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Rat Juxtaglomerular Cells are Endowed with DA-1 Dopamine Receptors Mediating Renin Release

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Summary: Under control conditions a primary culture containing about 80–90% of granular juxtaglomerular (JG) cells prepared from rat kidneys continuously released renin into the culture medium at a rate of 17.9 ± 1.4 ng angiotensin I/h per mg of cell proteins per 30 min (n = 14). Dopamine (1.0 μ*M*), the DA-1 dopamine receptor agonist fenoldopam (0.5 μ*M*), and isoproterenol (1.0 μ*M*) increased renin secretion markedly (130–200%). Propranolol (0.1 μ*M*) reduced the effects of isoproterenol significantly (80%), but not those of dopamine or fenoldopam. In contrast, SCH 23390 (0.01 μ*M*), a DA-1 dopamine receptor antagonist, inhibited markedly only the renin release evoked by the latter two agonists, whereas S-sulpiride (10 μ*M*), a DA-2 dopamine receptor antagonist, and phentolamine (10 μ*M*), a nonselective α-adrenoceptor antagonist, did not modify the effects of either dopamine or fenoldopam. In rats, pithed to eliminate reflexogenic mechanisms regulating renin release, at the end of a 15 min i.v. infusion of fenoldopam (20 μg/kg per min) there was a significant increase in plasma renin activity. This effect was completely prevented by SCH 23390 (0.1 mg/kg i.v.) but not significantly changed by S-sulpiride (0.3 mg/kg i.v.) or phentolamine (3.0 mg/kg i.v.) plus propranolol (0.75 mg/kg i.v.). In conclusion, these results indicate that DA-1 dopamine receptors are present in rat kidney JG cells and that pharmacological stimulation of these receptors with dopamine or fenoldopam leads to renin secretion. **Key Words:** Rat juxtaglomerular cells—Dopamine DA-1 and DA-2 receptors—Renin release.

Plasma renin originating from the kidney is the rate-limiting enzyme for the formation of angiotensin II, a potent vasopressor octapeptide that is believed to be one of the causative factors of hypertension (1).

Renin molecules are synthesized within, stored in, and released from renal juxtaglomerular (JG) cells that are differentiated smooth muscle cells located particularly in the media of the renal afferent arteriole, just adjacent to the glomerulus (2). The release of this enzyme into the blood stream is a process controlled by intrarenal baroreceptors, the sodium ion concentration sensed by the macula densa within the distal tubule, the sympathetic nervous system, humoral factors (e.g., angiotensin II, catecholamines, steroids), and plasma electrolytes. Because of the complexity of these control mechanisms, the determination of the site of action of drug-induced alterations on plasma renin activity (PRA) under in vivo conditions is a complicated task. Therefore, the development of cell cultures containing 80–90% of viable rat JG cells (3) can be of great help in assessing whether a drug can directly affect renin secretion (4).

The presence of dopamine receptors on JG cells has not yet been proven conclusively. Data from in vitro and in vivo studies on the renin releasing effects of dopamine are contradictory. This may be due to the ability of this catecholamine to stimulate various types of receptors (α- and β-adrenoceptors, DA-1, and DA-2 dopamine receptors) (5). In anesthetized dogs, intravenous dopamine was reported to increase PRA (6) whereas dopamine given via the renal artery slightly decreased the renal venous plasma renin activity (7). In contrast, in anesthetized (8) and conscious dogs (9), renin secretion

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rate was increased by the administration of dopamine into the renal artery and this effect was blocked by haloperidol but not by propranolol. Furthermore, in the isolated rat kidney (10), dopamine enhanced renin secretion and this effect was blocked by propranolol but not by haloperidol. Finally, in rat renal cortical cell preparations, dopamine caused a dose-dependent increase in renin release with no change in cAMP output. The renin response was found to be partially inhibited by racemic sulpiride (11).

Fenoldopam is a relatively selective agonist of DA-1 dopamine receptors that, like dopamine, produces in normal subjects (12) and in patients with mild hypertension, small decreases in blood pressure, and marked increases in sodium excretion and renal plasma flow. Furthermore, it elevates PRA not only in humans (12,13) but also in anesthetized dogs (14) and rats (15).

This investigation was planned to assess whether rat kidney JG cells are endowed with DA-1 dopamine receptors that, when stimulated by dopamine or fenoldopam, would lead to an increased release of renin. Experiments were also carried out in rats deprived of central autonomic nerve drive to the cardiovascular system to see whether the renin releasing effect of fenoldopam in JG cells could be demonstrated in a rather simple in vivo preparation in which the reflexogenic control was eliminated.

METHODS

JG cell preparation

Isolation of JG cells was carried out as already described (3,4,16). Briefly, after a 5 min in situ perfusion (10 ml/min) with citrate buffer kidneys were removed from male Sprague Dawley rats (Physiology Institute, Zürich University, Zürich, Switzerland) weighing 80–120 g. The renal cortex was separated from the medulla, minced, and incubated in a collagenase-trypsin solution. The obtained suspension was strained over a 22 μm sieve and the single cells were washed with a culture medium [RPMI 1640, 25 m*M* Hepes, 100 μg/ml streptomycin, 100 IU/ml penicillin, 2% (vol/vol) fetal bovine serum]. Aliquots containing 15 million cells were suspended in 30 ml of an isotonic 25% (vol/vol) Percoll solution and centrifuged at 15,000 r/min in a vertical rotor (SV-288, Sorvall) for 30 min. Four bands with distinct densities were regularly obtained. Band III (1.06 g/ml) cells were incubated in 7 cm^2 petri dishes (Greiner, Nürtingen, F.R.G.) with culture medium at 37°C in a humidified atmosphere of 95% air plus 5% CO_2. On the 2nd day of culture, when all of the experiments were performed, the attached cells were approximately 80–90% JG cells as identified by indirect immunofluorescence staining using a specific antibody against rat renin as described elsewhere (3).

Young rats were chosen for these experiments because the JG cells isolated from these animals had much higher rate of survival during the time of the culture. In our laboratory, basal renin release and the release of renin evoked by isoproterenol (1.0 μ*M*) on the second day of culture were not different between young and old (used for in vivo studies described in next section) rats.

To study the release of renin, the medium was withdrawn from the culture dishes and the cells were washed twice with warm (37°C) Hepes-buffered (pH 7.2) salt solution (composition in m*M*: NaCl, 132; KCl, 5.0; $MgSO_4$, 0.8; $CaCl_2$, 2.0; NaOAc, 10.0; Na_2HPO_4, 2.0; glucose, 10.0; Hepes, 20.0). Dishes were then filled with 2 ml of this solution. After a 5–10 min resting period, a 200 μl sample of the incubation medium was withdrawn for a first determination of renin activity, and this volume was immediately replaced by either 200 μl of either fresh (control preparations) incubation medium or 200 μl of solution containing the agents to be tested [agonists, antagonists, or agonists + antagonists (see next paragraph)]. After a 30-min period, another 200 μl sample was taken for a posttreatment determination of renin activity. The samples were centrifuged, and the supernatant was collected and stored at −80°C until assay. The cells were lysed by the addition of 1 ml of 1 N NaOH per dish to determine of protein content (3). Renin activity was assessed by its ability to generate angiotensin I (AI) from the plasma of bilaterally nephrectomized rats as previously described (3). AI was measured by radioimmunoassay (Isotopen-Dienst, West, Teufen, Switzerland) and renin activity is reported as ng AI/h per mg of total cellular protein per 30 min. It should be noted that 2 million cells yielded approximately 1 mg of total proteins.

The effects of dopamine (1.0 and 10.0 μ*M*), fenoldopam (0.5 and 5.0 μ*M*), isoproterenol (1.0 μ*M*), propranolol (0.1 μ*M*), SCH 23390 (0.01 μ*M*), S-sulpiride (10.0 μ*M*), and phentolamine (10.0 μ*M*) were studied on baseline renin release. The concentrations of the agonists were chosen to produce over 100% increase in renin release. Dopamine, isoproterenol, and fenoldopam were also investigated in combination with propranolol, SCH 23390, S-sulpiride, or phentolamine. It should be noted that a control group of juxtaglomerular (JG) cell preparations was run together with the preparations exposed to the agonists or antagonists.

Pithed rat preparations

Male normotensive Sprague Dawley rats (Charles River Laboratories, St Aubin-lès-Elbeuf, France) weighing 230–260 g were briefly anesthetized with ether, pithed, and then immediately ventilated artificially (Rodent Ventilator, Type 7025, Hugo Sachs Electronics, March, West Germany) with 1 ml of room air per 100 g body weight delivered 40–50 times per minute.

Blood pressure was measured from a cannulated left carotid artery by means of a transducer (Statham, model P23Dd) connected to an appropriate amplifier and recorded on a polygraph (Graphtec, Linearcorder Mark VII, Graphtec Corporation, Tokyo, Japan). Intravenous administrations were given via the cannulated left femoral vein.

Rats were pretreated with either saline (0.1 ml/kg i.v.), SCH 23390 (0.1 mg/kg), or S-sulpiride (0.3 mg/kg), and 10 min later an intravenous infusion of either saline (0.033 ml/min over 15 min) or fenoldopam (20 μg/kg per min over 15 min) was initiated. At the end of the 15 min infusion period, a blood sample (1.5 ml) was collected from the carotid artery catheter into ice-cooled tubes containing 25 μl of a solution of 10 mg/ml of sodium EDTA in distilled water. The experiment was then terminated. The

blood was centrifuged for 10 min at 400 *g* at 4°C. The plasma was then separated and stored at −80°C until plasma renin activity (PRA) was measured (17).

Analysis of results

Results (mean ± SEM) are reported as absolute values. An unpaired *t* test was used to assess significant differences ($p < 0.05$).

Drugs

Drugs used were dopamine HCl (Sigma Chemical Co., St Louis, MO, USA), fenoldopam mesylate (SK & F Laboratories, Philadelphia, PA, USA) (−)-isoproterenol bitartrate (Sigma), phentolamine mesylate (Ciba-Geigy Ltd., Basel, Switzerland), propranolol HCl (ICI, Macclesfield, UK), SCH 23390 maleate (Schering Corporation, Bloomsfield, NJ, USA) and S-sulpiride (Ravizza, Milan, Italy).

All doses reported in the text refer to the base weights of the compounds. All drugs were dissolved in isotonic saline.

RESULTS

Studies on rat JG cells

Under baseline conditions, the renin secretion rate of our preparation of JG cells was 17.9 ± 1.4 ng AI/h per mg total protein per 30 min (n = 14). Because 2 million cells yielded approximately 1 mg of cell proteins, the amount of renin liberated by each cell under control conditions was approximately 9.0 ± 0.8 fg AI/h for the 30-min experimental period.

Effects of propranolol, SCH 23390, S-sulpiride, and phentolamine on renin secretion

In the concentrations used, these antagonists did not significantly modify the baseline renin secretion of JG cells at the end of a 30-min contact time (Table 1).

Effects of isoproterenol on renin release

JG cells exposed for 30 min to isoproterenol (1.0 μ*M*) released three times more renin than the matched control preparation. This effect was inhibited significantly (80%) by propranolol (Fig. 1).

Effects of dopamine and fenoldopam on renin release

Dopamine (1.0 μ*M*) and fenoldopam (0.5 μ*M*) enhanced JG cell renin releasing activity by 140 and 130%, respectively (Figs. 2 and 3). On the basis of the effects produced by these concentrations of agonists, on six separate experimental days, fenoldopam was found to be approximately twice as potent as dopamine. Moreover, a concentration of 5 μ*M* of fenoldopam increased renin secretion by 320% (baseline secretion of 19.4 ± 2.3 ng AI/h per mg protein per 30 min, n = 4), whereas 10 μ*M* of dopamine exerted effects similar to those of a 1.0 μ*M* concentration.

TABLE 1. *Effects of four receptor antagonists and their solvent (incubation medium) on renin secreted by JG cells (n = 8 per treatment) isolated from rat kidneys*

Treatment	Concentration (μ*M*)	Renin secretion (ng AI/h per mg prot per 30 min)
Solvent	—	16.5 ± 1.3
SCH 23390	0.01	17.8 ± 1.1
Propranolol	0.1	15.8 ± 1.4
S-Sulpiride	10.0	14.2 ± 1.2
Phentolamine	10.0	16.9 ± 1.7

Effects of propranolol, SCH 23390, S-sulpiride and phentolamine on dopamine and fenoldopam-induced increase in renin secretion

SCH 23390 (0.01 μ*M*), a DA-1 receptor antagonist, entirely blocked the increase in renin secretion evoked by dopamine (Fig. 2) and reduced by 73% the effects of fenoldopam (Fig. 3). In experiments reported elsewhere (18,19), the same concentration of SCH 23390 reduced the effects of dopamine and fenoldopam by 92 and 80%, respectively. In this study, the corresponding inhibitions produced by a lower concentration of SCH 23390 (0.001 μ*M*) were 51 and 60%.

The preferential DA-2 antagonist S-sulpiride, as well as phentolamine and propranolol, failed to modify significantly the effects of these agonists.

Studies in pithed rats

In pithed rats, at the end of the 15 min i.v. infusion of fenoldopam (15 μg/kg per min i.v.), there was a significant elevation in PRA as compared with preparations receiving saline. The effect of fenoldopam was prevented by SCH 23390 but was not significantly modified by either S-sulpiride or a combination of propranolol and phentolamine (Fig. 4). The value of PRA in rats given only these antagonists was of the same magnitude as that of control animals (Fig. 4).

As reported elsewhere (20), fenoldopam produced a small increase in mean carotid artery blood pressure in pithed rats and this effect was inhibited significantly by SCH 23390.

DISCUSSION

Two distinct subtypes of dopamine receptors, DA-1 and DA-2 receptors, have been identified in the cardiovascular system. Stimulation of DA-1 receptors evokes an active vasorelaxation that is particularly pronounced in certain vascular regions such as the kidney and the mesentery artery. In contrast, DA-2 receptor activation leads to a decrease in norepinephrine release that in intact animals manifests itself with a passive decrease in vascular tone and heart rate (5,21,22).

In anesthetized normotensive rats (20) and dogs (14), in conscious spontaneously hypertensive rats (20), and in man (12,13), the DA-1 receptor agonist fenoldopam decreases blood pressure, increases

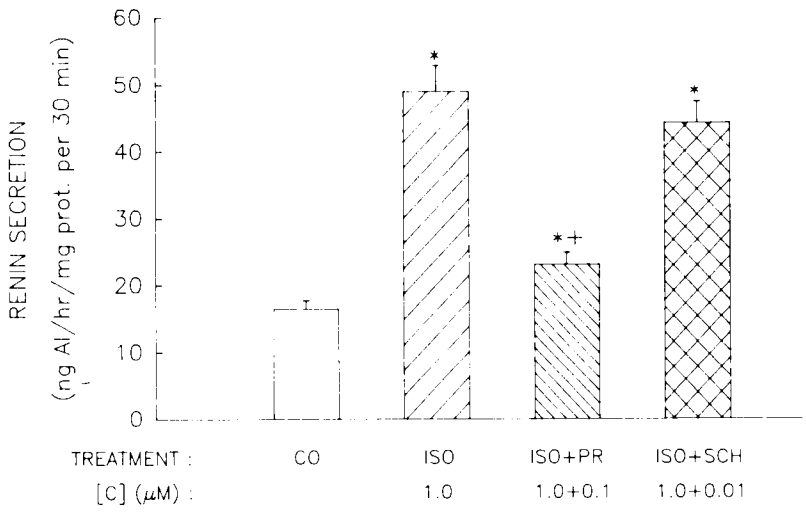

FIG. 1. Effects of isoproterenol (ISO), propranolol (PR) + ISO and SCH 23390 (SCH) + ISO on the renin released by a primary culture of rat JG cells (n = 8 per treatment). The control (CO) refers to cell dishes (n = 8) receiving no treatment. An asterisk indicates that the response is significantly different from that of control ($p < 0.05$, *t* test). A cross indicates that the response is significantly different from that of ISO. AI, angiotensin I.

renal blood flow, and activates the renin-angiotensin system. The mechanisms responsible for the latter effect remain to be determined. Therefore, a primary purpose of this investigation was to examine whether or not fenoldopam and dopamine could evoke renin release from rat isolated JG cells and, if so, to characterize the type of receptors mediating this effect.

Addition of dopamine or fenoldopam to a preparation of JG cells significantly enhanced renin secretion. Inasmuch as the effect of dopamine was not modified by a concentration of propranolol that was sufficient to markedly inhibit the large increase in renin secretion evoked by isoproterenol, it can be concluded that is it not mediated by β-adrenoceptors, which under certain experimental conditions can be stimulated by dopamine (5,21). Thus, whereas these results differ from those found in perfused rat kidneys where the dopamine-induced elevation in renin secretion was reduced by an extremely high concentration (200 μ*M*) of propranolol and not by the dopamine receptor blocker haloperidol (50 μ*M*) (10), they are in agreement with those found in anesthetized (8) and conscious (9) dogs where dopamine induced an elevation in plasma renin that was sensitive to blockade by haloperidol but not by propranolol. Similarly, in our JG cell preparations, a low concentration (0.01 μ*M*) of the selective DA-1 receptor antagonist SCH 23390 (23), but not propranolol (0.1 μ*M*), inhibited the renin releasing activity of dopamine and fenoldopam. Furthermore, phentolamine failed to modify the effects of these DA-1 receptor agonists. Thus, α-adrenoceptors do not participate to the renin releasing activity of fenoldopam and dopamine.

Taken together, our results lead to the conclusion that rat JG cells possess receptors that, on the basis of their pharmacological characteristics, should be designated as belonging to the DA-1 subtype. S-sulpiride, a relatively selective blocker of DA-2 receptors (24) even at a concentration of 10 μ*M*, failed to prevent the increase in renin release

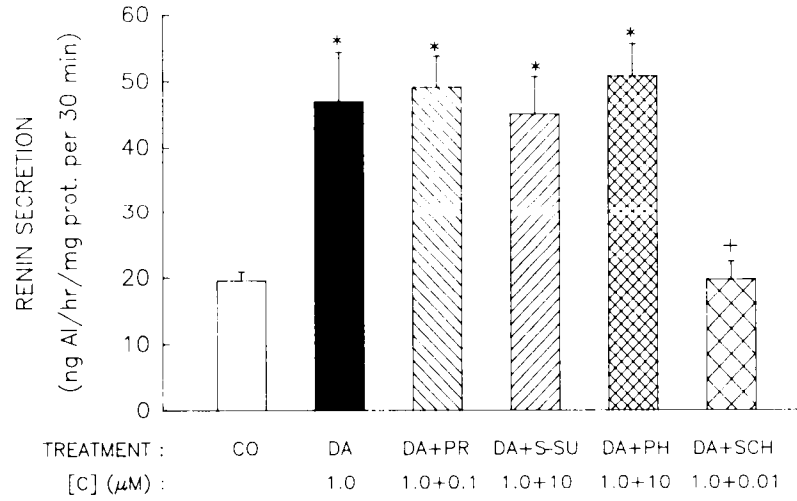

FIG. 2. Effects of SCH 23390 (SCH) and S-sulpiride (S-SU), phentolamine (PH), and propranolol (PR) on the renin production evoked by dopamine (DA) in a primary culture of rat JG cells (n = 6 per group). The control (CO) refers to cell dishes (n = 6) receiving no treatment. An asterisk indicates that the response is significantly different from that of control ($p < 0.05$, *t* test). A cross indicates a significant difference from DA response.

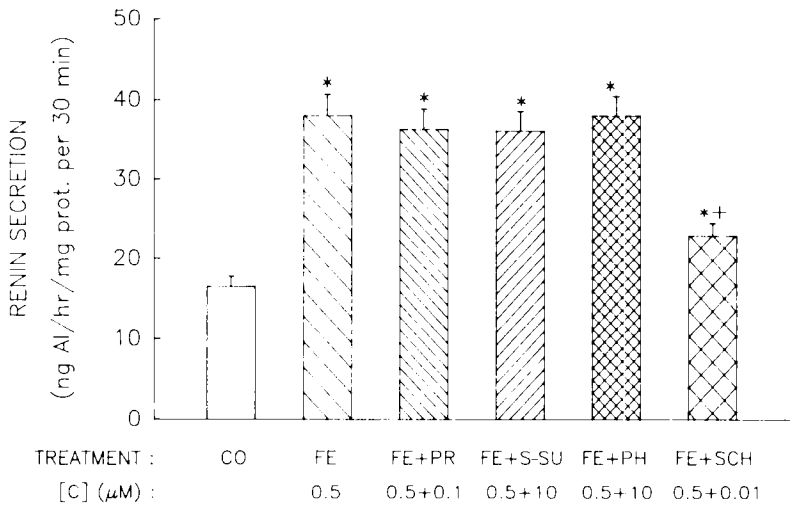

FIG. 3. Effects of SCH 23390 (SCH), S-sulpiride (S-SU), and phentolamine (PH) on the renin secretion evoked by fenoldopam (FE) in a primary culture of rat JG cells (n = 8 per group). The control (CO) refers to cell dishes (n = 8) receiving no treatment. An asterisk indicates that the response is significantly different from control ($p < 0.05$, *t* test). A cross indicates that the response is significantly different from that of FE.

evoked by fenoldopam or dopamine whereas their effects were almost entirely blocked by only 0.01 μ*M* of the selective DA-1 dopamine receptor antagonist SCH 23390. Thus, our results do not support the proposal of Williams et al. (11) that renin released by dopamine in rat renal cortex cells is mediated by DA-2 receptors. Their conclusion was based on two distinct sets of results that could be interpreted differently. Firstly, the partial reduction of the dopamine-induced renin release by a large concentration of RS-sulpiride (10 μ*M*) may also be due to the DA-1 receptor blocking properties of the racemic mixture of this antagonist (24). Secondly, the reported increase in renin release produced by a very high concentration (100 μ*M*) of the DA-2 dopamine receptor agonist bromocriptine was not demonstrated to be inhibited by a selective DA-2 dopamine receptor antagonist.

The effects produced by fenoldopam in isolated JG cells were not restricted to an in vitro phenomenon but also occurred in the whole animal. In rats in which reflexogenic mechanisms were abolished by pithing, fenoldopam produced a significant increase in PRA that was prevented by SCH 23390 but not by S-sulpiride or phentolamine plus propranolol. It should be noted that the dose of S-sulpiride used in this study has been shown to be sufficient to block entirely all the vascular effects of the DA-2 dopamine receptor agonist quinpirole. Furthermore, quinpirole in intact rats (25), in contrast to fenoldopam (20), decreases PRA. Thus, the small but not significant inhibition of fenoldopam-induced renin increase by S-sulpiride in pithed rats (Fig. 4) is possibly due to the DA-1 dopamine receptor antagonist properties of the latter compound (24).

The results (20,25) obtained in pithed rats with fenoldopam mirror those obtained in isolated JG cells. Evidently, this simple in vivo investigation does not allow us to conclude that fenoldopam in-

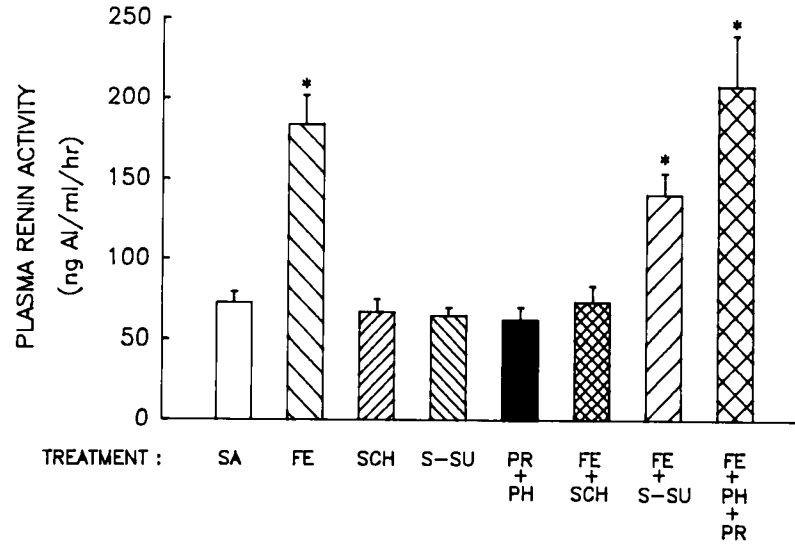

FIG. 4. Plasma renin activities (PRA) measured at the end of a 15 min i.v. infusion of either saline (SA, 0.03 ml/kg per min) or fenoldopam (FE, 20 μg/kg per min) in pithed rats (n = 8–12 per group) pretreated 10 min earlier with intravenous saline (0.25 ml/kg), SCH 23390 (SCH, 0.1 mg/kg), S-sulpiride (S-SU, 0.3 mg/kg), or phentolamine (PH, 3.0 mg/kg i.v.) plus propranolol (PR, 0.75 mg/kg i.v.). An asterisk indicates a significant difference from control (SA) treatment ($p < 0.05$, unpaired *t* test).

creases PRA in pithed rats solely by a direct action on JG cells. Nonetheless, our results with various receptor antagonists demonstrate that in this preparation deprived of reflexogenic controls, the fenoldopam-induced renin release was not due to an indirect mechanism (e.g., blood borne catecholamines) but to a direct effect via activation of DA-1 dopamine receptors. However, it is not possible to know whether the latter receptors are on JG cells and/or on other renal sites (e.g., on the distal tubule) involved on the regulation of renin release.

This investigation demonstrates that isolated rat JG cells are a useful model to assess whether compounds can directly release renin. The determination of mechanisms of renin release by compounds such as fenoldopam producing hypotension, renal vasodilation, increases in sodium excretion, and diuresis, is an extremely difficult task particularly in small research animals such as the rat.

A pertinent question raised by our findings is whether or not DA-1 dopamine receptors on JG cells are the site of action of endogenous dopamine and whether they participate actively in the complex physiological regulation of renin release. At present, we cannot answer these issues. However, if dopaminergic fibers demonstrated in the dog kidney innervate JG cells (26), it may then be reasonable to assume that neuronally released dopamine could lead to renin release.

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