Glutamatergic–Dopaminergic Balance in the Brain

Its importance in motor disorders and schizophrenia

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Summary

Dopamine appears to be of less importance in the regulation of psychomotor functions than was previously thought. A central dopaminergic-glutamatergic balance may be important for both akinetic motor disorders and psychosis. In Parkinson's disease glutamate antagonists may counteract central glutamatergic hyperactivity and may be of value as anti-parkinsonian drugs. An increase of dopaminergic activity and/or a reduction of glutamatergic activity may contribute to the development of paranoid hallucinatory psychosis in schizophrenic patients and of pharmacotoxic psychosis in Parkinson's disease. Because of possibly severe side-effects of glutamatergic antagonists and agonists in the treatment of akinesia and psychosis, the development ot partial glutamate agonists/antagonists could be an alternative strategy capable of producing antipsychotic or anti-kinetic effects with only mild adverse reaction.

Zusammenfassung

Gleichgewicht zwischen zentralen glutaminergen und dopaminergen Mechanismen / Relevanz für Bewegungsstörungen und Schizophrenie
Dopamin scheint von geringerer Bedeutung für die Steuerung psychomotorischer Funktionen zu sein als man bisher angenommen hat. Ein Gleichgewicht zwischen dopaminergen und glutamatergen Mechanismen ist möglicherweise sowohl für akinetische Bewegungsstörungen als auch für Psychosen bedeutsam. Beim Morbus Parkinson könnten Glutamat-Antagonisten einer glutamatergen Überaktivität im Gehirn entgegenwirken und als Medikamente wirksam sein. Eine erhöhte dopaminerge Aktivität und/oder eine verminderte glutamaterge Aktivität können zur Entwicklung von paranoid-halluzinatorischen Psychosen bei Schizophrenen und von pharmakotoxischen Psychosen bei Parkinson-Patienten beitragen. Wegen möglicherweise schwerwiegender Nebenwirkungen von Glutamat-Antagonisten und -Agonisten bei der Behandlung von Akinesie und Psychose könnte die Entwicklung von partiellen Glutamat-Agonisten und -Antagonisten eine alternative Therapiestrategie darstellen, die antipsychotische und antikinetische Wirkungen mit nur geringen Nebenwirkungen erzielt.

1. Dopamine and Parkinson's disease

The loss of dopamine in the striatum as a result of the neuronal degeneration in the substantia nigra pars compacta has been thought to be the major pathochemical correlate of the main symptoms of Parkinson's disease such as akinesia and rigidity (Ehringer and Hornykiewicz 1960). The discovery of dopaminergic deficiency in the basal ganglia led to the use of replacement therapies including L-dopa (levodopa) treatment (Birkmayer and Hornykiewicz 1961), dopaminergic agonists such as bromocriptine (Calne et al. 1974) and lisuride (Frieling 1988), and the selective monoamine oxidase B inhibitor L-deprenyl (Birkmayer et al. 1975). These therapeutic strategies can improve the parkinsonian symptoms either alone or in combination with one another for a period of time. They are, however, unable to check the progression of the nigrostriatal degeneration. Furthermore, a number of unwanted side-effects including dyskinesia and psychosis are observed, in particular following prolonged administration of L-dopa. The disadvantages of current therapeutic approaches require the development of alternative forms of treatment.

Dopamine has been shown in recent animal studies to be of less importance in the regulation of psychomotor functions than was previously believed. For example, a pronounced locomotor stimulation can be produced in mice depleted of monoaminergic stores following suppression of glutamatergic neurotransmission (Carlsson and Carlsson 1989a, 1989b). This finding raises the question whether glutamate antagonists may be of benefit in the treatment of Parkinson's disease.

2. Glutamate antagonists and the therapy of Parkinson's disease

There is increasing evidence that the dopaminergic nigrostriatal system and the strio-nigral γ-aminobutyric acid (GABA)/substance P system are only one part of a motor loop system which is formed by the basal ganglia and the motor thalamus and receives information from wide cortical areas and projects to distinct premotor cortical areas (Albin et al. 1989). The degeneration of the dopaminergic

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nigro-striatal pathway in Parkinson's disease results in profound changes within this motor loop. Enhanced glutamatergic activity is assumed to occur in the subthalamic nucleus due to a decreased GABAergic input from the lateral globus pallidus. Hyperactivity of the glutamatergic projection neurones in the subthalamic nucleus enhances activity in the basal ganglia output nuclei, i.e. the substantia nigra pars reticulata and the internal segment of the globus pallidus. The consequence of these alterations is a pathological degree of tonic activity in the basal ganglia output system directed to the motor thalamus and brainstem (Albin et al. 1989). This simplified model of basal ganglia pathophysiology in Parkinson's disease suggests that antiglutamatergic drugs may be of therapeutic benefit (Klockgether and Turski 1989).

The validity of the concept of glutamatergic hyperactivity in Parkinson's disease and the potential for antiglutamatergic therapy are underlined by studies with rodents demonstrating that dizocilpine, a non-competitive antagonist at the N-methyl-D-aspartate (NMDA) receptor subtype of the glutamate receptor, stimulates locomotor activity in monoamine-depleted mice (Carlsson and Carlsson 1989a) and rats (Klockgether and Turski 1990) and reverses neuroleptic-induced catalepsy in rats (Schmidt and Bubser 1989, Mehta and Ticku 1990). In monkeys rendered parkinsonian with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) both the competitive NMDA receptor antagonist CPP (($\pm$)-2-carboxypiperazine-4-yl-propyl-1-phosphonic acid) and the quisqualate receptor antagonist NBQX (6-nitro-7-sulphamobenzo[f]quinoxaline-2,3-dione) increase locomotor activity when administered with a threshold dose of L-DOPA (Löschmann et al. 1991).

The only antiglutamatergic drugs available for the treatment of Parkinson's disease are the non-competitive NMDA receptor antagonists amantadine and memantine (Kornhuber et al. 1991), which have moderate antiakinetic efficacy compared to dopamimetic substances. The action of memantine at the NMDA receptor might well explain its antiparkinsonian activity, since the K_i value of memantine at the PCP binding site of the NMDA receptor is lower than the brain concentration reached in the treatment of Parkinson's disease (Kornhuber et al. 1991, Wesemann et al. 1980). The finding that the K_i value of amantadine is about 20 times lower than that of memantine is in agreement with the clinical experience that the mean daily dose of amantadine in the treatment of Parkinson's disease is about 5—10 times higher than that of memantine.

Decreased glutamatergic function has been postulated to be a significant factor in the pathophysiology of schizophrenia (Kim et al. 1980, Kornhuber et al. 1989, 1990; see below). Antiglutamatergic treatment of Parkinson's diesease carries therefore the risk of psychotic side-effects. Amantadine is known to have mild antiakinetic effects in parkinsonian patients and psychosis is a frequent adverse reaction (Danielczyk 1980). The occurrence of pharmacotoxic psychosis has been examined following administration of memantine in patients with Parkinson's disease (Table 1). Four parkinsonian subjects received memantine in addition to their usual antiparkinsonian medication. Only one patient showed a mild improvement of his motor symptoms. The other three patients did not benefit from additional memantine administration. In two out of these three, however, memantine produced psychosis. Memantine administered in doses producing little or no antiparkinsonian effects appears to be likely to cause pharmacotoxic psychosis.

In Parkinson's disease there is a lack of data confirming a disturbance of glutamatergic function in limbic and cortical areas and supporting a glutamatergic hypothesis of pharmacotoxic psychosis. However, the fact that meman-

Table 1: Clinical effects of memantine in patients with Parkinson's disease.

Patient	M. G.	J. S.	H. E.	H. P.
Age	84	64	66	87
Sex	female	male	male	female
Duration of disease (years)	6	7	3	12
Hoehn & Yahr stage[a]	IV—V	IV—V	IV—V	IV—V
Basic therapy (daily dose in mg)	L-dopa (150), amantadine sulfate (200), terguride (1.5)	L-dopa (50), amantadine sulfate (300), terguride (0.75)	procyclidine (7.5)	amantadine sulfate (100), terguride (1.5)
Additional daily dose of memantine	30 mg for 3 weeks	20 mg for 1 week	10 mg for 6 weeks	10 mg for 2 weeks
Clinical effect of memantine	mild improvement of motor symptoms	no improvement of motor symptoms, pharmacotoxic psychosis	no improvement of motor symptoms	no improvement of motor symptoms, pharmacotoxic psychosis
Motor score — Prior to memantine administration	80	70	80	85
— Following memantine administration	60	70	80	85
Psychosis Score — Prior to memantine administration	0	0	0	0
— Following memantine administration	0	2	0	1

The improvement of motor symptoms was rated according to a modified Webster scale (Webster 1968, Birkmayer and Neumayer 1972) composed of 10 items with scores ranging from 0 (normal function) and 10 (total incapacitation).

The degree of pharmacotoxic psychosis was rated according to Moskowitz (1978): stage 1 = insomnia, vivid dreams, stage 2 = hallucinations, paranoid ideation, stage 3 = delirium, confusion.

[a] The stage of Parkinson's disease was rated according to Hoehn and Yahr (1967): I = unilateral disease, II = bilateral disease without impairment of balance, III = bilateral disease with some postural instability, IV = severe disability, V = wheelchair bound or bedridden unless aided.

tine has a considerable potential to induce pharmacotoxic psychosis at threshold doses which produce minor antiakinetic effects, may suggest that glutamatergic activity in areas responsible für psychosis is reduced. Since under-active glutamatergic systems may be further inhibited by NMDA receptor antagonists, psychotic side-effects are likely to occur.

3. Glutamatergic systems in schizophrenia

Research into the function of L-glutamate in the central nervous system has led to the hypothesis that decreased glutamatergic neurotransmission may play a role in the pathophysiology of psychosis (Kim et al. 1980, Kornhuber et al. 1989, 1990). An important contribution to this hypothesis is the observation that the psychotomimetic compound phencyclidine acts at the NMDA receptor subtype of the receptors activated by glutamate (Anis et al. 1983). The psychosis evoked by phencyclidine is regarded to be the best current pharmacological model of schizophrenia (Allen and Young 1978, Snyder 1980) because this drug produces both productive psychotic symptoms and negative symptoms (Petersen and Stillman 1978). It has been reported that phencyclidine blocks responses of central neurones to NMDA (Anis et al. 1983) and it has become increasingly clear that phen-

cyclidine acts as an open channel blocker of the NMDA receptor-coupled ion channel (Foster and Fagg 1987) and is a non-competitive glutamate antagonist.

Despite the psychotomimetic actions of phencyclidine and related substances in humans, data supporting the hypothesis of decreased glutamatergic function in schizophrenia is limited. Markers for glutamatergic neurotransmission are particularly high in brain areas thought to be involved in the pathogenesis of schizophrenia such as the entorhinal region, frontal cortex and hippocampus (Fagg and Foster 1983). Developmental disturbances of the second neuronal layer of the entorhinal region has been found in schizophrenic patients (Jakob and Beckmann 1986) suggesting a dysfunction of the glutamatergic perforant pathway.

A decreased release of glutamate has been observed in the frontal and temporal cortex of schizophrenic patients (Sherman et al. 1991) while increased NMDA receptor density has been measured in the temporal and parietal cortex (Suga et al. 1990). In the putamen, increased (Kornhuber et al. 1989) and unaltered (Suga et al. 1990, Weissmann et al. 1991) NMDA receptor densities have been reported. With regard to the other glutamate receptor subtypes, unchanged quisqualate receptor densities have been found in the frontal, temporal and parietal cortex (Kurumaji et al. 1990) while kainate receptor binding is increased in the frontal cortex (Deakin et al. 1989, Nishikawa et al. 1983) and unchanged (Deakin et al. 1989) or decreased (Kerwin et al. 1988, Harrison et al. 1991) in the hippocampus. The total biochemical data available is of value only as a starting point for further research since both the number of studies and the number of the brain regions examined are limited. For example, the most vulnerable brain regions in schizophrenia, the entorhinal cortex (Jakob and Beckmann 1986) and the prefrontal cortex (Benes et al. 1986) have not been studied in detail and only preliminary biochemical evidence exists to suggest that NMDA receptor density is marginally increased in the entorhinal cortex (Kornhuber et al. 1989).

4. The glutamatergic-dopaminergic link in schizophrenia

Of the hypotheses put forward to explain the biochemical basis of schizophrenia and in particular paranoid hallucinatory symptoms, the dopamine hypothesis has been the most influential. The dopamine hypothesis of schizophrenia is based mainly on indirect pharmacological observations. The biochemical data available, however, indicate that there may be no absolute dopaminergic hyperactivity in the brain (Kornhuber et al. 1990). The biochemical abnormality in schizophrenia may well be located in another neurotransmitter system which is somehow linked to dopaminergic neurones. The dopaminergic and glutamatergic systems are closely linked to one another, thus possibly explaining the therapeutic action of neuroleptic drugs (Kim et al. 1980). Dopamine functionally antagonizes the glutamatergic system. For example, activation of the dopaminergic system reduces glutamate release from cortico-striatal terminals while neuroleptic drugs reactivate the glutamate release (Kornhuber and Kornhuber 1986).

The glutamate hypothesis of schizophrenia unifies the structural alterations found in the cerebral cortex in schizophrenic patients, the psychotomimetic effects of phencyclidine and the therapeutic activity of dopamine antagonists in the treatment of schizophrenia.

5. Conclusion

The importance of a central dopaminergic-glutamatergic balance in akinesia and psychosis is summarized in Fig.
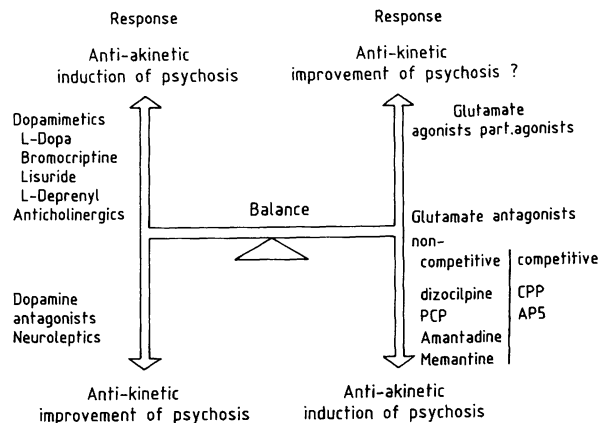

Fig. 1: Simplified illustration of glutamatergic and dopaminergic balances in the brain: importance in akinesia and schizophrenia. PCP = phencyclidine, CPP = (±)-2-carboxypiperazine-4-yl-propyl-1-phosphonic acid, AP5 = 2-amino-5-phosphonopentanoic acid.

1. An increase of dopaminergic activity and/or a reduction of glutamatergic activity may contribute to the development of paranoid hallucinatory psychosis in schizophrenic patients and of pharmacotoxic psychosis in Parkinson's disease. Both dopamine antagonists and glutamate agonists should therefore be of therapeutic benefit in these conditions. By contrast, a loss of dopaminergic activity or glutamatergic hyperactivity may result in akinesia. According to this assumption dopamimetic compounds as well as glutamate antagonists should have antiakinetic properties.

The possible efficacy of NMDA antagonists in Parkinson's disease could be a useful addition to the established dopamimetic therapy. It is well known that all dopamimetic substances cause pharmacotoxic psychosis in Parkinson's disease and are able to aggravate productive symptoms in schizophrenia. It is not known, however, whether competitive NMDA receptor antagonists, which are known to enhance locomotor activity in animal models of Parkinson's disease (Svensson et al. 1991, Löschmann et al. 1991), have potent antiakinetic efficacy in Parkinson's diesease or whether these substances also create the adverse reactions of dopamimetics and non-competitive NMDA receptor antagonists.

Further biochemical, pharmacological and clinical evidence is required in order to provide a clearer understanding of the biological alterations underlying psychotic disturbances. Assuming that glutamate plays a crucial role in schizophrenia, new therapeutic strategies involving the NMDA receptor-ionophore complex should be developed. Enhancement of the glutamatergic tone in the brain for the treatment of schizophrenia may produce neurotoxic and convulsive side-effects (Meldrum and Garthwaite 1990).

Because of possibly severe side-effects of glutamatergic agonists and antagonists in the treatment of akinesia and psychosis, the development of partial glutamate agonists/antagonists could be an alternative strategy capable of producing anti-psychotic or anti-kinetic effects with only mild adverse reactions.

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Dopaminergic and Serotonergic Effects of Clozapine

Implications for a unique clinical profile

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Summary

The clinical profile of clozapine (CAS 5786-21-0) is characterized by superior efficacy in reducing the positive and negative symptoms of schizophrenia and a greatly reduced propensity to elicit acute extrapyramidal symptoms (e.g., Parkinsonian symptoms), long-term effects (e.g., tardive dyskinesia) and hyperprolactinemia. For these reasons clozapine is considered the prototypic atypical antipsychotic. The failure of clozapine to elevate serum prolactin concentrations may be related to the stimulatory effect of clozapine on tuberoinfundibular dopamine neurons and/or the failure of clozapine to achieve effective blockade of pituitary dopamine D_2 receptors. The lack of acute blockade of striatal D_2 receptors by clozapine and the failure of chronic clozapine treatment to suppress striatal dopamine release, relative to that produced by typical antipsychotic agents, may account for the lack of acute extrapyramidal symptoms and tardive dyskinesia, respectively, associated with the use of clozapine. Although the neurochemical substrates that subserve the unique preclinical and clinical profile of clozapine have not been determined unequivocally, clozapine and other purported atypical antipsychotic agents produce a greater antagonism of $5-HT_2$ receptors relative to D_2 receptors than is the case for typical antipsychotics. Clozapine also exerts antagonism of D_1 receptors. It is proposed that the selective interaction of clozapine among D_2, D_1, D_4 and $5-HT_2$ receptors results in a distinctive alteration in the function of pre- and postsynaptic dopamine elements.

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