kubitza M, Van Rooijen N, Lang B, et al. Tonic neurogenic inhibition of interleukin-6 secretion from murine spleen caused by opioidergic transmission. Am J Physiol. 1998;274(4):R997–1003. https://doi.org/10.1152/ajpregu.1998.274.4.R997
141 Straub RH, Herrmann M, Frauenholz T, Berkmiller G, Lang B, Schölmerich J, et al. Neuroimmune control of interleukin-6 secretion in the murine spleen. Differential -adrenergic effects of electrically released endogenous norepinephrine under various endotoxin conditions. J Neuroimmunol. 1996;71(1–2):37–43. https://doi.org/10.1016/s0165-5728(96)00126-9
142 Straub RH, Herrmann M, Berkmiller G, Frauenholz T, Lang B, Schölmerich J, et al. Neuronal regulation of interleukin 6 secretion in murine spleen: adrenergic and opioidergic control. J Neurochem. 1997;68(4):1633–9. https://doi.org/10.1046/j.1471-4159.1997.68041633.x
143 Guest CM, Kammerer WH, Cecil RL, Berson SA. Epinephrine, pregnenolone and testosterone in the treatment of rheumatoid arthritis. J Am Med Assoc. 1950;143(4):338–44. https://doi.org/10.1001/jama.1950.02910390010003
144 Herfort RA. Extended sympathectomy in the treatment of chronic arthritis. J Am Geriatr Soc. 1957;5(11):904–15. https://doi.org/10.1111/j.1532-5415.1957.tb00490.x
145 Dick WC, Jubb R, Buchanan WW, Williamson J, Whaley K, Porter BB. Studies on the sympathetic control of normal and diseased synovial blood vessels: the effect of alpha and beta receptor stimulation and inhibition, monitored by the 133xenon clearance technique. Clin Sci. 1971;40(2):197–209. https://doi.org/10.1042/cs0400197
146 Lam FY, Ferrell WR. Acute inflammation in the rat knee joint attenuates sympathetic vasoconstriction but enhances neuropeptide-mediated vasodilatation assessed by laser Doppler perfusion imaging. Neuroscience. 1993;52(2):443–9. https://doi.org/10.1016/0306-4522(93)90170-k
147 Jolliffe VA, Anand P, Kidd BL. Assessment of cutaneous sensory and autonomic axon reflexes in rheumatoid arthritis. Ann Rheum Dis. 1995;54(4):251–5. https://doi.org/10.1136/ard.54.4.251
148 McDougall JJ. Abrogation of alpha-adrenergic vasoactivity in chronically inflamed rat knee joints. Am J Physiol Regul Integr Comp Physiol. 2001;281(3):R821–7. https://doi.org/10.1152/ajpregu.2001.281.3.R821
149 Levine JD, Moskowitz MA, Basbaum AI. The contribution of neurogenic inflammation in experimental arthritis. J Immunol. 1985;135(2):843s–7s. https://doi.org/10.4049/jimmunol.135.2.843
150 Levine JD, Fye K, Heller P, Basbaum AI, Whiting-O'Keefe Q. Clinical response to regional intravenous guanethidine in patients with rheumatoid arthritis. J Rheumatol. 1986;13(6):1040–3.
151 Levine JD, Coderre TJ, Helms C, Basbaum AI. Beta 2-adrenergic mechanisms in experimental arthritis. Proc Natl Acad Sci U S A. 1988;85(12):4553–6. https://doi.org/10.1073/pnas.85.12.4553
152 Coderre TJ, Basbaum AI, Helms C, Levine JD. High-dose epinephrine acts at alpha 2-adrenoceptors to suppress experimental arthritis. Brain Res. 1991;544(2):325–8. https://doi.org/10.1016/0006-8993(91)90073-5
153 Felten DL, Felten SY, Bellinger DL, Lorton D. Noradrenergic and peptidergic innervation of secondary lymphoid organs: role in experimental rheumatoid arthritis. Eur J Clin Invest. 1992;22(Suppl 1):37–41.
154 Lorton D, Bellinger D, Duclos M, Felten SY, Felten DL. Application of 6-hydroxydopamine into the fatpads surrounding the draining lymph nodes exacerbates adjuvant-induced arthritis. J Neuroimmunol. 1996;64(2):103–13. https://doi.org/10.1016/0165-5728(95)00150-6
155 Lorton D, Lubahn C, Klein N, Schaller J, Bellinger DL. Dual role for noradrenergic innervation of lymphoid tissue and arthritic joints in adjuvant-induced arthritis. Brain Behav Immun. 1999;13(4):315–34. https://doi.org/10.1006/brbi.1999.0564
156 Härle P, Mobius D, Carr DJ, Schölmerich J, Straub RH. An opposing time-dependent immune-modulating effect of the sympathetic nervous system conferred by altering the cytokine profile in the local lymph nodes and spleen of mice with type II collagen-induced arthritis. Arthritis Rheum. 2005;52(4):1305–13. https://doi.org/10.1002/art.20987
157 Härle P, Pongratz G, Albrecht J, Tarner IH, Straub RH. An early sympathetic nervous system influence exacerbates collagen-induced arthritis via CD4+CD25+ cells. Arthritis Rheum. 2008;58(8):2347–55. https://doi.org/10.1002/art.23628
158 Capellino S, Cosentino M, Wolff C, Schmidt M, Grifka J, Straub RH. Catecholamine-producing cells in the synovial tissue during arthritis: modulation of sympathetic neurotransmitters as new therapeutic target. Ann Rheum Dis. 2010;69(10):1853–60. https://doi.org/10.1136/ard.2009.119701
159 Capellino S, Weber K, Gelder M, Härle P, Straub RH. First appearance and location of catecholaminergic cells during experimental arthritis and elimination by chemical sympathectomy. Arthritis Rheum. 2012;64(4):1110–8. https://doi.org/10.1002/art.33431
160 Jenei-Lanzl Z, Capellino S, Kees F, Fleck M, Lowin T, Straub RH. Anti-inflammatory effects of cell-based therapy with tyrosine hydroxylase-positive catecholaminergic cells in experimental arthritis. Ann Rheum Dis. 2015;74(2):444–51. https://doi.org/10.1136/annrheumdis-2013-203925
161 Pongratz G, Straub RH. Role of peripheral nerve fibres in acute and chronic inflammation in arthritis. Nat Rev Rheumatol. 2013;9(2):117–26. https://doi.org/10.1038/nrrheum.2012.181
162 Pongratz G, Straub RH. The sympathetic nervous response in inflammation. Arthritis Res Ther. 2014;16(6):504. https://doi.org/10.1186/s13075-014-0504-2
163 Schaible HG, Straub RH. Function of the sympathetic supply in acute and chronic experimental joint inflammation. Auton Neurosci. 2014;182:55–64. https://doi.org/10.1016/j.autneu.2013.12.004
164 Klatt S, Stangl H, Kunath J, Lowin T, Pongratz G, Straub RH. Peripheral elimination of the sympathetic nervous system stimulates immunocyte retention in lymph nodes and ameliorates collagen type II arthritis. Brain Behav Immun. 2016;54:201–10. https://doi.org/10.1016/j.bbi.2016.02.006
165 Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med. 2010;267(6):543–60. https://doi.org/10.1111/j.1365-2796.2010.02218.x
166 Straub RH, Günzler C, Miller LE, Cutolo M, Schölmerich J, Schill S. Anti-inflammatory cooperativity of corticosteroids and norepinephrine in rheumatoid arthritis synovial tissue in vivo and in vitro. FASEB J. 2002;16(9):993–1000. https://doi.org/10.1096/fj.02-0085com
167 Pereira da Silva JA, Carmo-Fonseca M. Peptide containing nerves in human synovium: immunohistochemical evidence for decreased innervation in rheumatoid arthritis. J Rheumatol. 1990;17(12):1592–9.
168 Mapp PI, Walsh DA, Garrett NE, Kidd BL, Cruwys SC, Polak JM, et al. Effect of three animal models of inflammation on nerve fibres in the synovium. Ann Rheum Dis. 1994;53(4):240–6. https://doi.org/10.1136/ard.53.4.240
169 Miller LE, Jüsten HP, Schölmerich J, Straub RH. The loss of sympathetic nerve fibers in the synovial tissue of patients with rheumatoid arthritis is accompanied by increased norepinephrine release from synovial macrophages. FASEB J. 2000;14(13):2097–107. https://doi.org/10.1096/fj.99-1082com
170 Straub RH, Grum F, Strauch UG, Capellino S, Bataille F, Bleich A, et al. Anti-inflammatory role of sympathetic nerves in chronic intestinal inflammation. Gut. 2008;57(7):911–21. https://doi.org/10.1136/gut.2007.125401

171 Koeck FX, Bobrik V, Fassold A, Grifka J, Kessler S, Straub RH. Marked loss of sympathetic nerve fibers in chronic Charcot foot of diabetic origin compared to ankle joint osteoarthritis. J Orthop Res. 2009;27(6):736–41. https://doi.org/10.1002/jor.20807
172 Haas S, Capellino S, Phan NQ, Bohm M, Luger TA, Straub RH, et al. Low density of sympathetic nerve fibers relative to substance P-positive nerve fibers in lesional skin of chronic pruritus and prurigo nodularis. J Dermatol Sci. 2010;58(3):193–7. https://doi.org/10.1016/j.jdermsci.2010.03.020
173 Ferrero S, Haas S, Remorgida V, Camerini G, Fulcheri E, Ragni N, et al. Loss of sympathetic nerve fibers in intestinal endometriosis. Fertil Steril. 2010;94(7):2817–9. https://doi.org/10.1016/j.fertnstert.2010.06.069
174 Lorton D, Lubahn C, Sweeney S, Major A, Lindquist CA, Schaller J, et al. Differences in the injury/sprouting response of splenic noradrenergic nerves in Lewis rats with adjuvant-induced arthritis compared with rats treated with 6-hydroxydopamine. Brain Behav Immun. 2009;23(2):276–85. https://doi.org/10.1016/j.bbi.2008.10.004
175 Straub RH, Lowin T, Klatt S, Wolff C, Rauch L. Increased density of sympathetic nerve fibers in metabolically activated fat tissue surrounding human synovium and mouse lymph nodes in arthritis. Arthritis Rheum. 2011;63(11):3234–42. https://doi.org/10.1002/art.30516
176 Dietrich P, Moleda L, Kees F, Müller M, Straub RH, Hellerbrand C, et al. Dysbalance in sympathetic neurotransmitter release and action in cirrhotic rats: impact of exogenous neuropeptide Y. J Hepatol. 2013;58(2):254–61. https://doi.org/10.1016/j.jhep.2012.09.027
177 Ghilardi JR, Freeman KT, Jimenez-Andrade JM, Coughlin K, Kaczmarska MJ, Castaneda-Corral G, et al. Neuroplasticity of sensory and sympathetic nerve fibers in the painful arthritic joint. Arthritis Rheum. 2012;64(7):2223–32. https://doi.org/10.1002/art.34385
178 Jimenez-Andrade JM, Mantyh PW. Sensory and sympathetic nerve fibers undergo sprouting and neuroma formation in the painful arthritic joint of geriatric mice. Arthritis Res Ther. 2012;14(3):R101. https://doi.org/10.1186/ar3826
179 Widenfalk B. Sympathetic innervation of normal and rheumatoid synovial tissue. Scand J Plast ReConstr Surg Hand Surg. 1991;25(1):31–3. https://doi.org/10.3109/02844319109034920
180 Wu P, Li W, Lv R, Cheng X, Lian F, Cai W, et al. Hyperactive lateral habenula mediates the comorbidity between rheumatoid arthritis and depression-like behaviors. Brain Behav Immun. 2024;117:412–27. https://doi.org/10.1016/j.bbi.2024.02.006
181 Jenei-Lanzl Z, Grässel S, Pongratz G, Kees F, Miosge N, Angele P, et al. Norepinephrine inhibition of mesenchymal stem cell and chondrogenic progenitor cell chondrogenesis and acceleration of chondrogenic hypertrophy. Arthritis Rheumatol. 2014;66(9):2472–81. https://doi.org/10.1002/art.38695
182 Szentivanyi A. The beta adrenergic theory of the atopic abnormality in bronchial asthma. J Allergy. 1968;42(4):203–32. https://doi.org/10.1016/s0021-8707(68)90117-2
183 Camoretti-Mercado B, Lockey RF. The β-adrenergic theory of bronchial asthma: 50 years later. J Allergy Clin Immunol. 2019;144(5):1166–8. https://doi.org/10.1016/j.jaci.2019.07.010
184 Amrani Y, Bradding P. β2-Adrenoceptor function in asthma. Adv Immunol. 2017;136:1–28. https://doi.org/10.1016/bs.ai.2017.06.003
185 Barnes PJ, Dollery CT, MacDermot J. Increased pulmonary alpha-adrenergic and reduced beta-adrenergic receptors in experimental asthma. Nature. 1980;285(5766):569–71. https://doi.org/10.1038/285569a0
186 Emala CW, Kuhl J, Hungerford CL, Hirshman CA. TNF-alpha inhibits isoproterenol-stimulated adenylyl cyclase activity in cultured airway smooth muscle cells. Am J Physiol. 1997;272(4 Pt 1):L644–50. https://doi.org/10.1152/ajplung.1997.272.4.L644
187 Spengler RN, Chensue SW, Giacherio DA, Blenk N, Kunkel SL. Endogenous norepinephrine regulates tumor necrosis factor-alpha production from macrophages in vitro. J Immunol. 1994;152(6):3024–31. https://doi.org/10.4049/jimmunol.152.6.3024
188 Malfait AM, Malik AS, Marinova-Mutafchieva L, Butler DM, Maini RN, Feldmann M. The β2-adrenergic agonist salbutamol is a potent suppressor of established collagen-induced arthritis: mechanisms of action. J Immunol. 1999;162(10):6278–83. https://doi.org/10.4049/jimmunol.162.10.6278
189 Baerwald C, Graefe C, von Wichert P, Krause A. Decreased density of beta-adrenergic receptors on peripheral blood mononuclear cells in patients with rheumatoid arthritis. J Rheumatol. 1992;19(2):204–10.
190 Baerwald CG, Laufenberg M, Specht T, von Wichert P, Burmester GR, Krause A. Impaired sympathetic influence on the immune response in patients with rheumatoid arthritis due to lymphocyte subset-specific modulation of beta 2-adrenergic receptors. Br J Rheumatol. 1997;36(12):1262–9. https://doi.org/10.1093/rheumatology/36.12.1262
191 Baerwald CG, Wahle M, Ulrichs T, Jonas D, von Bierbrauer A, von Wichert P, et al. Reduced catecholamine response of lymphocytes from patients with rheumatoid arthritis. Immunobiology. 1999;200(1):77–91. https://doi.org/10.1016/s0171-2985(99)80034-5
192 Wahle M, Kolker S, Krause A, Burmester GR, Baerwald CG. Impaired catecholaminergic signalling of B lymphocytes in patients with chronic rheumatic diseases. Ann Rheum Dis. 2001;60(5):505–10. https://doi.org/10.1136/ard.60.5.505
193 Wahle M, Hanefeld G, Brunn S, Straub RH, Wagner U, Krause A, et al. Failure of catecholamines to shift T-cell cytokine responses toward a Th2 profile in patients with rheumatoid arthritis. Arthritis Res Ther. 2006;8(5):R138. https://doi.org/10.1186/ar2028
194 Howlett LA, Lancaster MK. Reduced cardiac response to the adrenergic system is a key limiting factor for physical capacity in old age. Exp Gerontol. 2021;150:111339. https://doi.org/10.1016/j.exger.2021.111339
195 Lombardi MS, Kavelaars A, Schedlowski M, Bijlsma JW, Okihara KL, Van de Pol M, et al. Decreased expression and activity of G-protein-coupled receptor kinases in peripheral blood mononuclear cells of patients with rheumatoid arthritis. FASEB J. 1999;13(6):715–25. https://doi.org/10.1096/fasebj.13.6.715
196 Lombardi MS, Kavelaars A, Cobelens PM, Schmidt RE, Schedlowski M, Heijnen CJ. Adjuvant arthritis induces down-regulation of G protein-coupled receptor kinases in the immune system. J Immunol. 2001;166(3):1635–40. https://doi.org/10.4049/jimmunol.166.3.1635
197 Lorton D, Bellinger DL. Molecular mechanisms underlying β-adrenergic receptor-mediated cross-talk between sympathetic neurons and immune cells. Int J Mol Sci. 2015;16(3):5635–65. https://doi.org/10.3390/ijms16035635
198 Lorton D, Bellinger DL, Schaller JA, Shewmaker E, Osredkar T, Lubahn C. Altered sympathetic-to-immune cell signaling via beta(2)-adrenergic receptors in adjuvant arthritis. Clin Dev Immunol. 2013;2013:764395. https://doi.org/10.1155/2013/764395
199 Jenei-Lanzl Z, Zwingenberg J, Lowin T, Anders S, Straub RH. Proinflammatory receptor switch from Gαs to Gαi signaling by β-arrestin-mediated PDE4 recruitment in mixed RA synovial cells. Brain Behav Immun. 2015;50:266–74. https://doi.org/10.1016/j.bbi.2015.07.020
200 Ge M, Wu L, He F, Tai Y, Fang R, Han D, et al. CP-25 inhibits the hyperactivation of rheumatic synoviocytes by suppressing the switch in G(αs)-G(αi) coupling to the β(2)-adrenergic receptor. Cell Commun Signal. 2023;21(1):346. https://doi.org/10.1186/s12964-023-01358-z
201 Sato Y, Schaible HG, Schmidt RF. Reactions of cardiac postganglionic sympathetic neurons to movements of normal and inflamed knee joints. J Auton Nerv Syst. 1985;12:1–13. https://doi.org/10.1016/0165-1838(85)90036-0
202 Sato A, Sato Y, Schmidt RF. Catecholamine secretion and adrenal nerve activity in response to movements of normal and inflamed knee joints in cats. J Physiol. 1986;375(611–24):611–24. https://doi.org/10.1113/jphysiol.1986.sp016136

203 Tanaka H, Ueta Y, Yamashita U, Kannan H, Yamashita H. Biphasic changes in behavioral, endocrine, and sympathetic systems in adjuvant arthritis in Lewis rats. Brain Res Bull. 1996;39(1):33–7. https://doi.org/10.1016/0361-9230(95)02037-3

204 Straub RH. The brain and immune system prompt energy shortage in chronic inflammation and ageing. Nat Rev Rheumatol. 2017;13(12):743–51. https://doi.org/10.1038/nrrheum.2017.172

205 Leden I, Eriksson A, Lilja B, Sturfelt G, Sundkvist G. Autonomic nerve function in rheumatoid arthritis of varying severity. Scand J Rheumatol. 1983;12(2):166–70. https://doi.org/10.3109/03009748309102905

206 Perry F, Heller PH, Kamiya J, Levine JD. Altered autonomic function in patients with arthritis or with chronic myofascial pain. Pain. 1989;39(1):77–84. https://doi.org/10.1016/0304-3959(89)90177-2

207 Kuis W, de Jong-de Vos van Steenwijk-Sinnema CG, Kavelaars A, Prakken B, Helders PJ, Heijnen CJ. The autonomic nervous system and the immune system in juvenile rheumatoid arthritis. Brain Behav Immun. 1996;10(4):387–98. https://doi.org/10.1006/brbi.1996.0034

208 Toussirot E, Bahjaoui-Bouhaddi M, Poncet JC, Cappelle S, Henriet MT, Wendling D, et al. Abnormal autonomic cardiovascular control in ankylosing spondylitis. Ann Rheum Dis. 1999;58(8):481–7. https://doi.org/10.1136/ard.58.8.481

209 Barendregt PJ, Tulen JH, van den Meiracker AH, Markusse HM. Spectral analysis of heart rate and blood pressure variability in primary Sjogren's syndrome. Ann Rheum Dis. 2002;61(3):232–6. https://doi.org/10.1136/ard.61.3.232

210 Dekkers JC, Geenen R, Godaert GL, Bijlsma JW, van Doornen LJ. Elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease. Clin Exp Rheumatol. 2004;22(1):63–70.

211 Härle P, Straub RH, Wiest R, Mayer A, Schölmerich J, Atzeni F, et al. Increase of sympathetic outflow measured by neuropeptide Y and decrease of the hypothalamic-pituitary-adrenal axis tone in patients with systemic lupus erythematosus and rheumatoid arthritis: another example of uncoupling of response systems. Ann Rheum Dis. 2006;65(1):51–6. https://doi.org/10.1136/ard.2005.038059

212 Straub RH, Herfarth H, Falk W, Andus T, Schölmerich J. Uncoupling of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis in inflammatory bowel disease? J Neuroimmunol. 2002;126(1–2):116–25. https://doi.org/10.1016/s0165-5728(02)00047-4

213 Adlan AM, Paton JF, Lip GY, Kitas GD, Fisher JP. Increased sympathetic nerve activity and reduced cardiac baroreflex sensitivity in rheumatoid arthritis. J Physiol. 2017;595(3):967–81. https://doi.org/10.1113/JP272944

214 Snow MH, Mikuls TR. Rheumatoid arthritis and cardiovascular disease: the role of systemic inflammation and evolving strategies of prevention. Curr Opin Rheumatol. 2005;17(3):234–41. https://doi.org/10.1097/01.bor.0000159924.97019.25

215 Liao KP, Solomon DH. Mechanistic insights into the link between inflammation and cardiovascular disease: rheumatoid arthritis as a human model of inflammation. Circ Cardiovasc Imaging. 2014;7(4):575–7. https://doi.org/10.1161/CIRCIMAGING.114.002235

216 Mehta PK, Levit RD, Wood MJ, Aggarwal N, O'Donoghue ML, Lim SS, et al. Chronic rheumatologic disorders and cardiovascular disease risk in women. Am Heart J. 2023;27:100267. https://doi.org/10.1016/j.ahjo.2023.100267

217 Straub RH, Ehrenstein B, Gunther F, Rauch L, Trendafilova N, Boschiero D, et al. Increased extracellular water measured by bioimpedance and by increased serum levels of atrial natriuretic peptide in RA patients-signs of volume overload. Clin Rheumatol. 2017;36(5):1041–51. https://doi.org/10.1007/s10067-016-3286-x

218 Günther F, Ehrenstein B, Hartung W, Boschiero D, Fleck M, Straub RH. Increased extracellular water measured by bioimpedance analysis and increased serum levels of atrial natriuretic peptide in polymyalgia rheumatica patients: signs of volume overload. Z Rheumatol. 2021;80(2):140–8. https://doi.org/10.1007/s00393-020-00845-9

219 Meltzer SJ, Meltzer C. On a difference in the influence upon inflammation between the section of the sympathetic nerve and the removal of the sympathetic ganglion. J Med Res. 1903;10(1):135–41.

220 Lundberg JM, Saria A, Brodin E, Rosell S, Folkers K. A substance P antagonist inhibits vagally induced increase in vascular permeability and bronchial smooth muscle contraction in the Guinea pig. Proc Natl Acad Sci U S A. 1983;80:1120–4. https://doi.org/10.1073/pnas.80.4.1120

221 Saria A, Martling CR, Dalsgaard CJ, Lundberg JM. Evidence for substance P-immunoreactive spinal afferents that mediate bronchoconstriction. Acta Physiol Scand. 1985;125(3):407–14. https://doi.org/10.1111/j.1748-1716.1985.tb07736.x

222 McDonald DM. Respiratory tract infections increase susceptibility to neurogenic inflammation in the rat trachea. Am Rev Respir Dis. 1988;137(6):1432–40. https://doi.org/10.1164/ajrccm/137.6.1432

223 McDonald DM, Mitchell RA, Gabella G, Haskell A. Neurogenic inflammation in the rat trachea. II. Identity and distribution of nerves mediating the increase in vascular permeability. J Neurocytol. 1988;17(5):605–28. https://doi.org/10.1007/BF01260989

224 Kowalski ML, Didier A, Kaliner MA. Neurogenic inflammation in the airways. I. Neurogenic stimulation induces plasma protein extravasation into the rat airway lumen. Am Rev Respir Dis. 1989;140(1):101–9. https://doi.org/10.1164/ajrccm/140.1.101

225 Norris AA, Leeson ME, Jackson DM, Holroyde MC. Modulation of neurogenic inflammation in rat trachea. Pulm Pharmacol. 1990;3:180–4. https://doi.org/10.1016/0952-0600(90)90014-a

226 Belvisi MG, Barnes PJ, Rogers DF. Neurogenic inflammation in the airways: characterisation of electrical parameters for vagus nerve stimulation in the Guinea pig. J Neurosci Methods. 1990;32(2):159–67. https://doi.org/10.1016/0165-0270(90)90173-d

227 Huang HT. Unilateral cervical vagotomy decreases the magnitude of neurogenic inflammation induced by capsaicin in the ipsilateral bronchial tree of rats. Anat Embryol. 1993;188(4):363–70. https://doi.org/10.1007/BF00185945

228 Bluthe RM, Walter V, Parnet P, Laye S, Lestage J, Verrier D, et al. Lipopolysaccharide induces sickness behaviour in rats by a vagal mediated mechanism. C R Acad Sci III. 1994;317(6):499–503.

229 Watkins LR, Goehler LE, Relton JK, Tartaglia N, Silbert L, Martin D, et al. Blockade of interleukin-1 induced hyperthermia by subdiaphragmatic vagotomy: evidence for vagal mediation of immune-brain communication. Neurosci Lett. 1995;183(1–2):27–31. https://doi.org/10.1016/0304-3940(94)11105-r

230 Konsman JP, Luheshi GN, Bluthé RM, Dantzer R. The vagus nerve mediates behavioural depression, but not fever, in response to peripheral immune signals; a functional anatomical analysis. Eur J Neurosci. 2000;12:4434–46. https://doi.org/10.1046/j.0953-816x.2000.01319.x

231 Williams RM, Berthoud HR, Stead RH. Vagal afferent nerve fibres contact mast cells in rat small intestinal mucosa. Neuroimmunomodulation. 1997;4(5–6):266–70. https://doi.org/10.1159/000097346

232 Mazelin L, Theodorou V, More J, Fioramonti J, Bueno L. Protective role of vagal afferents in experimentally-induced colitis in rats. J Auton Nerv Syst. 1998;73(1):38–45. https://doi.org/10.1016/s0165-1838(98)00113-1

233 Ghia JE, Blennerhassett P, Collins SM. Vagus nerve integrity and experimental colitis. Am J Physiol Gastrointest Liver Physiol. 2007;293(3):G560–7. https://doi.org/10.1152/ajpgi.00098.2007

234 Willemze RA, Welting O, van Hamersveld HP, Meijer SL, Folgering JHA, Darwinkel H, et al. Neuronal control of experimental colitis occurs via sympathetic intestinal innervation. Neurogastroenterol Motil. 2018;30(3). https://doi.org/10.1111/nmo.13163

235 Brinkman DJ, Simon T, Ten Hove AS, Zafeiropoulou K, Welting O, van Hamersveld PHP, et al. Electrical stimulation of the splenic nerve bundle ameliorates dextran sulfate sodium-induced colitis in mice. J Neuroinflammation. 2022;19(1):155. https://doi.org/10.1186/s12974-022-02504-z
236 Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000;405(6785):458–62. https://doi.org/10.1038/35013070
237 Bernik TR, Friedman SG, Ochani M, DiRaimo R, Ulloa L, Yang H, et al. Pharmacological stimulation of the cholinergic antiinflammatory pathway. J Exp Med. 2002;195(6):781–8. https://doi.org/10.1084/jem.20011714
238 Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature. 2003;421(6921):384–8. https://doi.org/10.1038/nature01339
239 Saeed RW, Varma S, Peng-Nemeroff T, Sherry B, Balakhaneh D, Huston J, et al. Cholinergic stimulation blocks endothelial cell activation and leukocyte recruitment during inflammation. J Exp Med. 2005;201(7):1113–23. https://doi.org/10.1084/jem.20040463
240 Huston JM, Ochani M, Rosas-Ballina M, Liao H, Ochani K, Pavlov VA, et al. Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. J Exp Med. 2006;203(7):1623–8. https://doi.org/10.1084/jem.20052362
241 Rosas-Ballina M, Ochani M, Parrish WR, Ochani K, Harris YT, Huston JM, et al. Splenic nerve is required for cholinergic antiinflammatory pathway control of TNF in endotoxemia. Proc Natl Acad Sci U S A. 2008;105(31):11008–13. https://doi.org/10.1073/pnas.0803237105
242 Rosas-Ballina M, Olofsson PS, Ochani M, Valdes-Ferrer SI, Levine YA, Reardon C, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011;334(6052):98–101. https://doi.org/10.1126/science.1209985
243 Bratton BO, Martelli D, McKinley MJ, Trevaks D, Anderson CR, McAllen RM. Neural regulation of inflammation: no neural connection from the vagus to splenic sympathetic neurons. Exp Physiol. 2012;97(11):1180–5. https://doi.org/10.1113/expphysiol.2011.061531
244 Martelli D, McKinley MJ, McAllen RM. The cholinergic anti-inflammatory pathway: a critical review. Auton Neurosci. 2014;182:65–9. https://doi.org/10.1016/j.autneu.2013.12.007
245 Martelli D, Yao ST, McKinley MJ, McAllen RM. Reflex control of inflammation by sympathetic nerves, not the vagus. J Physiol. 2014;592(7):1677–86. https://doi.org/10.1113/jphysiol.2013.268573
246 Komegae EN, Farmer DGS, Brooks VL, McKinley MJ, McAllen RM, Martelli D. Vagal afferent activation suppresses systemic inflammation via the splanchnic anti-inflammatory pathway. Brain Behav Immun. 2018;73:441–9. https://doi.org/10.1016/j.bbi.2018.06.005
247 Heider TR, Koruda MJ, Farrell TM, Behrns KE. Acute vagotomy does not augment the systemic inflammatory response in patients with peptic ulcer disease. Am Surg. 2004;70(4):342–6. https://doi.org/10.1177/000313480407000415
248 Corcoran C, Connor TJ, O'Keane V, Garland MR. The effects of vagus nerve stimulation on pro- and anti-inflammatory cytokines in humans: a preliminary report. Neuroimmunomodulation. 2005;12(5):307–9. https://doi.org/10.1159/000087109
249 Barone L, Colicchio G, Policicchio D, Di Clemente F, Di Monaco A, Meglio M, et al. Effect of vagal nerve stimulation on systemic inflammation and cardiac autonomic function in patients with refractory epilepsy. Neuroimmunomodulation. 2007;14:331–6. https://doi.org/10.1159/000127360
250 Fujita T, Yanaga K. Clinical influence of vagotomy on postoperative acute phase response. Langenbecks Arch Surg. 2007;392(2):127–30. https://doi.org/10.1007/s00423-006-0099-4
251 Majoie HJ, Rijkers K, Berfelo MW, Hulsman JA, Myint A, Schwarz M, et al. Vagus nerve stimulation in refractory epilepsy: effects on pro- and anti-inflammatory cytokines in peripheral blood. Neuroimmunomodulation. 2011;18(1):52–6. https://doi.org/10.1159/000315530
252 Aalbers MW, Klinkenberg S, Rijkers K, Verschuure P, Kessels A, Aldenkamp A, et al. The effects of vagus nerve stimulation on pro- and anti-inflammatory cytokines in children with refractory epilepsy: an exploratory study. Neuroimmunomodulation. 2012;19(6):352–8. https://doi.org/10.1159/000341402
253 Waldburger JM, Boyle DL, Pavlov VA, Tracey KJ, Firestein GS. Acetylcholine regulation of synoviocyte cytokine expression by the alpha7 nicotinic receptor. Arthritis Rheum. 2008;58(11):3439–49. https://doi.org/10.1002/art.23987
254 van Maanen MA, Lebre MC, van der Poll T, Larosa GJ, Elbaum D, Vervoordeldonk MJ, et al. Stimulation of nicotinic acetylcholine receptors attenuates collagen-induced arthritis in mice. Arthritis Rheum. 2009;60(1):114–22. https://doi.org/10.1002/art.24177
255 Li T, Zuo X, Zhou Y, Wang Y, Zhuang H, Zhang L, et al. The vagus nerve and nicotinic receptors involve inhibition of HMGB1 release and early pro-inflammatory cytokines function in collagen-induced arthritis. J Clin Immunol. 2010;30(2):213–20. https://doi.org/10.1007/s10875-009-9346-0
256 van Maanen MA, Stoof SP, Larosa GJ, Vervoordeldonk MJ, Tak PP. Role of the cholinergic nervous system in rheumatoid arthritis: aggravation of arthritis in nicotinic acetylcholine receptor α7 subunit gene knockout mice. Ann Rheum Dis. 2010;69(9):1717–23. https://doi.org/10.1136/ard.2009.118554
257 Levine YA, Koopman FA, Faltys M, Caravaca A, Bendele A, Zitnik R, et al. Neurostimulation of the cholinergic anti-inflammatory pathway ameliorates disease in rat collagen-induced arthritis. PLoS One. 2014;9(8):e104530. https://doi.org/10.1371/journal.pone.0104530
258 Bassi GS, Dias DPM, Franchin M, Talbot J, Reis DG, Menezes GB, et al. Modulation of experimental arthritis by vagal sensory and central brain stimulation. Brain Behav Immun. 2017;64:330–43. https://doi.org/10.1016/j.bbi.2017.04.003
259 Bassi GS, Ulloa L, Santos VR, Del Vecchio F, Delfino-Pereira P, Rodrigues GJ, et al. Cortical stimulation in conscious rats controls joint inflammation. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;84(Pt A):201–13. https://doi.org/10.1016/j.pnpbp.2018.02.013
260 Bonaz B, Sinniger V, Hoffmann D, Clarençon D, Mathieu N, Dantzer C, et al. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. Neurogastroenterol Motil. 2016;28(6):948–53. https://doi.org/10.1111/nmo.12792
261 Koopman FA, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. Proc Natl Acad Sci U S A. 2016;113(29):8284–9. https://doi.org/10.1073/pnas.1605635113
262 Brock C, Brock B, Aziz Q, Møller HJ, Pfeiffer Jensen M, Drewes AM, et al. Transcutaneous cervical vagal nerve stimulation modulates cardiac vagal tone and tumor necrosis factor-alpha. Neurogastroenterol Motil. 2017;29(5). https://doi.org/10.1111/nmo.12999
263 Brock C, Rasmussen SE, Drewes AM, Møller HJ, Brock B, Deleuran B, et al. Vagal nerve stimulation-modulation of the anti-inflammatory response and clinical outcome in psoriatic arthritis or ankylosing spondylitis. Mediators Inflamm. 2021;2021:9933532. https://doi.org/10.1155/2021/9933532
264 Marsal S, Corominas H, de Agustín JJ, Pérez-García C, López-Lasanta M, Borrell H, et al. Non-invasive vagus nerve stimulation for rheumatoid arthritis: a proof-of-concept study. Lancet Rheumatol. 2021;3(4):e262–9. https://doi.org/10.1016/S2665-9913(20)30425-2
265 Drewes AM, Brock C, Rasmussen SE, Møller HJ, Brock B, Deleuran BW, et al. Short-term transcutaneous non-invasive vagus nerve stimulation may reduce disease activity and pro-inflammatory cytokines in rheumatoid arthritis: results of a pilot study. Scand J Rheumatol. 2021;50(1):20–7. https://doi.org/10.1080/03009742.2020.1764617

266 Venborg J, Wegeberg AM, Kristensen S, Brock B, Brock C, Pfeiffer-Jensen M. The effect of transcutaneous vagus nerve stimulation in patients with polymyalgia rheumatica. Pharmaceuticals. 2021;14(11):1166. https://doi.org/10.3390/ph14111166
267 Baker MC, Kavanagh S, Cohen S, Matsumoto AK, Dikranian A, Tesser J, et al. A randomized, double-blind, sham-controlled, clinical trial of auricular vagus nerve stimulation for the treatment of active rheumatoid arthritis. Arthritis Rheumatol. 2023;75(12):2107–15. https://doi.org/10.1002/art.42637
268 Hench PS. The analgesic effect of hepatitis and jaundice in chronic arthritis, fibrositis, and sciatic pain. Ann Intern Med. 1934;7:1278–94.
269 Poupon R. Ursodeoxycholic acid and bile-acid mimetics as therapeutic agents for cholestatic liver diseases: an overview of their mechanisms of action. Clin Res Hepatol Gastroenterol. 2012;36(Suppl 1):S3–12. https://doi.org/10.1016/S2210-7401(12)70015-3
270 Hench PS. The ameliorating effect of pregnancy on chronic atrophic (infectious, rheumatoid) arthritis, fibrositis, and intermittent hydrarthrosis. Proc Staff Meetings Mayo Clinic. 1938;13:161–7.
271 Mason HL, Hoehn WM, Kendal EC. Chemical studies of the suprarenal cortex: IV. Structures of compounds C, D, E, F, AND G. J Biol Chem. 1938;124:459–74.
272 Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocortical hormone in arthritis: preliminary report. Ann Rheum Dis. 1949;8(2):97–104. https://doi.org/10.1136/ard.8.2.97
273 Buttgereit F, Burmester GR, Straub RH, Seibel MJ, Zhou H. Exogenous and endogenous glucocorticoids in rheumatic diseases. Arthritis Rheum. 2011;63:1–9. https://doi.org/10.1002/art.30070
274 Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev. 2007;2007(1):CD006356. https://doi.org/10.1002/14651858.CD006356
275 Pincus T, Sokka T, Cutolo M. The past versus the present, 1980-2004: reduction of mean initial low-dose, long-term glucocorticoid therapy in rheumatoid arthritis from 10.3 to 3.6 mg/day, concomitant with early methotrexate, with long-term effectiveness and safety of less than 5 mg/day. Neuroimmunomodulation. 2015;22(1–2):89–103. https://doi.org/10.1159/000362735
276 Hwang YG, Saag K. The safety of low-dose glucocorticoids in rheumatic diseases: results from observational studies. Neuroimmunomodulation. 2015;22(1–2):72–82. https://doi.org/10.1159/000362727
277 Santiago T, da Silva JA. Safety of glucocorticoids in rheumatoid arthritis: evidence from recent clinical trials. Neuroimmunomodulation. 2015;22(1–2):57–65. https://doi.org/10.1159/000362726
278 Buttgereit F, Doering G, Schaeffler A, Witte S, Sierakowski S, Gromnica-Ihle E, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. Lancet. 2008;371(9608):205–14. https://doi.org/10.1016/S0140-6736(08)60132-4
279 Buttgereit F, Mehta D, Kirwan J, Szechinski J, Boers M, Alten RE, et al. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). Ann Rheum Dis. 2013;72(2):204–10. https://doi.org/10.1136/annrheumdis-2011-201067
280 Cutolo M, Iaccarino L, Doria A, Govoni M, Sulli A, Marcassa C. Efficacy of the switch to modified-release prednisone in rheumatoid arthritis patients treated with standard glucocorticoids. Clin Exp Rheumatol. 2013;31(4):498–505.
281 Buttgereit F. Getting better at quantifying the toxicity of glucocorticoids. Lancet Rheumatol. 2023;5(7):e368–e370. https://doi.org/10.1016/S2665-9913(23)00159-5
282 Masi AT, Chrousos GP, Bornstein SR. Enigmas of adrenal androgen and glucocorticoid dissociation in premenopausal onset rheumatoid arthritis. J Rheumatol. 1999;26(2):247–50.
283 Straub RH, Bijlsma JW, Masi A, Cutolo M. Role of neuroendocrine and neuroimmune mechanisms in chronic inflammatory rheumatic diseases-The 10-year update. Semin Arthritis Rheum. 2013;43(3):392–404. https://doi.org/10.1016/j.semarthrit.2013.04.008
284 Straub RH, Buttgereit F, Cutolo M. Alterations of the hypothalamic-pituitary-adrenal axis in systemic immune diseases: a role for misguided energy regulation. Clin Exp Rheumatol. 2011;29(5 Suppl 68):S23-31.
285 David K, Dingemanse E, Freud J, Laqueur E. Über krystallinisches männliches Hormon aus Hoden (Testosteron), wirksamer als aus Harn oder aus Cholesterin bereitetes Androsteron. Biol Chem. 1935;233(5–6):281–3. https://doi.org/10.1515/bchm2.1935.233.5-6.281
286 Butenandt A, Hanisch G. Über Testosteron. Umwandlung des Dehydro-androsterons in Androstendiol und Testosteron; ein Weg zur Darstellung des Testosterons aus Cholesterin. Biol Chem. 1935;237(1–3):89–97. https://doi.org/10.1515/bchm2.1935.237.1-3.89
287 Davison RA, Koets P, Kuzell WC. Excretion of 17-ketosteroids in ankylosing spondylarthritis and in rheumatoid arthritis; a preliminary report. J Clin Endocrinol Metab. 1947;7(3):201–4. https://doi.org/10.1210/jcem-7-3-201
288 Howard RP, Venning EH, Fisk GH. Rheumatoid arthritis. II. Studies of adrenocortical and hypophyseal function and the effects thereon of testosterone and pregnenolone therapy. Can Med Assoc J. 1950;63(4):340–2.
289 Feher GK, Feher T, Zahumenszky Z. Study on the inactivation mechanism of androgens in rheumatoid arthritis: excretory rate of free and conjugated 17-ketosteroids. Endokrinologie. 1979;73(2):167–72.
290 Jungers P, Nahoul K, Pelissier C, Dougados M, Tron F, Bach JF. Low plasma androgens in women with active or quiescent systemic lupus erythematosus. Arthritis Rheum. 1982;25(4):454–7. https://doi.org/10.1002/art.1780250415
291 Masi AT, Josipovic DB, Jefferson WE. Low adrenal androgenic-anabolic steroids in women with Rheumatoid Arthritis (RA): gas-liquid chromatographic studies of RA patients and matched normal control women indicating decreased 11-deoxy-17-ketosteroid excretion. Semin Arthritis Rheum. 1984;14:1–23. https://doi.org/10.1016/0049-0172(84)90005-2
292 Lahita RG, Bradlow HL, Ginzler E, Pang S, New M. Low plasma androgens in women with systemic lupus erythematosus. Arthritis Rheum. 1987;30(3):241–8. https://doi.org/10.1002/art.1780300301
293 Cutolo M, Balleari E, Giusti M, Monachesi M, Accardo S. Sex hormone status of male patients with rheumatoid arthritis: evidence of low serum concentrations of testosterone at baseline and after human chorionic gonadotropin stimulation. Arthritis Rheum. 1988;31(10):1314–7. https://doi.org/10.1002/art.1780311015
294 Ishmael WK, Hellbaum A, Kuhn JF, Duffy M. The effects of certain steroid compounds on various manifestations of rheumatoid arthritis. J Okla State Med Assoc. 1949;42(10):434–7.
295 Devis R, van Goidsenhiven F, Lemmens P, Lederer J, Demuylder C. Arthritis rheumatoid therapy with testosterone propionate. Ann Endocrinol. 1950;11(6):637–43.
296 Steinberg AD, Melez KA, Raveche ES, Reeves JP, Boegel WA, Smathers PA, et al. Approach to the study of the role of sex hormones in autoimmunity. Arthritis Rheum. 1979;22(11):1170–6. https://doi.org/10.1002/art.1780221103
297 Melez KA, Boegel WA, Steinberg AD. Therapeutic studies in New Zealand mice. VII. Successful androgen treatment of NZB/NZW F1 females of different ages. Arthritis Rheum. 1980;23(1):41–7. https://doi.org/10.1002/art.1780230108
298 Talal N. Sex steroid hormones and systemic lupus erythematosus. Arthritis Rheum. 1981;24(8):1054–6. https://doi.org/10.1002/art.1780240811
299 da Silva JA, Larbre JP, Spector TD, Perry LA, Scott DL, Willoughby DA. Protective effect of androgens against inflammation induced cartilage degradation in male rodents. Ann Rheum Dis. 1993;52(4):285–91. https://doi.org/10.1136/ard.52.4.285

300 da Silva JA, Larbre JP, Seed MP, Cutolo M, Villaggio B, Scott DL, et al. Sex differences in inflammation induced cartilage damage in rodents. The influence of sex steroids. J Rheumatol. 1994;21(2):330–7.
301 Cutolo M, Balleari E, Giusti M, Intra E, Accardo S. Androgen replacement therapy in male patients with rheumatoid arthritis. Arthritis Rheum. 1991;34:1–5. https://doi.org/10.1002/art.1780340102
302 Bijlsma JW, Huber-Bruning O, Thijssen JH. Effect of oestrogen treatment on clinical and laboratory manifestations of rheumatoid arthritis. Ann Rheum Dis. 1987;46(10):777–9. https://doi.org/10.1136/ard.46.10.777
303 Booji A, Biewenga-Booji CM, Huber-Bruning O, Cornelis C, Jacobs JW, Bijlsma JW. Androgens as adjuvant treatment in postmenopausal female patients with rheumatoid arthritis. Ann Rheum Dis. 1996;55(11):811–5. https://doi.org/10.1136/ard.55.11.811
304 van Vollenhoven RF, Engleman EG, McGuire JL. An open study of dehydroepiandrosterone in systemic lupus erythematosus. Arthritis Rheum. 1994;37(9):1305–10. https://doi.org/10.1002/art.1780370906
305 van Vollenhoven RF, Engleman EG, McGuire JL. Dehydroepiandrosterone in systemic lupus erythematosus. Results of a double-blind, placebo-controlled, randomized clinical trial. Arthritis Rheum. 1995;38(12):1826–31. https://doi.org/10.1002/art.1780381216
306 van Vollenhoven RF, Morabito LM, Engleman EG, McGuire JL. Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months. J Rheumatol. 1998;25(2):285–9.
307 Petri MA, Lahita RG, van Vollenhoven RF, Merrill JT, Schiff M, Ginzler EM, et al. Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2002;46(7):1820–9. https://doi.org/10.1002/art.10364
308 Petri MA, Mease PJ, Merrill JT, Lahita RG, Iannini MJ, Yocum DE, et al. Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematosus. Arthritis Rheum. 2004;50(9):2858–68. https://doi.org/10.1002/art.20427
309 Skare TL, Hauz E, de Carvalho JF. Dehydroepiandrosterone (DHEA) supplementation in rheumatic diseases: a systematic review. Mediterr J Rheumatol. 2023;34(3):292–301. https://doi.org/10.31138/mjr.20230825.dd
310 Ungar F, Miller AM, Dorfman RI. Metabolism of dehydroepiandrosterone and Δ5-ANDROSTENE-3β, 17β-DIOL. J Biol Chem. 1954;206(2):597–605. https://doi.org/10.1016/s0021-9258(19)50827-4
311 Castagnetta LA, Carruba G, Granata OM, Stefano R, Miele M, Schmidt M, et al. Increased estrogen formation and estrogen to androgen ratio in the synovial fluid of patients with rheumatoid arthritis. J Rheumatol. 2003;30(12):2597–605.
312 Schmidt M, Weidler C, Naumann H, Anders S, Schölmerich J, Straub RH. Androgen conversion in osteoarthritis and rheumatoid arthritis synoviocytes - androstenedione and testosterone inhibit estrogen formation and favor production of more potent 5alpha-reduced androgens. Arthritis Res Ther. 2005;7(5):R938–48. https://doi.org/10.1186/ar1769
313 Cutolo M, Straub RH. Sex steroids and autoimmune rheumatic diseases: state of the art. Nat Rev Rheumatol. 2020;16(11):628–44. https://doi.org/10.1038/s41584-020-0503-4
314 Cutolo M, Accardo S, Villaggio B, Clerico P, Indiveri F, Carruba G, et al. Evidence for the presence of androgen receptors in the synovial tissue of rheumatoid arthritis patients and healthy controls. Arthritis Rheum. 1992;35(9):1007–15. https://doi.org/10.1002/art.1780350905
315 Cutolo M, Accardo S, Villaggio B, Clerico P, Bagnasco M, Coviello DA, et al. Presence of estrogen-binding sites on macrophage-like synoviocytes and CD8+, CD29+, CD45RO+ T lymphocytes in normal and rheumatoid synovium. Arthritis Rheum. 1993;36(8):1087–97. https://doi.org/10.1002/art.1780360809
316 van der Goes MC, Straub RH, Wenting MJ, Capellino S, Jacobs JW, Jahangier ZN, et al. Intra-articular glucocorticoid injections decrease the number of steroid hormone receptor positive cells in synovial tissue of patients with persistent knee arthritis. Ann Rheum Dis. 2012;71(9):1552–8. https://doi.org/10.1136/annrheumdis-2011-201019
317 Straub RH, Härle P, Yamana S, Matsuda T, Takasugi K, Kishimoto T, et al. Anti-interleukin-6 receptor antibody therapy favors adrenal androgen secretion in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2006;54(6):1778–85. https://doi.org/10.1002/art.21826
318 Ernestam S, Hafstrom I, Werner S, Carlstrom K, Tengstrand B. Increased DHEAS levels in patients with rheumatoid arthritis after treatment with tumor necrosis factor antagonists: evidence for improved adrenal function. J Rheumatol. 2007;34(7):1451–8.
319 Alexander WR, Duthie JJ. Progesterone in the treatment of rheumatoid arthritis; a clinical trial in five cases. Lancet. 1950;1(6599):297. https://doi.org/10.1016/s0140-6736(50)92000-9
320 Kyle LH, Crain DC. The clinical and metabolic effects of progesterone and anhydrohydroxyprogesterone in rheumatoid arthritis. Ann Intern Med. 1950;32(5):878–88. https://doi.org/10.7326/0003-4819-32-5-878
321 Kling DH. Treatment of rheumatoid arthritis with progesterone and pregnenolone. Ann West Med Surg. 1950;4(8):378–82.
322 Cuchacovich M, Tchernitchin A, Gatica H, Wurgaft R, Valenzuela C, Cornejo E. Intraarticular progesterone: effects of a local treatment for rheumatoid arthritis. J Rheumatol. 1988;15(4):561–5.
323 Toivanen P, Määttä K, Suolanen R, Tykkyläinen R. Effect of estrone and progesterone on adjuvant arthritis in rats. Med Pharmacol Exp Int J Exp Med. 1967;17(1):33–42. https://doi.org/10.1159/000137052
324 Jansson L, Holmdahl R. Oestrogen induced suppression of collagen arthritis. IV: progesterone alone does not affect the course of arthritis but enhances the oestrogen-mediated therapeutic effect. J Reprod Immunol. 1989;15(2):141–50. https://doi.org/10.1016/0165-0378(89)90033-8
325 Ganesan K, Balachandran C, Manohar BM, Puvanakrishnan R. Comparative studies on the interplay of testosterone, estrogen and progesterone in collagen induced arthritis in rats. Bone. 2008;43(4):758–65. https://doi.org/10.1016/j.bone.2008.05.025
326 da Silva JA, Colville-Nash P, Spector TD, Scott DL, Willoughby DA. Inflammation-induced cartilage degradation in female rodents. Protective role of sex hormones. Arthritis Rheum. 1993;36(7):1007–13. https://doi.org/10.1002/art.1780360719
327 Khalkhali-Ellis Z, Seftor EA, Nieva DRC, Handa RJ, Price RH Jr, Kirschmann DA, et al. Estrogen and progesterone regulation of human fibroblast-like synoviocyte function in vitro: implications in rheumatoid arthritis. J Rheumatol. 2000;27(7):1622–31.
328 Hughes GC, Martin D, Zhang K, Hudkins KL, Alpers CE, Clark EA, et al. Decrease in glomerulonephritis and Th1-associated autoantibody production after progesterone treatment in NZB/NZW mice. Arthritis Rheum. 2009;60(6):1775–84. https://doi.org/10.1002/art.24548
329 Hughes GC, Choubey D. Modulation of autoimmune rheumatic diseases by oestrogen and progesterone. Nat Rev Rheumatol. 2014;10(12):740–51. https://doi.org/10.1038/nrrheum.2014.144
330 De Neef JC. Treatment of disseminated lupus erythematosus with stilbesterol. Ned Tijdschr Geneeskd. 1958;102(5):246–8.
331 Chapel TA, Burns RE. Oral contraceptives and exacerbation of lupus erythematosus. Am J Obstet Gynecol. 1971;110(3):366–9. https://doi.org/10.1016/0002-9378(71)90730-7
332 Tarzy BJ, Garcia CR, Wallach EE, Zweiman B, Myers AR. Rheumatic disease, abnormal serology, and oral contraceptives. Lancet. 1972;2(7776):501–3. https://doi.org/10.1016/s0140-6736(72)91903-4
333 Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med. 2005;142(12 Pt 1):953–62. https://doi.org/10.7326/0003-4819-142-12_part_1-200506210-00004

334 Rojas-Villarraga A, Torres-Gonzalez JV, Ruiz-Sternberg AM. Safety of hormonal replacement therapy and oral contraceptives in systemic lupus erythematosus: a systematic review and meta-analysis. PLoS One. 2014;9(8):e104303. https://doi.org/10.1371/journal.pone.0104303
335 Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005;353(24):2550–8. https://doi.org/10.1056/NEJMoa051135
336 Stern R, Fishman J, Brusman H, Kunkel HG. Systemic lupus erythematosus associated with klinefelter's syndrome. Arthritis Rheum. 1977;20(1):18–22. https://doi.org/10.1002/art.1780200103
337 Rovensky J, Imrich R, Lazurova I, Payer J. Rheumatic diseases and Klinefelter's syndrome. Ann N Y Acad Sci. 2010;1193:1–9. https://doi.org/10.1111/j.1749-6632.2009.05292.x
338 Seminog OO, Seminog AB, Yeates D, Goldacre MJ. Associations between Klinefelter's syndrome and autoimmune diseases: English national record linkage studies. Autoimmunity. 2015;48(2):125–8. https://doi.org/10.3109/08916934.2014.968918
339 Harris VM, Sharma R, Cavett J, Kurien BT, Liu K, Koelsch KA, et al. Klinefelter's syndrome (47,XXY) is in excess among men with Sjogren's syndrome. Clin Immunol. 2016;168:25–9. https://doi.org/10.1016/j.clim.2016.04.002
340 Lahita RG, Bradlow HL, Kunkel HG, Fishman J. Alterations of estrogen metabolism in systemic lupus erythematosus. Arthritis Rheum. 1979;22(11):1195–8. https://doi.org/10.1002/art.1780221106
341 Bucala R, Lahita RG, Fishman J, Cerami A. Increased levels of 16 alpha-hydroxyestrone-modified proteins in pregnancy and in systemic lupus erythematosus. J Clin Endocrinol Metab. 1985;60(5):841–7. https://doi.org/10.1210/jcem-60-5-841
342 Weidler C, Härle P, Schedel J, Schmidt M, Schölmerich J, Straub RH. Patients with rheumatoid arthritis and systemic lupus erythematosus have increased renal excretion of mitogenic estrogens in relation to endogenous antiestrogens. J Rheumatol. 2004;31(3):489–94.
343 Duvic M, Steinberg AD, Klassen LW. Effect of the anti-estrogen, Nafoxidine, on NZB/W autoimmune disease. Arthritis Rheum. 1978;21(4):414–7. https://doi.org/10.1002/art.1780210403
344 Sturgess AD, Evans DT, Mackay IR, Riglar A. Effects of the oestrogen antagonist tamoxifen on disease indices in systemic lupus erythematosus. J Clin Lab Immunol. 1984;13(1):11–4.
345 Holmdahl R, Carlsten H, Jansson L, Larsson P. Oestrogen is a potent immunomodulator of murine experimental rheumatoid disease. Br J Rheumatol. 1989;28(Suppl 1):54–71. https://doi.org/10.1093/rheumatology/xxviii.suppl_1.54
346 Carlsten H, Holmdahl R, Tarkowski A, Nilsson LA. Oestradiol- and testosterone-mediated effects on the immune system in normal and autoimmune mice are genetically linked and inherited as dominant traits. Immunology. 1989;68(2):209–14.
347 Hazes JM, Dijkmans BA, Vandenbroucke JP, Cats A. Oral contraceptive treatment for rheumatoid arthritis: an open study in 10 female patients. Br J Rheumatol. 1989;28(Suppl 1):28–30. https://doi.org/10.1093/rheumatology/xxviii.suppl_1.28
348 Sambrook P, Birmingham J, Champion D, Kelly P, Kempler S, Freund J, et al. Postmenopausal bone loss in rheumatoid arthritis: effect of estrogens and androgens. J Rheumatol. 1992;19(3):357–61.
349 Carlsten H, Nilsson N, Jonsson R, Backman K, Holmdahl R, Tarkowski A. Estrogen accelerates immune complex glomerulonephritis but ameliorates T cell-mediated vasculitis and sialadenitis in autoimmune MRL lpr/lpr mice. Cell Immunol. 1992;144(1):190–202. https://doi.org/10.1016/0008-8749(92)90236-i
350 Straub RH. The complex role of estrogens in inflammation. Endocr Rev. 2007;28(5):521–74. https://doi.org/10.1210/er.2007-0001
351 Mizoguchi Y, Ikemoto Y, Yamamoto S, Morisawa S. Studies on the effects of estrogen on the antibody response in asymptomatic HB virus carrier. Hepatogastroenterology. 1985;32(3):109–12.
352 Whitacre CC. Sex differences in autoimmune disease. Nat Immunol. 2001;2(9):777–80. https://doi.org/10.1038/ni0901-777
353 Mays S, Prowse T, George M, Brickley M. Latitude, urbanization, age, and sex as risk factors for vitamin D deficiency disease in the Roman Empire. Am J Phys Anthropol. 2018;167(3):484–96. https://doi.org/10.1002/ajpa.23646
354 Glisson F. A treatise of the rickets: being a disease common to children. London: P. Cole; 1651.
355 Hopkins FG. The analyst and the medical man. Analyst. 1906;31(369):385–404. https://doi.org/10.1039/an906310385b
356 Mellanby E. An experimental investigation on rickets. Lancet.. 1919;196:407–12.
357 Chick H, Dalyell EJH, Hume M, Smith H, Mackay H. The aetiology of rickets in infants: prophylactic and curative observations at the Vienna University Kinderklinik. Lancet. 1922;200(5157):7–11. https://doi.org/10.1016/s0140-6736(01)00835-2
358 McCollum EV, Simmonds N, Becker J, Shipley PG. Studies on experimental rickets. XXI. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. J Biol Chem. 1922;53(2):293–312. https://doi.org/10.1016/s0021-9258(18)85783-0
359 Hess AF, Weinstock M. Antirachitic properties imparted to inert fluids and to green vegetables by ultraviolet irradiation. J Biol Chem. 1924;62(2):301–13. https://doi.org/10.1016/s0021-9258(18)85064-5
360 Steenbock H. The induction of growth promoting and calcifying properties in a ration by exposure to light. Science. 1924;60(1549):224–5. https://doi.org/10.1126/science.60.1549.224
361 Hess AF, Weinstock M, Heelman FD. The antirachitic value of irradiated phytosterol and cholesterol. J Biol Chem. 1925;63:305–9.
362 Windaus A, Hess A. Sterine und antirachitisches Vitamin. Nachrichten von der Gesellschaft der Wissenschaften zu Göttingen. 1926:175–84.
363 Rosenheim O, Webster TA. Further observations on the photo-chemical formation of vitamin D. J Soc Chem Ind. 1926;45:932.
364 Wolf G. The discovery of vitamin D: the contribution of Adolf Windaus. J Nutr. 2004;134(6):1299–302. https://doi.org/10.1093/jn/134.6.1299
365 Rosenheim O, Webster TA. The parent substance of vitamin D. Biochem J. 1927;21(2):389–97. https://doi.org/10.1042/bj0210389
366 Haussler MR, Myrtle JF, Norman AW. The association of a metabolite of vitamin D3 with intestinal mucosa chromatin in vivo. J Biol Chem. 1968;243(15):4055–64. https://doi.org/10.1016/s0021-9258(18)93278-3
367 Tsai HC, Norman AW. Studies on calciferol metabolism. J Biol Chem. 1973;248(17):5967–75. https://doi.org/10.1016/s0021-9258(19)43495-9
368 Brumbaugh PF, Haussler MR. 1α,25-Dihydroxycholecalciferol receptors in intestine. J Biol Chem. 1974;249(4):1251–7. https://doi.org/10.1016/s0021-9258(19)42968-2
369 Norman AW, Roth J, Orci L. The vitamin D endocrine system: steroid metabolism, hormone receptors, and biological response (calcium binding proteins). Endocr Rev. 1982;3(4):331–66. https://doi.org/10.1210/edrv-3-4-331
370 Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. Science. 1983;221(4616):1181–3. https://doi.org/10.1126/science.6310748
371 McDonnell DP, Mangelsdorf DJ, Pike JW, Haussler MR, O'Malley BW. Molecular cloning of complementary DNA encoding the avian receptor for vitamin D. Science. 1987;235(4793):1214–7. https://doi.org/10.1126/science.3029866
372 Baker AR, McDonnell DP, Hughes M, Crisp TM, Mangelsdorf DJ, Haussler MR, et al. Cloning and expression of full-length cDNA encoding human vitamin D receptor. Proc Natl Acad Sci U S A. 1988;85(10):3294–8. https://doi.org/10.1073/pnas.85.10.3294
373 Haussler MR, Whitfield K, Haussler CA, Hsieh J-C, Jurutka PW. Nuclear vitamin D receptor: natural ligands, molecular structure–function and transcriptional control of vital genes. In: Feldman D, Pike JW, Adams JS, editors. Vitamin D. 3rd ed. San Diego: Academic Press; 2011. p. 137–70.

374 DeLuca HF, Suda T, Schnoes HK, Tanaka Y, Holick MF. 25,26-dihydroxycholecalciferol, a metabolite of vitamin D3 with intestinal calcium transport activity. Biochemistry. 1970;9(24):4776–80. https://doi.org/10.1021/bi00826a022
375 Cutolo M, Smith V, Paolino S, Gotelli E. Involvement of the secosteroid vitamin D in autoimmune rheumatic diseases and COVID-19. Nat Rev Rheumatol. 2023;19(5):265–87. https://doi.org/10.1038/s41584-023-00944-2
376 Teymoori-Rad M, Shokri F, Salimi V, Marashi SM. The interplay between vitamin D and viral infections. Rev Med Virol. 2019;29(2):e2032. https://doi.org/10.1002/rmv.2032
377 Cutolo M, Paolino S, Smith V. Evidences for a protective role of vitamin D in COVID-19. RMD Open. 2020;6(3):e001454. https://doi.org/10.1136/rmdopen-2020-001454
378 Abe E, Miyaura C, Sakagami H, Takeda M, Konno K, Yamazaki T, et al. Differentiation of mouse myeloid leukemia cells induced by 1 alpha, 25-dihydroxyvitamin D3. Proc Natl Acad Sci U S A. 1981;78(8):4990–4. https://doi.org/10.1073/pnas.78.8.4990
379 Bar-Shavit Z, Noff D, Edelstein S, Meyer M, Shibolet S, Goldman R. 1,25-dihydroxyvitamin D3 and the regulation of macrophage function. Calcif Tissue Int. 1981;33:673–6. https://doi.org/10.1007/BF02409507
380 Tsoukas CD, Provvedini DM, Manolagas SC. 1,25-dihydroxyvitamin D3: a novel immunoregulatory hormone. Science. 1984;224(4656):1438–40. https://doi.org/10.1126/science.6427926
381 Cutolo M, Plebani M, Shoenfeld Y, Adorini L, Tincani A. Vitamin D endocrine system and the immune response in rheumatic diseases. Vitam Horm. 2011;86:327–51. https://doi.org/10.1016/B978-0-12-386960-9.00014-9
382 Cutolo M, Gotelli E. The 2023s growing evidence confirming the relationship between vitamin D and autoimmune diseases. Nutrients. 2023;15(22):4760. https://doi.org/10.3390/nu15224760
383 Wimalawansa SJ. Infections and autoimmunity-the immune system and vitamin D: a systematic review. Nutrients. 2023;15(17):3842. https://doi.org/10.3390/nu15173842
384 Schwartz N, Stock AD, Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nat Rev Rheumatol. 2019;15(3):137–52. https://doi.org/10.1038/s41584-018-0156-8
385 McCLARY AR, Meyer E, Weitzman EL. Observations on the role of the mechanism of depression in some patients with disseminated lupus erythematosus. Psychosom Med. 1955;17(4):311–21. https://doi.org/10.1097/00006842-195507000-00006
386 Heine BE. Psychiatric aspects of systemic lupus erythematosus. Acta Psychiatr Scand. 1969;45(4):307–26. https://doi.org/10.1111/j.1600-0447.1969.tb07132.x
387 Moldofsky H, Chester WJ. Pain and mood patterns in patients with rheumatoid arthritis. A prospective study. Psychosom Med. 1970;32(3):309–18. https://doi.org/10.1097/00006842-197005000-00009
388 Robinson H, Kirk RF Jr, Frye RL. A psychological study of rheumatoid arthritis and selected controls. J Chronic Dis. 1971;23(10):791–801. https://doi.org/10.1016/0021-9681(71)90009-9
389 Zaphiropoulos G, Burry HC. Proceedings: a study of depression in rheumatoid disease. Ann Rheum Dis. 1973;32(6):593–5. https://doi.org/10.1136/ard.32.6.593-b
390 Robinson ET, Hernandez LA, Dick WC, Buchanan WW. Depression in rheumatoid arthritis. J R Coll Gen Pract. 1977;27(180):423–7.
391 Moos RH, Solomon GF. Minnesota multiphasic personality inventory response patterns in patients with rheumatoid arthritis. J Psychosom Res. 1964;8:17–28. https://doi.org/10.1016/0022-3999(64)90018-2
392 Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis. The arthritis impact measurement scales. Arthritis Rheum. 1980;23(2):146–52. https://doi.org/10.1002/art.1780230203
393 Hawley DJ, Wolfe F. Anxiety and depression in patients with rheumatoid arthritis: a prospective study of 400 patients. J Rheumatol. 1988;15(6):932–41.
394 Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137–45. https://doi.org/10.1002/art.1780230202
395 Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473–83.
396 Blalock SJ, DeVellis RF, Brown GK, Wallston KA. Validity of the center for epidemiological studies depression scale in arthritis populations. Arthritis Rheum. 1989;32(8):991–7. https://doi.org/10.1002/anr.1780320808
397 Nicassio PM, Wallston KA. Longitudinal relationships among pain, sleep problems, and depression in rheumatoid arthritis. J Abnorm Psychol. 1992;101(3):514–20. https://doi.org/10.1037//0021-843x.101.3.514
398 Hawley DJ, Wolfe F. Depression is not more common in rheumatoid arthritis: a 10-year longitudinal study of 6,153 patients with rheumatic disease. J Rheumatol. 1993;20(12):2025–31.
399 DeVellis BM. The physiological impact of arthritis: prevalence of depression. Arthritis Care Res. 1995;8(4):284–9. https://doi.org/10.1002/art.1790080413
400 Smarr KL, Parker JC, Kosciulek JF, Buchholz JL, Multon KD, Hewett JE, et al. Implications of depression in rheumatoid arthritis: do subtypes really matter? Arthritis Care Res. 2000;13(1):23–32. https://doi.org/10.1002/1529-0131(200002)13:1<23::aid-art5>3.0.co;2-w
401 Söderlin MK, Hakala M, Nieminen P. Anxiety and depression in a community-based rheumatoid arthritis population. Scand J Rheumatol. 2000;29(3):177–83. https://doi.org/10.1080/030097400750002067
402 Covic T, Tyson G, Spencer D, Howe G. Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors. J Psychosom Res. 2006;60(5):469–76. https://doi.org/10.1016/j.jpsychores.2005.09.011
403 Smedstad LM, Vaglum P, Kvien TK, Moum T. The relationship between self-reported pain and sociodemographic variables, anxiety, and depressive symptoms in rheumatoid arthritis. J Rheumatol. 1995;22(3):514–20.
404 Smedstad LM, Vaglum P, Moum T, Kvien TK. The relationship between psychological distress and traditional clinical variables: a 2 year prospective study of 216 patients with early rheumatoid arthritis. Br J Rheumatol. 1997;36(12):1304–11. https://doi.org/10.1093/rheumatology/36.12.1304
405 Creamer P, Lethbridge-Cejku M, Costa P, Tobin JD, Herbst JH, Hochberg MC. The relationship of anxiety and depression with self-reported knee pain in the community: data from the Baltimore Longitudinal Study of Aging. Arthritis Care Res. 1999;12(1):3–7. https://doi.org/10.1002/1529-0131(199902)12:1<3::aid-art2>3.0.co;2-k
406 Cardenas DD, Kutner NG. The problem of fatigue in dialysis patients. Nephron. 1982;30(4):336–40. https://doi.org/10.1159/000182512
407 Stoff E, Bacon MC, White PH. The effects of fatigue, distractibility, and absenteeism on school achievement in children with rheumatic diseases. Arthritis Care Res. 1989;2:49–53. https://doi.org/10.1002/anr.1790020205
408 Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121–3. https://doi.org/10.1001/archneur.1989.00520460115022
409 Connor H. Doctors and "educational overpressure" in nineteenth-century Britain: a fatigue state that divided medical opinion. Eur J Hist Med Health. 2022;80(1):3–38. https://doi.org/10.1163/26667711-bja10026
410 Hart BL. Behavior of sick animals. Vet Clin North Am Food Anim Pract. 1987;3(2):383–91. https://doi.org/10.1016/s0749-0720(15)31159-2
411 Hart BL. Biological basis of the behavior of sick animals. Neurosci Biobehav Rev. 1988;12(2):123–37. https://doi.org/10.1016/s0149-7634(88)80004-6
412 Fleshner M, Goehler LE, Schwartz BA, McGorry M, Martin D, Maier SF, et al. Thermogenic and corticosterone responses to intravenous cytokines (IL-1beta and TNF-alpha) are attenuated by subdiaphragmatic vagotomy. J Neuroimmunol. 1998;86(2):134–41. https://doi.org/10.1016/s0165-5728(98)00026-5

413 Bluthé RM, Dantzer R, Kelley KW. Interleukin-1 mediates behavioural but not metabolic effects of tumor necrosis factor alpha in mice. Eur J Pharmacol. 1991;209:281–3. https://doi.org/10.1016/0014-2999(91)90184-r
414 Bluthé RM, Dantzer R, Kelley KW. Effects of interleukin-1 receptor antagonist on the behavioral effects of lipopolysaccharide in rat. Brain Res. 1992;573(2):318–20. https://doi.org/10.1016/0006-8993(92)90779-9
415 Kent S, Bluthe RM, Dantzer R, Hardwick AJ, Kelley KW, Rothwell NJ, et al. Different receptor mechanisms mediate the pyrogenic and behavioral effects of interleukin 1. Proc Natl Acad Sci U S A. 1992;89(19):9117–20. https://doi.org/10.1073/pnas.89.19.9117
416 Avitsur R, Yirmiya R. Cytokines inhibit sexual behavior in female rats: I. Synergistic effects of tumor necrosis factor alpha and interleukin-1. Brain Behav Immun. 1999;13(1):14–32. https://doi.org/10.1006/brbi.1999.0555
417 Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med. 2001;344(13):961–6. https://doi.org/10.1056/NEJM200103293441303
418 Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;41(9):1552–63. https://doi.org/10.1002/1529-0131(199809)41:9<1552::AID-ART5>3.0.CO;2-W
419 Moreland LW. Drugs that block tumour necrosis factor: experience in patients with rheumatoid arthritis. Pharmacoeconomics. 2004;22(2 Suppl 1):39–53. https://doi.org/10.2165/00019053-200422001-00005
420 Fleischmann R, Stern R, Iqbal I. Anakinra: an inhibitor of IL-1 for the treatment of rheumatoid arthritis. Expert Opin Biol Ther. 2004;4(8):1333–44. https://doi.org/10.1517/14712598.4.8.1333
421 Omdal R, Gunnarsson R. The effect of interleukin-1 blockade on fatigue in rheumatoid arthritis: a pilot study. Rheumatol Int. 2005;25(6):481–4. https://doi.org/10.1007/s00296-004-0463-z
422 Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet. 2006;367(9504):29–35. https://doi.org/10.1016/S0140-6736(05)67763-X
423 Moreland LW, Genovese MC, Sato R, Singh A. Effect of etanercept on fatigue in patients with recent or established rheumatoid arthritis. Arthritis Rheum. 2006;55(2):287–93. https://doi.org/10.1002/art.21838
424 Korte SM, Straub RH. Fatigue in inflammatory rheumatic disorders: pathophysiological mechanisms. Rheumatology. 2019;58(Suppl 5):v35–50. https://doi.org/10.1093/rheumatology/kez413
425 Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008;9(1):46–56. https://doi.org/10.1038/nrn2297
426 Straub RH. Concepts of evolutionary medicine and energy regulation contribute to the etiology of systemic chronic inflammatory diseases. Brain Behav Immun. 2011;25:1–5. https://doi.org/10.1016/j.bbi.2010.08.002
427 Straub RH. Evolutionary medicine and chronic inflammatory state: known and new concepts in pathophysiology. J Mol Med. 2012;90(5):523–34. https://doi.org/10.1007/s00109-012-0861-8
428 Spies CM, Straub RH, Buttgereit F. Energy metabolism and rheumatic diseases: from cell to organism. Arthritis Res Ther. 2012;14(3):216–25. https://doi.org/10.1186/ar3885
429 Straub RH. Interaction of the endocrine system with inflammation: a function of energy and volume regulation. Arthritis Res Ther. 2014;16(1):203–17. https://doi.org/10.1186/ar4484
430 Straub RH. Insulin resistance, selfish brain, and selfish immune system: an evolutionarily positively selected program used in chronic inflammatory diseases. Arthritis Res Ther. 2014;16(Suppl 2):S4. https://doi.org/10.1186/ar4688
431 Straub RH, Cutolo M, Pacifici R. Evolutionary medicine and bone loss in chronic inflammatory diseases – a theory of inflammation-related osteopenia. Semin Arthritis Rheum. 2015;45(2):220–8. https://doi.org/10.1016/j.semarthrit.2015.04.014
432 Straub RH, Schradin C. Chronic inflammatory systemic diseases: an evolutionary trade-off between acutely beneficial but chronically harmful programs. Evol Med Public Health. 2016;2016(1):37–51. https://doi.org/10.1093/emph/eow001
433 Filippa MG, Tektonidou MG, Mantzou A, Kaltsas GA, Chrousos GP, Sfikakis PP, et al. Adrenocortical dysfunction in rheumatoid arthritis: A narrative review and future directions. Eur J Clin Invest. 2022;52(1):e13635. https://doi.org/10.1111/eci.13635
434 Walker SE, Allen SH, McMurray RW. Prolactin and autoimmune disease. Trends Endocrinol Metab. 1993;4(5):147–51. https://doi.org/10.1016/1043-2760(93)90103-L
435 Delgado M, Abad C, Martinez C, Leceta J, Gomariz RP. Vasoactive intestinal peptide prevents experimental arthritis by downregulating both autoimmune and inflammatory components of the disease. Nat Med. 2001;7(5):563–8. https://doi.org/10.1038/87887
436 Gonzalez-Rey E, Anderson P, Delgado M. Emerging roles of vasoactive intestinal peptide: a new approach for autoimmune therapy. Ann Rheum Dis. 2007;66(Suppl 3):iii70–6. https://doi.org/10.1136/ard.2007.078519