CENTRAL β -ADRENERGIC RECEPTORS FOR BLOOD PRESSURE REGULATION IN SPONTANEOUSLY HYPERTENSIVE RATS

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The role of central catecholaminergic mechanisms in blood pressure regulation has been studied in spontaneously hypertensive rats (SHR) by Yamori et al. (1-4). These studies on norepinephrine (NE) synthesizing enzymes or NE turnover of the brain (1, 2) and central depressor effect of α -agonists (3-5) indicated that noradrenergic mechanisms in the central nervous system (CNS), particularly, α -receptors act as sympatho-inhibitory or depressor mechanisms which may be inadequate in SHR (3-6) as well as in other hypertensive states. The existence of such central sympatho-inhibitory mechanisms in rats was further confirmed pharmacologically (7-10) or by the induction of temporal hypertension following the destruction of central noradrenergic mechanisms (11).

On the other hand, failure of the development of renal (12), DOCA (13) or spontaneous (13) hypertension after the destruction of central catecholaminergic mechanisms indicated the possible existence of central catecholaminergic pressor mechanisms (6). The pressor effect of centrally administered β -agonist (isoproterenol, salbutamol) and its abolishment by the pretreatment of β -blocker (propranolol) were observed in conscious cats (14, 15). These findings suggested that central catecholaminergic pressor mechanisms might be related to β -receptors in the brain.

Therefore, effects of centrally administered β -agonists and β -blockers were observed in rats, especially in SHR, to investigate the role of central β -receptors in blood pressure regulation in hypertensive states (16). Central β -receptors were further analyzed according to β_1 - and β_2 -subclassifications of peripheral β -receptors (17).

Twenty-five SHR at 12 to 15 weeks of age, and with established hypertension were used with 25 age-matched normotensive Wistar-Kyoto (WK) from which the SHR had been derived. Rats were fixed on a stereotaxic apparatus without anesthesia and the following drugs dissolved in 20 μ l of physiological saline were injected mainly into the right lateral ventricle with a microsyringe (16). β -agonist, isoproterenol (Sigma); α - and β_1 -agonist, nordefrine (Sterling-Winthrop Research Institute); β_2 -agonist, salbutamol (Sankyo Pharmaceutical) and orciprenaline (C.H. Boehringer-Sohn); β_1 -, β_2 -blocker, propranolol (Sumitomo Chemical); β_1 -blocker, practolol (Otsuka Pharmaceutical) and α -blocker, phentolamine (CIBA-Geigy). Each agent was freshly dissolved in physiological saline before injection. Direct blood pressure was recorded through a transplanted catheter into the femoral artery by a polygraph (Nihon Kohden, RP-5) connected with a transducer (Toyo-Baldwin, MPU-0.5). All numerical data were analyzed for statistical difference by student's *t*-test. The

intraventricular injection (i.vt.) of β -agonist, isoproterenol (0.5–10 μ g) decreased the blood pressure as well as α - and β_1 -agonist, nordefrine (1–50 μ g, i.vt.), but β_2 -agonist, salbutamol (0.5–30 μ g, i.vt.) and orciprenaline (0.5–10 μ g, i.vt.), increased the blood pressure in SHR and WK (Fig. 1.) β -blocker, propranolol (50–300 μ g, i.vt.), itself caused a transient rise, did not block the depressor effect of isoproterenol and nordefrine, but did block the pressor effect of orciprenaline.

The central pressor effect of salbutamol and orciprenaline or the depressor effect of nordefrine was not blocked by the pretreatment of β_1 -blocker, practolol (100 μ g, i.vt.). On the other hand, the pretreatment of α -blocker, phentolamine (100 μ g, i.vt.) blocked the depressor effect of isoproterenol and nordefrine. Therefore, the central depressor effect of isoproterenol and nordefrine may be mainly due to their α -effect.

FIG. 1. Central responses to β -agonists with or without the pretreatment of α - or β -blocker in SHR.

However, β_2 -agonist such as salbutamol and orciprenaline may cause central pressor responses through $\beta(\beta_2)$ -receptors.

Dose-response curve showed that depressor response to nordefrine, i.e., α -methyl norepinephrine (decarboxylated product of α -methyl dopa) was obviously greater in SHR than in WK (Fig. 2). This finding was consistent with Yamori et al's suggestions (3-6) that the central depressor effect of α -methyl dopa was mediated through α -methyl norepinephrine, and such a clear difference in dose-response curve indicated the involvement of central α -receptors in the hypertension of SHR. On the other hand, significantly increased central pressor response to salbutamol and orciprenaline, as shown in the dose-response curve, indicated the involvement of β_2 -receptors in the hypertensive state.

Dose-Response Curve for Central Effect of β -Agonists in SHR

FIG. 2. Dose-response curve to isoproterenol, nordefrine, orciprenaline and salbutamol in SHR and normotensive Wistar-Kyoto.

As isoproterenol has β_1 - as well as β_2 -effects, was no difference seen in the dose-response curve between in SHR and WK. The increased pressor effect of isoproterenol as a β_2 -agonist may be eliminated in SHR by its increased depressor effect as a β_1 -agonist.

The present experiment showed that the intraventricular injection of a β -agonist, isoproterenol, in rats caused a central depressor effect, which was neither blocked by a β -blocker, propranolol, nor by a β_1 -blocker, practolol, but was blocked by an α -blocker, phentolamine. β_2 -agonists, salbutamol and orciprenaline, caused a central pressor response which was blocked by the β -blocker, propranolol. As the central depressor responses to an α -agonist and pressor responses to a β_2 -agonist were significantly increased in SHR, our results herein indicate the possible involvement of not only central α -, but also $\beta(\beta_2)$ -receptors in the hypertensive state.

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EFFECT OF 2-(4-BENZYL-PIPERIDINO)-1-(4-HYDROXYPHENYL)-1-PROPANOL ON ADENYLATE CYCLASE AND 3',5'-CYCLIC AMP PHOSPHODIESTERASE *IN VITRO*

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It is well established that some vasodilator drugs like the nicotinic acid derivative exert marked effects through relaxation of vascular smooth muscle. Carron *et al.* (1) reported the synthesis and pharmacological characteristics of 2-piperidinoalkanol derivatives, and found 2-(4-benzyl-piperidino)-1-(4-hydroxyphenyl)-1-propanol-1-(+)-tartrate (BPHPP) to be a most potent vasodilator. The mechanisms of the pharmacological actions, however, remain unknown. 2-Piperidinoalkanol derivatives also display some prevailing α -adrenergic blocking effects; BPHPP has been found to be antagonistic to the epinephrine-induced contractions of the seminal vesicles (1). Since adenylate cyclase is stimulated by epinephrine, glucagon and other hormones (2), and since the biological effects of these hormones are due to the elevation of intracellular cyclic adenosine 3',5'-monophosphate (cyclic AMP) levels in the target organs (3), studies concerning the participation of BPHPP in the hormone-stimulating adenylate cyclase system are deemed worthy of interest.

During the course of the investigation of BPHPP on cyclic AMP metabolism, we observed that this agent inhibits both activities of adenylate cyclase and cyclic AMP phosphodiesterase *in vitro*.

Male rats of the Wistar strain, weighing from 180 to 200 g, were maintained on an