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Angiotensin converting enzyme inhibition prevents trophic and hypertensive effects of an antagonist of adenosine receptors

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Abstract

The continuous infusion of 1,3-dipropyl-8-sulfophenylxanthine (DPSPX), a non-selective antagonist of adenosine receptors, causes hypertension and marked cardiovascular structural changes in Wistar rats. Adenosine inhibits noradrenaline and renin release. We investigated the effects of sympathetic denervation, evaluated renin activity and the influence of angiotensin converting enzyme inhibition in DPSPX-treated rats. Captopril was given (30 or 100 mg kg^{-1} day^{-1}; p.o.) from day −1 to day 28. On day 0, constant infusions of DPSPX (90 μg kg^{-1} h^{-1}; i.p.) or vehicle were started. On day 28, fragments of the left ventricle, mesenteric and tail arteries were processed for morphological studies. Plasma renin activity was increased in DPSPX-treated animals. Sympathetic denervation delayed and partially prevented blood pressure rise. Angiotensin converting enzyme inhibition prevented DPSPX-induced hypertension and morphological changes. Our results, although pointing to the involvement of the sympathetic system, suggest that other mechanisms are involved. We could not differentiate between the trophic and anti-hypertensive effects of angiotensin converting enzyme inhibition.

Keywords: Adenosine receptor antagonist; Hypertension; 6-Hydroxydopamine; Angiotensin converting enzyme inhibition; Trophic effect

1. Introduction

A continuous infusion, during 7 days, of 1,3-dipropyl-8-sulfophenylxanthine (DPSPX), a non-selective antagonist of adenosine receptors (Daly et al., 1985), causes hypertension and cardiovascular structural changes in the rat (Albino-Teixeira et al., 1991; Matias et al., 1991). Blood pressure increases progressively, in a dose-related way until the seventh day, remaining stable thereafter in the rats infused with 90 μg kg^{-1} h^{-1}.

The mechanisms of DPSPX-induced hypertension are not known. Adenosine is an ubiquitous modulator of cellular activity. Its vasodilatory effects and ability to lower systemic blood pressure were first reported by Drury and Szent-Gyorgyi (1929). Adenosine inhibits noradrenaline release (Su, 1978; Fredholm and Hedqvist, 1980). Diminished purinergic modulation of the vascular adrenergic neurotransmission and subsensitivity of presynaptic adenosine A_1 receptors have been described in spontaneously hypertensive rats (Kamikawa et al., 1980; Kubo and Su, 1983; Illes et al., 1989). Evidence documenting the functional consequences of DPSPX-induced hypertension include reports of enhanced sympathetic neurotransmission in the rat tail artery without a change in postjunctional responses to noradrenaline (Guimarães et al., 1994, 1995; Guimarães and Albino-Teixeira, 1996; Karoon et al., 1995). The DPSPX-induced hypertension is associated with reduced cardiac sympathetic neurotransmission occurring at the postjunctional level (Rubino and Burnstock, 1995). A selective increase in mesenteric sensory-motor vasodilation was also reported in DPSPX-hypertensive rats (Ralevic et al., 1996).

Adenosine also inhibits renin release (Osswald et al., 1978; Spielman and Thompson, 1982), this effect having been demonstrated under basal as well as stimulated conditions. Endogenous adenosine tonically inhibits renin release and this effect is potentiated whenever the renin–angiotensin system is activated (Kuan et al., 1990). The interactions between adenosine and angiotensin II are interesting in the context of our experimental model (Kawasaki et al., 1982). Angiotensin II, besides potent vasoconstrictor effects, produces structural changes in blood vessels by mechanisms unrelated to pressure (Mulvany, 1991). The

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trophic changes induced by angiotensin II are similar to those described by us for DPSPX (Albino-Teixeira et al., 1991). The marked structural changes included increase in size of myocardial cell nuclei, increased thickness of the media, hypertrophy of smooth muscle cells, asymmetric hyperplasia of vascular smooth muscle, proliferation of subintimal cells of renal, mesenteric and tail arteries. Since these morphological changes are similar to those caused by angiotensin II, DPSPX-induced effects might be related to an increased production of angiotensin II.

Therefore, in this study, to further characterize the mechanism(s) involved in the genesis of this hypertensive model, we decided to investigate the effects of 6-hydroxydopamine-induced sympathetic denervation, to assess renin activity in DPSPX-infused rats and to evaluate the effects of angiotensin converting enzyme inhibition by captopril, on the trophic and hypertensive components.

2. Materials and methods

2.1. Animals

Male Wistar rats were kept two per cage under controlled environmental conditions (12 h light/dark cycle; room temperature 24 °C) with free access to food and tap water.

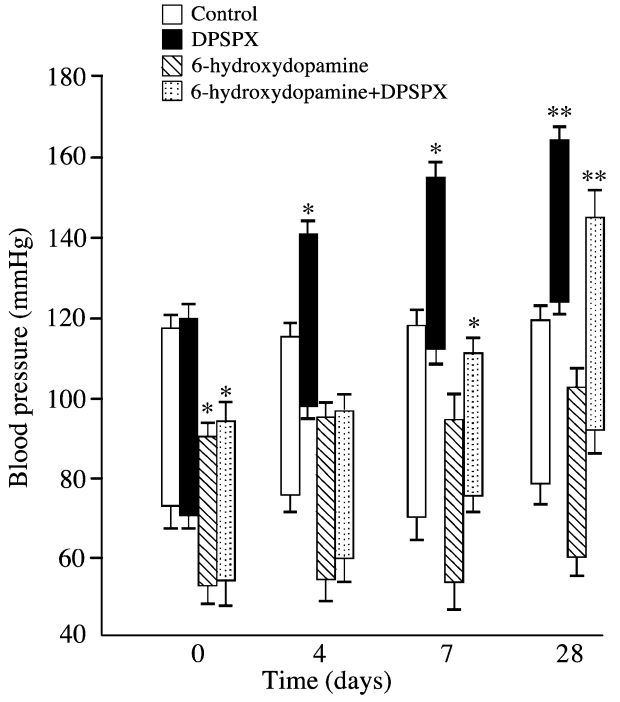

Fig. 1. Evolution of systolic and diastolic blood pressure (mm Hg) from control rats and rats treated with DPSPX (90 μg kg^{-1} h^{-1}), 6-hydroxydopamine (100 + 100 mg kg^{-1}) or 6-hydroxydopamine (100 + 100 mg kg^{-1}) + DPSPX (90 μg kg^{-1} h^{-1}). Values are mean ± S.D.; $n = 6$ rats in each group. * $p < 0.005$ vs. control; ** $p < 0.001$ vs. control; • $p < 0.05$ vs. 6-hydroxydopamine treated; •• $p < 0.001$ vs. 6-hydroxydopamine treated.

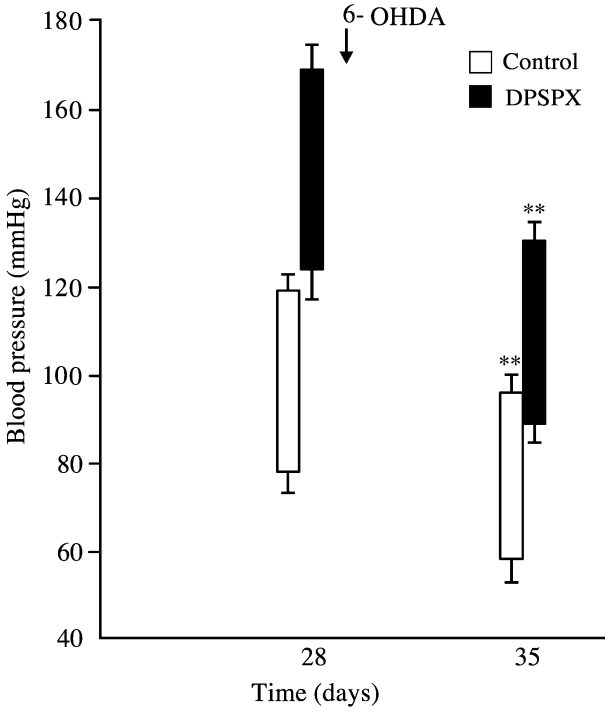

Fig. 2. Evolution of systolic and diastolic blood pressure (mm Hg) from control and DPSPX (90 μg kg^{-1} h^{-1})-treated rats at the end of the treatment before and after administration of 6-hydroxydopamine (100 + 100 mg kg^{-1}). Values are mean ± S.D.; $n = 6$ rats in each group. • $p < 0.001$ vs. control; •• $p < 0.001$ vs. DPSPX.

All the experiments were in accordance with the European Community guidelines for the use of experimental animals and approved by the institutional ethics committee. Systolic and diastolic blood pressure were measured in conscious animals (200–250 g body weight) with a tail cuff using a photoelectric pulse detector (LE 5000, LETICA, Barcelona, Spain). Four determinations were made each time and the

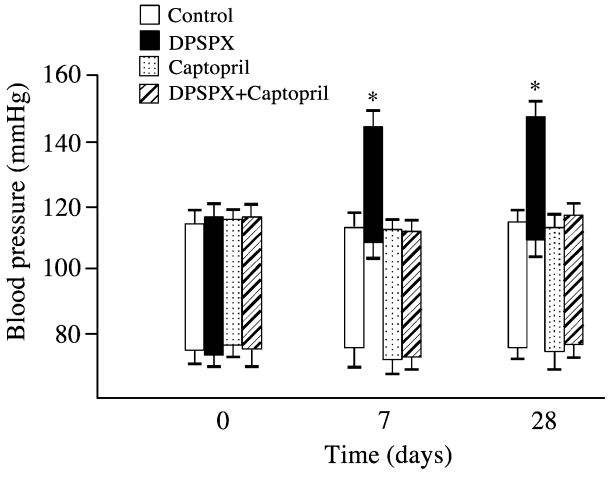

Fig. 3. Evolution of systolic and diastolic blood pressure (mm Hg) from control, DPSPX (90 μg kg^{-1} h^{-1}), captopril (100 mg kg^{-1} day^{-1}), and DPSPX + captopril-treated rats. Values are mean ± S.D.; $n = 6$ rats in each group. * $p < 0.05$ vs. control.

Table 1
Plasma renin activity

	Plasma renin activity (ng h^{-1} ml^{-1})
Control	16.4 ± 3.4
DPSPX (90 μg kg^{-1} h^{-1})	26.3 ± 4.2[a]
Captopril (100 mg kg^{-1} day^{-1})	36.1 ± 3.1[b]
DPSPX + captopril (90 μg kg^{-1} h^{-1} + 100 mg kg^{-1} day^{-1})	33.8 ± 2.3[c]

Values are mean ± S.D. ($n = 6$ in each group).
[a] Significantly different from control ($p < 0.01$).
[b] Significantly different from control ($p < 0.001$).
[c] Significantly different from DPSPX ($p < 0.01$).

means used for further calculations. Normotensive rats were selected after a 7-day period of adaptation to blood pressure measurements methodology.

2.2. Sympathetic denervation

The rats were treated with 6-hydroxydopamine (100 mg kg^{-1}) i.p. or saline, on days −8 and −3. On day 0, the rats were anaesthetised with pentobarbitone sodium (60 mg kg^{-1}) and constant infusions of either DPSPX (90 μg kg^{-1} h^{-1}) in saline or of plain saline were commenced using intraperitoneally implanted Alzet osmotic minipumps (model 2ML1; Alza, Palo Alto, CA, USA).

To study the effects of sympathetic denervation on established hypertension, 6-hydroxydopamine (l00 mg kg^{-1}) i.p. was injected on day 28 to DPSPX- or saline-treated rats that have not been previously denervated. At the end of the treatment period, the rats were killed by decapitation under ether anaesthesia. Fragments of left ventricle, mesenteric and tail arteries were used for catecholamine content determination to evaluate the effectiveness of sympathetic denervation.

The noradrenaline content was determined by high-pressure liquid chromatography with electrochemical detection (Albino-Teixeira et al., 1990).

2.3. Angiotensin converting enzyme inhibition

Normotensive rats selected as referred above were treated with captopril. The rats received the drug in their drinking water (30 or l00 mg kg^{-1} day^{-1}) from day −1 to day 28. On day 0, the rats were anaesthetised with intraperitoneally injected pentobarbitone sodium (60 mg kg^{-1}) and the Alzet minipumps loaded with DPSPX solution (90 μg kg^{-1} h^{-1}) or saline introduced into the peritoneal cavity. On day 28, under pentobarbitone anaesthesia, blood from the renal vein was collected for plasma renin activity determination and fragments of left ventricle, mesenteric and tail arteries were collected and processed for morphological studies. The methods used for morphological study were previously described (Azevedo and Soares-da-Silva, 1981; Albino-Teixeira et al., 1990). The thickness of mesenteric and tail arteries was measured with an ocular micrometer scale calibrated with an object micrometer. The smallest value in each section was taken to represent the real thickness of the media. Camera lucida drawings of all smooth muscle cells cut through the nucleus in the arteries and of all myocardial cell nuclei in the left ventricular sections were made at a final amplification of ×860. For smooth muscle cells, the diameter along the smallest axis of the cell sections was taken as the true diameter. For myocardial cell nuclei, the largest diameter and the axis perpendicular to it were measured. These two values were then used to calculate the mean diameter for each nucleus. All morphometric determinations were made by the same person in preparations identified by a code number, the meaning of which was unknown to the observer untill all measurements were concluded. Renin activity was determined by radioimmunoassay (Peninsula Laboratories, Belmont, CA, USA).

2.4. Drugs

Captopril was a gift from Bristol Meyers Squibb Portuguesa; all other drugs were purchased from Sigma (St. Louis, MO, USA).

Table 2
Systolic blood pressure (SBP) and heart to body weight ratio

	SBP (mm Hg)	Body weight (g)	Heart/body weight (mg/g)
Control	116 ± 3.2	300 ± 7.8	3.32 ± 0.05
DPSPX (90 μg kg^{-1} h^{-1})	149 ± 5.6[a]	305 ± 10.1	3.57 ± 0.08[a]
Captopril (30 mg kg^{-1} day^{-1})	112 ± 4.9	295 ± 9.4	3.29 ± 0.06
Captopril (100 mg kg^{-1} day^{-1})	110 ± 4.6	288 ± 10.1	3.28 ± 0.06
DPSPX + captopril (90 μg kg^{-1} h^{-1} + 30 mg kg^{-1} day^{-1})	120 ± 6.8[b]	297 ± 12.3	3.27 ± 0.08[b]
DPSPX + captopril (90 μg kg^{-1} h^{-1} + 100 mg kg^{-1} day^{-1})	118 ± 5.8[b]	292 ± 11.2	3.26 ± 0.02[b]

Values are mean ± S.D. ($n = 6$ in each group).
[a] Significantly different from control ($p < 0.01$).
[b] Significantly different from DPSPX ($p < 0.01$).

2.5. Statistical analysis

The results are expressed as arithmetic means ± S.D. Student *t*-test was applied to differences between means (unpaired experiments) and the difference considered significant when $p < 0.05$. Multiple comparisons were analysed by Thukey–Kramer test.

3. Results

3.1. Sympathetic denervation

Chemical denervation delayed the start of hypertension caused by DPSPX, shifting it from days 3/4 to days 6/7. Blood pressure values plateaued by the end of the second week and were in average 20 mm Hg lower than in animals which received only DPSPX (Fig. 1). When administered at the end of treatment, 6-hydroxydopamine produced a larger decrease in blood pressure (30 mm Hg) in hypertensive animals than in normotensive animals (20 mm Hg) (Fig. 2). However, after 6-hydroxydopamine, the blood pressure remained higher in DPSPX-treated animals than in control animals.

Determination of noradrenaline in different blood vessels showed that denervation was in fact obtained (the noradrenaline content of vessels of treated animals represented 5–10% of control values; results not shown).

3.2. Angiotensin converting enzyme inhibition

Administration of captopril 100 mg kg^{-1} day^{-1} (Fig. 3) or 30 mg kg^{-1} day^{-1} (data not shown) prevented the development of DPSPX-induced hypertension.

An increase in renin plasma activity, already elevated in DPSPX-treated animals, was caused (Table 1) by angiotensin converting enzyme inhibition.

Table 3
Mean diameter of myocyte nuclei

	Mean diameter (μm)
	Left ventricle
Control	4.98 ± 0.28
DPSPX (90 μg/kg h^{-1})	6.94 ± 0.51[a]
Captopril (30 mg/kg day^{-1})	5.01 ± 0.31
Captopril (100 mg/kg day^{-1})	5.06 ± 0.45
DPSPX + captopril (90 μg/kg h^{-1} + 30 mg/kg day^{-1})	5.04 ± 0.43[b]
DPSPX + captopril (90 μg/kg h^{-1} + 100 mg/kg day^{-1})	4.95 ± 0.65[b]

Values are mean ± S.D. ($n = 600–800$ cells in each group).
[a] Significantly different from control ($p < 0.001$).
[b] Significantly different from DPSPX ($p < 0.001$).

Table 4
Thickness of mesenteric and tail arteries

	Thickness (μm)	
	Tail artery	Mesenteric artery
Control	28.1 ± 10.7	45.0 ± 10.4
DPSPX (90 μg kg^{-1} h^{-1})	42.9 ± 9.6[a]	69.8 ± 11.1[a]
Captopril (30 mg kg^{-1} day^{-1})	29.7 ± 8.4	43.0 ± 10.1
Captopril (100 mg kg^{-1} day^{-1})	27.9 ± 12.1	42.3 ± 9.8
DPSPX + captopril (90 μg kg^{-1} h^{-1} + 30 mg kg^{-1} day^{-1})	28.4 ± 9.8[b]	47.3 ± 14.0[b]
DPSPX + captopril (90 μg kg^{-1} h^{-1} + 100 mg kg^{-1} day^{-1})	27.6 ± 10.9[b]	46.2 ± 13.1[b]

Values are mean ± S.D. ($n = 4$ in each group).
[a] Significantly different from control ($p < 0.001$).
[b] Significantly different from DPSPX ($p < 0.001$).

The heart to body weight ratio was significantly increased in DPSPX-treated rats. This increment was due to an increased weight of the ventricles. The total body weight was similar in all experimental groups included in the study. The DPSPX-induced increase in heart to body weight ratio was prevented by captopril (Table 2). The hypertrophic changes induced by DPSPX in the heart were prevented by angiotensin converting enzyme inhibition as shown by the morphometric studies (Table 3). Hyperplastic and hypertrophic changes induced by DPSPX in mesenteric and tail arteries were also prevented by captopril. The increased thickness of mesenteric and tail arteries caused by DPSPX infusion was prevented by captopril (Table 4). Angiotensin converting enzyme inhibition totally prevented smooth muscle cells hypertrophy of mesenteric and tail arteries in DPSPX-treated rats (Table 5).

In all these parameters, there was no difference between the effects of captopril 30 or 100 mg kg^{-1} day^{-1}, showing that at least the latter dose was supramaximal.

Table 5
Mean diameter of smooth muscle cells (SMCs)

	Mean diameter of SMCs (μm)	
	Tail artery	Mesenteric artery
Control	4.8 ± 0.57	3.81 ± 0.92
DPSPX (90 μg kg^{-1} h^{-1})	5.97 ± 2.15[a]	7.92 ± 1.17[a]
Captopril (30 mg kg^{-1} day^{-1})	3.98 ± 0.66	3.76 ± 0.88
Captopril (100 mg kg^{-1} day^{-1})	4.10 ± 0.79	3.68 ± 1.15
DPSPX + captopril (90 μg kg^{-1} h^{-1} + 30 mg kg^{-1} day^{-1})	3.90 ± 1.04[b]	3.84 ± 1.12[b]
DPSPX + captopril (90 μg kg^{-1} h^{-1} + 100 mg kg^{-1} day^{-1})	4.00 ± 0.90[b]	3.76 ± 1.17[b]

Values are mean ± S.D. ($n = 600–800$ cells in each group).
[a] Significantly different from control ($p < 0.001$).
[b] Significantly different from DPSPX ($p < 0.001$).

4. Discussion

Chemical sympathectomy has been used to evaluate the role of the adrenergic system in hypertensive models (Thoenen and Tranzer, 1973). 6-Hydroxydopamine selectively destroys adrenergic nerve fibers. In the periphery, when given in sufficient amount, 6-hydroxydopamine causes the degeneration of the great majority of sympathetic nerves without destroying the ganglion cell bodies or the adrenal medulla (Thoenen and Tranzer, 1973). The delayed rise in blood pressure and lower systolic and diastolic values recorded in 6-hydroxydopamine-treated animals suggest an involvement of the sympathetic system in the genesis and maintenance of high blood pressure in this model. In normotensive animals, the sympathetic nervous system (sympathetic nerves and adrenal medulla) is essential for the maintenance of blood pressure. After sympathetic denervation, the adrenal medulla has the capacity to partially compensate the loss of sympathetic nerves. Since we did not remove the adrenal glands, such an effect cannot be excluded in the hypertensive animals. However, the blood pressure fall caused acutely by sympathetic denervation at the end of the period of treatment favours our interpretation. Since the hypertension was reduced but not abolished by chemical sympathectomy, other mechanisms are certainly involved (structural changes in arteries; antagonism of the adenosine-induced vasodilator tone; antagonism of the adenosine-induced inhibition of renin release).

Adenosine has been postulated to restrain the renin release response to physiological stimuli (Jackson, 1991). According to the adenosine-brake hypothesis, the administration of adenosine receptor antagonists should augment the renin release response to the activation of the physiological pathways to renin release (Jackson, 1991). Since DPSPX did not interfere with the renin assay or the rate of elimination of renin from the circulation (Jackson, 1991), the increase in plasma renin activity reported by us to occur after DPSPX treatment is compatible with the hypothesis. The activation of this system would lead to an increase in angiotensin II and it is noteworthy that the hypertrophic/hyperplastic cardiovascular changes caused by DPSPX are similar to those described for angiotensin II infusions (Lever, 1986; Mulvany, 1991).

Angiotensin converting enzyme inhibition totally prevented the trophic effects of DPSPX as well as the blood pressure rise. We could not differentiate, even with the lower dose of captopril used, between the antihypertensive action and the inhibition of trophic modifications. Therefore, we are not able to attribute the relative participation of direct effects upon the vessel wall and myocardium and the effects of cardiovascular remodeling dependent on blood pressure rise (Folkow et al., 1958; Mulvany, 1983, 1991; Owens, 1985; Struyker Boudier et al., 1990). Thus, the prevention of trophic modifications cannot be ascribed to the hypothetical antagonism of the trophic actions of angiotensin II, due to angiotensin converting enzyme inhibition. In fact, it may entirely depend on the antihypertensive effect of captopril. However, indirect evidence, such as the increase in renin activity, the magnitude of the trophic effects of DPSPX which are not in proportion with the blood pressure rise, point to a composite effect, that is, both angiotensin and the hypertensive state appear to be responsible for the morphologic changes observed.

In summary, our results suggest an involvement of the sympathetic system in the genesis and maintenance of high blood pressure in this model. Besides, the renin–angiotensin system is activated in this hypertensive model, angiotensin converting enzyme inhibition prevents the development of hypertension as well as the hyperplastic and hypertrophic changes induced in the heart and arteries by DPSPX. Since the doses of captopril chosen prevented the hypertensive response to DPSPX, it is not possible to differentiate between the trophic and anti-hypertensive effects of angiotensin converting enzyme inhibition. These results are consistent with a major role for angiotensin II in both the maintenance of hypertension and in the development of hystopathological changes in the heart and vessels.

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References

Albino-Teixeira, A., Azevedo, I., Branco, D., Osswald, W., 1990. Purine agonists prevent trophic changes caused by sympathetic denervation. Eur. J. Pharmacol. 179, 141–149.

Albino-Teixeira, A., Matias, A., Polónia, J., Azevedo, I., 1991. Blockade of adenosine receptors causes hypertension and cardiovascular structural changes in the rat. J. Hypertens., Suppl. 9, S196–S197.

Azevedo, I., Soares-da-Silva, P., 1981. Are fibroblasts adrenergically innervated cells? Blood Vessels 18, 330–332.

Daly, J.W., Padgett, W., Shamim, M.T., Butts-Lamb, P., Waters, J., 1985. 1,3-Dialkyl-8-(*p*-sulfophenyl)xanthines: potent water-soluble antagonists for A1 and A2-adenosine receptors. J. Med. Chem. 28, 487–492.

Drury, A., Szent-Gyorgyi, A., 1929. The physiological activity of adenine compounds with special reference to their action upon the mammalian heart. J. Physiol. 68, 213–237.

Folkow, B., Grimby, G., Thulesius, O., 1958. Adaptive structural changes of the vascular walls in hypertension and their relation to the control of peripheral resistance. Acta Physiol. Scand. 44, 255–272.

Fredholm, B.B., Hedqvist, P., 1980. Modulation of neurotransmission by purine nucleotides and nucleosides. Biochem. Pharmacol. 29, 1635–1643.

Guimarães, S., Albino-Teixeira, A., 1996. Hypertension due to chronic blockade of P_1-purinoceptors. J. Auton. Pharmacol. 16, 367–370.

Guimarães, S., Paiva, M.Q., Moura, D., Vaz-da-Silva, M.J., Albino-Teixeira, A., 1994. Long-term administration of 1,3-dipropyl-8-sulfophenylxanthine (DPSPX) alters α_2-adrenoceptor-mediated effects at the pre-

but not at the postjunctional level. Naunyn-Schmiedeberg's Arch. Pharmacol. 350, 692–695.

Guimarães, S., Albino-Teixeira, A., Paiva, M.Q., 1995. Hypertension and enhanced β-adrenoceptor-mediated facilitation of noradrenaline release produced by chronic blockade of adenosine receptors. Br. J. Pharmacol. 114, 1595–1598.

Illes, P.H., Rickmann, I., Brod, B., Bucher, B., Stoclet, J.C., 1989. Subsensitivity of presynaptic adenosine A1-receptors in caudal arteries of spontaneously hypertensive rats. Eur. J. Pharmacol. 174, 237–251.

Jackson, E.K., 1991. Adenosine: a physiological brake on renin release. Annu. Rev. Pharmacol. Toxicol. 31, 1–35.

Kamikawa, Y., Cline Jr., W.H., Su, C., 1980. Diminished purinergic modulation of the vascular adrenergic neurotransmission in spontaneously hypertensive rats. Eur. J. Pharmacol. 66, 347–353.

Karoon, P., Rubino, A., Burnstock, G., 1995. Enhanced sympathetic neurotransmission in the tail artery of 1,3-dipropyl-8-sulfophenylxanthine (DPSPX)-treated rats. Br. J. Pharmacol. 116, 1918–1922.

Kawasaki, H., Cline Jr., W.H., Su, C., 1982. Enhanced angiotensin-mediated facilitation of adrenergic neurotransmission in spontaneously hypertensive rats. J. Pharmacol. Exp. Ther. 221, 112–116.

Kuan, C.J., Wells, J.N., Jackson, E.K., 1990. Endogenous adenosine restrains renin release in conscious rats. Circ. Res. 66, 637–646.

Kubo, T., Su, C., 1983. Effects of adenosine on [3H]norepinephrine release from perfused mesenteric arteries of SHR and renal hypertensive rats. Eur. J. Pharmacol. 87, 349–352.

Lever, A.F., 1986. Slow pressor mechanisms in hypertension: a role for hypertrophy of resistance vessels? J. Hypertens. 4, 512–524.

Matias, A., Albino-Teixeira, A., Polónia, J., Azevedo, I., 1991. Long-term administration of 1,3-dipropyl-8-sulfophenylxanthine causes arterial hypertension. Eur. J. Pharmacol. 193, 101–104.

Mulvany, M.J., 1983. Do resistance vessel abnormalities contribute to the elevated blood pressure of spontaneously-hypertensive rats? A review of some of the evidence. Blood Vessels 20, 1–22.

Mulvany, M.J., 1991. Is there a role for the vascular renin–angiotensin system in the determination of vascular structure? Blood Vessels 28, 224–230.

Osswald, H., Schmitz, H.J., Kemper, R., 1978. Renal action of adenosine: effect on renin secretion in the rat. Naunyn-Schmiedeberg's Arch. Pharmacol. 303, 95–99.

Owens, G.K., 1985. Differential effects of antihypertensive drug therapy on vascular smooth muscle cell hypertrophy, hyperploidy, and hyperplasia in the spontaneously hypertensive rat. Circ. Res. 56, 526–536.

Ralevic, V., Rubino, A., Burnstock, G., 1996. Augmented sensory-motor vasodilatation of the rat mesenteric arterial bed after chronic infusion of the P1-purinoceptor antagonist, DPSPX. Br. J. Pharmacol. 118, 1675–1680.

Rubino, A., Burnstock, G., 1995. Changes in sympathetic neurotransmission and adrenergic control of cardiac contractility during 1,3-dipropyl-8-sulfophenylxanthine-induced hypertension. J. Pharmacol. Exp. Ther. 275, 422–428.

Spielman, W.S., Thompson, C.I., 1982. A proposed role for adenosine in the regulation of renal hemodynamics and renin release. Am. J. Physiol. 242, F423–F435.

Struyker Boudier, H.A., van Bortel, L.M., De Mey, J.G., 1990. Remodeling of the vascular tree in hypertension: drug effects. Trends Pharmacol. Sci. 11, 240–245.

Su, C., 1978. Purinergic inhibition of adrenergic transmission in rabbit blood vessels. J. Pharmacol. Exp. Ther. 204, 351–361.

Thoenen, H., Tranzer, J.P., 1973. The pharmacology of 6-hydroxydopamine. Annu. Rev. Pharmacol. 13, 169–180.