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Central pressor activity of cimetidine in spontaneously hypertensive rats

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The systemic blood pressure effect of cimetidine given intracerebroventricularly (i.c.v.) in anaesthetized spontaneously hypertensive (SH) rats has been investigated. Cimetidine (250 μg i.c.v.) caused a gradual long lasting rise in mean in mean arterial blood pressure with maximum of 31·6 ± 4·5 mm Hg. Chemical degeneration of catecholaminergic neurons with 6-OHDA treatment, central administration of phentolamine and prazosin, and the bilaterial adrenalectomy significantly inhibited the pressor response of cimetidine, while propranolol (i.c.v.) had no effect. From these results it appears that the hypertensive response of cimetidine is mediated by central catecholaminergic pathways and is due to an increase in efferent sympathetic outflow and release of catecholamine from the adrenal medulla.

Central administration of H_2-receptor antagonists has been shown to increase blood pressure in anaesthetized animals (Finch & Hicks 1976; Karppanen et al 1977: Paakkari et al 1982), the mechanism of which is unclear. It is probably not due to H_2-receptor blockade, since activation of central histamine receptors causes hypertension (Finch & Hicks 1976; Finch et al 1978; Karppanen et al 1977), however the in-vivo experiments of Albinus & Sewing (1974) and Brimblecombe et al (1975) have shown that the peripheral effects of burimamide and metiamide were not directly related to H_2-receptor blockade, but were catecholamine-dependent. It has also been proposed that central administration of metiamide increases blood pressure through a mechanism involving a GABA-receptor antagonism (Antonaccio et al 1981). Studies in our laboratory showed that in anaesthetized spontaneously hypertensive (SH) rats, central administration of the H_2-receptor antagonist cimetidine, caused a sustained rise in perfusion pressure of autoperfused hindquarters (Dohadwalla & Dadkar 1981). The present study was undertaken to elucidate the mechanism responsible for vasoconstrictor action of centrally administered cimetidine in SH rats.

Materials and methods

Male SH rats (230–250 g) the strain developed by Okamoto & Aoki (1963) were used. Permanent cannulation of lateral cerebroventricles was performed stereotaxically on pentobarbitone sodium anaesthetized animals. The skull was exposed and a small hole was made through the parietal bone with the tip of 20 gauge needle, at the co-ordinate of L 1–1·5 mm, P 1·0 mm with respect to bregma. The polyethylene cannula was inserted into the cerebral ventricle, to the depth of 4·5 mm below the outer surface and fixed to the skull with dental acrylic which also enveloped a small stainless steel screw. These rats were allowed to rest for

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Table 1. Effect of various treatment on the cimetidine-(250 μg i.c.v.) induced rise in mean arterial blood pressure (MBP) in anaesthetized SH rats. Values represent mean ± s.e.m. Number of animals are given in parentheses.

Treatment group	Dose and route	Mean arterial blood presure (mm Hg) Initial	After treatment[a]	Cimetidine-induced rise in MBP (mm Hg)
Saline (8)	10 μl (i.c.v.)	178 ± 7·9	—	31·6 ± 4·5
Phentolamine (8)	200 μg ,,	196 ± 12·6	175 ± 8·7	16·2 ± 5·4*
Prazosin (8)	20 μg ,,	192 ± 8·3	168 ± 7·7	6·4 ± 4·9***
Propranolol (8)	200 μg ,,	182 ± 9·1	171 ± 8·8	42·5 ± 9·6
6-OHDA (8)	[b]3 × 250 μg (i.c.v.)	—	152 ± 4·3	8·1 ± 2·9***
6-OHDA (8)	[c]100 mg kg^{-1} (i.v.)	—	103 ± 3·9	13·7 ± 2·9**
Adrenalectomy (10)	—	—	146 ± 5·0	7·2 ± 4·6**

[a] Mean arterial blood pressure (mm Hg) in animals before administration of cimetidine.
[b] Pretreated with 3 injections of 6-OHDA over 5 days and on day 7 the animals received cimetidine.
[c] 6-OHDA was administered 24 h before cimetidine.
Significant difference from control group *$P < 0·05$, **$P < 0·005$, ***$P < 0·001$. Statistical analysis with Student's t-test.

two to three days. On the day of the experiment, they were anaesthetized with pentobarbitone sodium (35 mg kg^{-1} i.p.) and the blood pressure was recorded on a Hellige physiological recorder using Statham P 23 Db pressure transducer. The site of intracerebroventricular (i.c.v.) injection was confirmed at the end of the experiment by injection of 10 μl of Evans Blue, and subsequent microscopic examination.

The drugs used were: cimetidine (SK&F), phentolamine hydrochloride (Ciba-Geigy), propranolol hydrochloride (ICI), prazosin hydrochloride (Pfizer) and 6-hydroxydopamine (6-OHDA) hydrobromide (Sigma). All drugs were dissolved in 0·9% sodium chloride except 6-OHDA and cimetidine. 6-OHDA was dissolved in 1% ascorbic acid and cimetidine in 0·1 M HCl, and the pH 6 was adjusted with 0·1 M NaOH. All the drug solutions were injected into the lateral ventricle in a volume of 10 μl by means of Hamilton syringe. Results were expressed as mean ± s.e.m. Statistical analysis of the results was by Student t-test. Differences were considered to be significant at $P < 0·05$ level.

Effect of cimetidine i.v. and i.c.v.

Cimetidine (50–250 μg) injected into the lateral ventricle resulted in an increase in systemic blood pressure in a dose-dependent manner. At a dose of 250 μg (i.c.v.), cimetidine produced 31·6 ± 4·5 mm Hg rise in blood pressure. The onset of the pressor effect was gradual and maximum peak effect was observed at 20–30 min. The blood pressure returned to basal level in 80–90 min. Intravenous administration of cimetidine (250 μg) had no effect on the blood pressure indicating the lack of direct effect on the peripheral vascular system. To examine whether the cimetidine-induced hypertensive response is mediated via catecholaminergic pathways, the effect of pretreatment with the α-adrenoceptor antagonists phentolamine (200 μg), prazosin (20 μg) and propranolol (200 μg) administered i.c.v. 30 min before cimetidine was studied.

Effect of cimetidine after chemical sympathectomy

To clarify the mode of action of cimetidine further, chemical sympathectomy was performed both on central and peripheral nerves with 6-OHDA. Chemical degeneration of central catecholaminergic neurons was achieved by treating animals with three injections (250 μg i.c.v.) of 6-OHDA at 48 h intervals over 5 days. Cimetidine was administered on the 7th day following the first 6-OHDA treatment. To achieve peripheral sympathectomy, 6-OHDA (100 mg kg^{-1} i.v.) was administered 24 h before cimetidine.

Results and discussion

Pretreatment of the animals with phentolamine and prazosin, significantly inhibited the pressor effect of cimetidine, prazosin showing greater inhibition than phentolamine (Table 1). The β-adrenoceptor antagonist propranolol failed to block the hypertensive response of cimetidine (Table 1). These results suggest that cimetidine releases noradrenaline and activates excitatory α-adrenoceptors in the hypothalamus which in turn cause the rise in blood pressure. Further support for this hypothesis comes from the observation that central administration of cimetidine decreases noradrenaline concentrations in the hypothalamus, presumably by releasing noradrenaline from presynaptic site to synaptic cleft, rather than by inhibition of its synthesis (Nowak 1980).

Central degeneration of catecholamine pathways by 6-OHDA significantly inhibited the pressor effect of cimetidine (Table 1), providing further evidence that noradrenergic circuits within central nervous system might be involved in cimetidine-induced rise in blood pressure. Systemic administration of 6-OHDA (100 mg kg^{-1}) also significantly inhibited the hypertensive response of cimetidine (Table 1). Taken together, these results suggest that the pressor action of cimetidine is mediated through central catecholamine pathways and is due to an increase in efferent sympathetic outflow.

After peripheral sympathectomy, the pressor response of cimetidine though decreased, was found to be less inhibited than that of central sympathectomy. This finding raised doubts as to whether in addition to

increased efferent sympathetic outflow, there could be some other factors involved in cimetidine-induced rise in blood pressure. It has been demonstrated that H_2-receptor antagonists metiamide and burimamide possess catecholamine-releasing properties in the periphery (Ganellin & Owen 1977). Furthermore, systemic administration of 6-OHDA does not destroy the chromaffin tissues of the adrenal medulla and the release of catecholamines remains intact (White et al 1979). These observations led us to study the participation of the adrenal medulla in presor action of cimetidine. Bilateral adrenalectomy was performed 3–4 days before the administration of cimetidine. In adrenalectomized SH rats, pressor response of cimetidine given i.c.v. was significantly reduced compared with controls (Table 1), suggesting the participation of the adrenal medulla in cimetidine-induced rise in blood pressure.

Our findings indicate that pressor action of i.c.v. administration of cimetidine is mediated through central catecholaminergic pathways and is due to an increase in efferent sympathetic outflow and release of catecholamines from the adrenal medulla.

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Effect of morphine on the tissue cyclic AMP and cyclic GMP content in two strains of mice

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The effect of morphine on the cyclic (c) AMP and cyclic (c) GMP concentrations in several organs, and its reversal by naloxone have been investigated in C57BL and DBA strains of mice. Morphine increased the cAMP contents in lungs and muscle, and the cGMP contents in lungs, intestine, heart, liver and muscle in a naloxone-reversible way in C57BL mice only. This is consistent with our previous observation that morphine increased plasma cyclic nucleotide levels in C57BL mice, whereas such an increase was marginal in the DBA strain. These results show that there is a strain difference in the effect of morphine on tissue cyclic nucleotide contents and the possible origin of the plasma cyclic nucleotides which are increased by morphine.

In previous studies, we showed that opioids increase plasma cyclic (c) AMP and cyclic (c) GMP in the ddY strain of male mice (Muraki et al 1979, 1983). We examined the mechanism by which morphine raised plasma cAMP and cGMP concentrations, and suggested that the increase is the result of the morphine-induced activation of the sympathetic and parasympathetic nervous system; the origin of the plasma cyclic nucleotides was assumed to be the peripheral organs but not the central nervous system. Wehmann et al (1974) suggested that the lungs and the small intestine are the site of production of both cAMP and cGMP in dogs, whereas Strange & Mjøs (1975) showed liver to be the major source of the glucagon-stimulated increase in plasma cAMP concentrations.

It is well-known that there is a marked strain difference in the reactivity to opioids (Brase et al 1977; Oliverio et al 1983). The C57BL/6(C57) and DBA/2(DBA) strains of mice especially show many contrasting responses to opioids (Trabucchi et al 1976; Horowitz et al 1977; Frigeni et al 1978, 1981). The administration of opioids increases the locomotor activity in C57 mice, but decreases it in DBA mice, which are more sensitive to the analgesic effect of opioids than are C57 mice (Oliverio & Castellano 1974). We reported that morphine increased plasma cAMP and cGMP levels in C57 mice, whereas the increase was negligible in the DBA strain (Muraki et al 1982).

The purpose of the present study has been to examine the effect of morphine on the cyclic nucleotide concentrations in selected organs of two strains of mice, C57 and DBA, to determine the possible sources of the

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