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Evidence that a novel dopamine receptor agonist, RDS-127 [2-di-n-propylamino-4,7-dimethoxyindane] has some centrally mediated cardiovascular actions†

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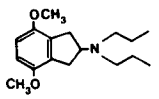
The cardiovascular effects of RDS-127 [2-di-n-propylamino-4,7-dimethoxyindane] were examined in normotensive, anaesthetized rats. RDS-127 given i.v. (12·5–125 μg kg^{-1}) produced dose-dependent bradycardia. The bradycardic effect was 20·5 times more potent when the drug was administered intracerebroventricularly (i.c.v.) than when given i.v. RDS-127 produced a slight, but significant hypotension. Haloperidol given i.c.v. or i.v. reversed these bradycardic and hypotensive actions, whereas phentolamine was ineffective. Methylatropine partially reduced the bradycardic effect. These results suggest that RDS-127 activates central DA receptors to produce hypotension and bradycardia in rats.

In recent years dopamine (DA) receptors in the central nervous system and in the vasculature have been shown to mediate sympathoinhibitory and vasodilatory actions (see Lokhandwala & Barrett 1982). These discoveries have led to the search for DA receptor agonists that would be useful in the treatment of a variety of cardiovascular disturbances.

This laboratory has been interested in developing selective DA analogues which have low emetic liability, are effective following oral administration, and which could be useful therapeutic agents. Our structure-activity investigations have revealed the unexpectedly potent central dopaminergic actions of RDS-127 [2-di-n-propylamino-4,7-dimethoxyindane, I] in rats (Arnerić et al 1983). RDS-127 has



RDS-127
I

central DA receptor agonist properties which are more potent and of longer duration than apomorphine. Like the ergot alkaloids, RDS-127 is effective following oral administration, yet it is less emetic than apomorphine, bromocriptine, lergotrile or pergolide (Arnerić & Long 1983). RDS-127 has been shown to potently inhibit sympathetic neurotransmission to the heart of cats by activating peripheral presynaptic DA receptors (Sindelar et al 1982). Although RDS-127 has potent central dopaminergic actions and peripheral antihypertensive capabilities, it is unknown whether, like apomorphine or dipropyldopamine (Barnett & Fiore 1971; Cavero et al 1981; Finch & Hersom 1976), RDS-127 has any cardiovascular effects that are mediated by central DA receptors. We now report its effects on arterial pressure and heart rate in anaesthetized rats following i.v. or i.v.c. administration.

MATERIALS AND METHODS

Male Sprague-Dawley rats (175–250 g) were anaesthetized with chloral hydrate (400 mg kg^{-1} i.p.). Cannulae were acutely implanted in the jugular vein (i.v.) and in the lateral cerebral ventricle (i.c.v.) for drug administration. The cannula in the lateral ventricle was implanted stereotaxically (nose bar, −4·0 mm; posterior from bregma 1·5 mm; lateral 1·5 mm; vertical from dura) and drugs were given in a volume of 3 μl. Central injection sites were confirmed histologically by injection of an equivalent volume of Fast Green dye after the experiment. All compounds were dissolved in 0·9% NaCl (saline). Solutions given i.v. were administered as a bolus dose in a volume of 1 ml kg^{-1}. When used, antagonists were administered 15 min before RDS-127. The antagonist experiments were performed in separate groups of animals. The carotid artery was cannulated and arterial blood pressure was monitored using a Beckman 511 recorder and Statham (P23Cb) transducer. Integrated heart rate was measured with a Beckman Model 9811 Cardiotachometer.

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Data were analysed by analysis of variance. Treatment differences were detected by using Duncan's new multiple range test (Steel & Torrie 1960). A 3 × 3 parallel line bioassay by Finney (1952) was used to determine parallelism and the potency ratios. The probability level of $P < 0.05$ was chosen as the criterion of statistical significance. Values reported in the text and figures are the mean ± s.e.m.

A detailed procedure for the synthesis and structural verification of RDS-127 is given by Sindelar et al (1982). Apomophine hydrochloride, chloral hydrate and atropine methyl nitrate were purchased from Sigma; haloperidol from McNeil; and phentolamine hydrochloride was a gift from Ciba-Geigy. Chloral hydrate was dissolved in distilled water.

RESULTS

RDS-127 given i.v. produced dose-dependent bradycardia and a slight accompanying hypotension (Fig. 1B). The decrease in blood pressure did not appear dose-related. The mean changes in mean arterial pressure and heart rate from pre-drug values were determined approximately 3–4 min following RDS-127 (Fig. 1C, D, respectively). The duration of these effects ranged from 15–30 min depending on dose.

Haloperidol (0·2 mg kg^{-1} i.v.) totally abolished the bradycardic effect of RDS-127, while phentolamine (0·5 mg kg^{-1} i.v.) had no significant effect (Fig. 1D). Methylatropine (0·5 mg kg^{-1} i.v.) did not prevent the bradycardic effect of low doses of RDS-127, whereas the effect of a higher dose of RDS-127 was significantly attenuated. The basal heart rates 15 min after the antagonist pretreatments were not significantly different from control [saline (control): 395 ± 15 beats min^{-1}; haloperidol: 426 ± 20 beats min^{-1}; methylatropine: 402 ± 23 beats min^{-1}; phentolamine: 399 ± 16 beats min^{-1}]. It was found that phentolamine and methylatropine did not modify the hypotensive effects of RDS-127 whereas haloperidol blocked the effect (Fig. 1C). Mean arterial pressures 15 min after antagonists were not different from control for haloperidol and methylatropine, but was significantly reduced with phentolamine, $P < 0.05$ [saline (control): 80 ± 3 mmHg; haloperidol: 78 ± 3 mmHg; methylatropine: 75 ± 4 mmHg; phentolamine: 52 ± 3 mmHg].

The cardiovascular effects of RDS-127 were qualitatively similar following i.c.v. administration (Figs 2A, 3A, B). However, the bradycardic effects of RDS-127 were 20·5 more potent when given i.c.v. than when given i.v. (Fig. 2B). Haloperidol given i.v. reversed the effects of centrally administered RDS-127 (Fig. 2A). Haloperidol (0·01 mg kg^{-1}) administered i.c.v. prevented the previously observed effects of RDS-127 given i.c.v. and converted the bradycardic and depressor actions of RDS-127 into tachycardic and pressor responses, respectively (Fig. 3A, B).

DISCUSSION

This study indicates that in normotensive, anaesthetized rats, RDS-127 interacts with DA receptors in the central nervous system to primarily produce bradycardia. The results obtained with methylatropine suggest that at low doses of RDS-127 bradycardia is mediated by decreased sympathetic transmission to the heart, whereas cholinergic effects

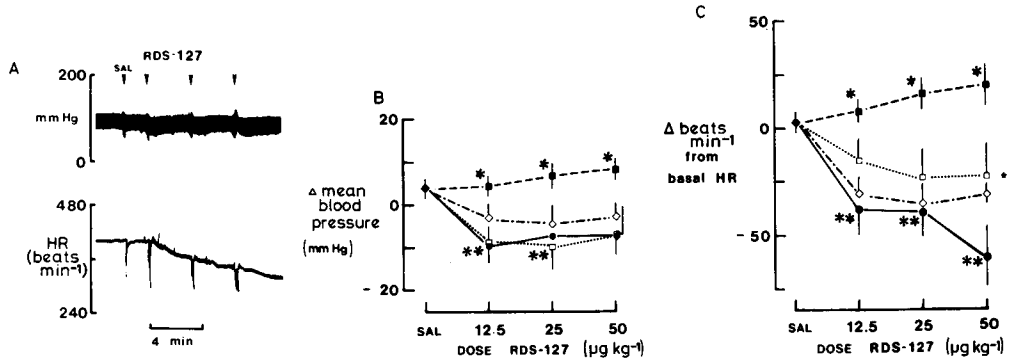

FIG. 1.A. Arterial blood pressure and integrated heart rate tracing from an anaesthetized rat receiving RDS-127. RDS-127 was given in a cumulative dose of 12·5, 25·0 and 50·0 μg kg^{-1} i.v. Note that saline (SAL) administration had no apparent effect on heart rate or blood pressure. B. Effect of increasing doses of RDS-127 on mean arterial pressure changes. Treatments were: control (saline) + RDS-127, n = 6–11 (●); haloperidol + RDS-127, n = 6 (■); phentolamine + RDS-127, n = 4 (◇); methylatropine + RDS-127, n = 4 (□). ** Indicates the value is statistically decreased from the basal value, $P < 0.05$. C. Effect of increasing doses of RDS-127 on changes in heart rate. Treatments are the same as designated in panel C. ** Indicates the value is statistically decreased from the basal value, $P < 0.05$. * Indicates the value is statistically different from the saline + RDS-127 group, $P < 0.05$.

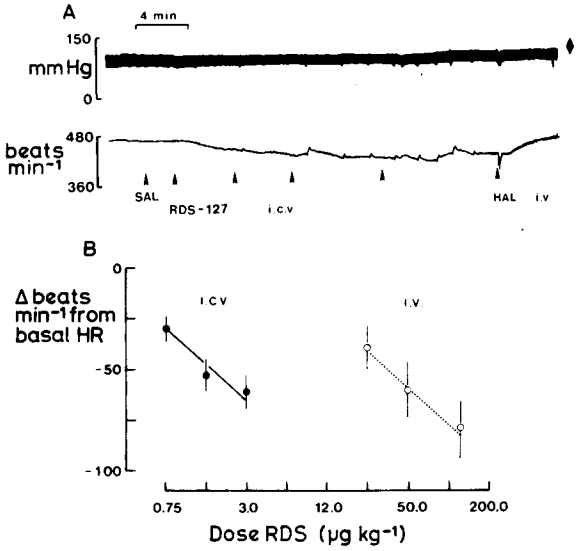

FIG. 2. A. Arterial blood pressure and integrated heart rate tracing from an anaesthetized rat receiving RDS-127 into the lateral ventricle. RDS-127 was administered in cumulative doses of 0·75, 1·5 and 3·0 μg kg^{-1}. Note that saline (SAL) given centrally had no apparent effect. Haloperidol (HAL, 0·2 mg kg^{-1}, i.v.) rapidly reversed the cardiovascular effects of RDS-127. B. The potency of RDS-127 to produce bradycardia following intracerebroventricular (i.c.v.) or intravenous (i.v.) administration. RDS-127 given i.c.v. is 20·5 times more potent than when given i.v. (n = 4).

become important only with higher doses. The results are consistent with other potent central dopaminergic actions of RDS-127 (Arnerić et al 1983).

A major reason for using chloral hydrate anaesthetized rats was to see whether cardiovascular alterations occurred in the same dose-range as the inhibitory action of RDS-127 on extracellularly recorded unit activity in the substantia nigra (Arnerić et al 1983). Recent evidence suggests that afferents from the substantia nigra innervate the medullary vasomotor centre (Ruggerio et al 1979), and that a descending dopaminergic pathway from the midbrain to the intermediolateral column of the thoracic spinal cord exists (Lindvall & Björklund 1982). Indeed, after finding that haloperidol pretreatment and spinal transection blocked the hypotensive action of apomorphine in cats, Barnett & Fiore (1971) suggested that a likely site of action for apomorphine would be in the midbrain area since there is a high concentration of dopamine in the substantia nigra, and there are many pathways for affecting blood pressure in this area. However, since the ID100 to inhibit unit firing was 3·0 μg kg^{-1} i.v., and the cardiovascular effects reported here occurred in the range of 12·5–50 μg kg^{-1} i.v., it is unlikely that the cardiovascular effects are associated in any way with the dopaminergic actions previously described for the nigrostriatal DA system.

The site(s) in the central nervous system where RDS-127 mediates the observed cardiovascular effects are unknown. The conclusion that RDS-127 is interacting centrally with DA receptors is drawn from the following evidence. First, RDS-127 is 20·5 time more potent when administered i.c.v. than when given i.v. Second, small injections of haloperidol (2·0–2·5 μg, i.c.v.) blocked the cardiovascular responses to centrally administered RDS-127.

It is unlikely that RDS-127 lowered heart rate by acting at peripheral DA receptors that decrease cardiac sympathetic transmission, since unlike the dog and cat (Long et al 1975), the rat does not have a pharmacologically functional complement of these receptors (Cavero et al 1981). However, it is posible that RDS-127 lowered heart rate through interactions with central sites. Compounds like *NN*-di-n-propyldopamine (DPDA) and apomorphine also act

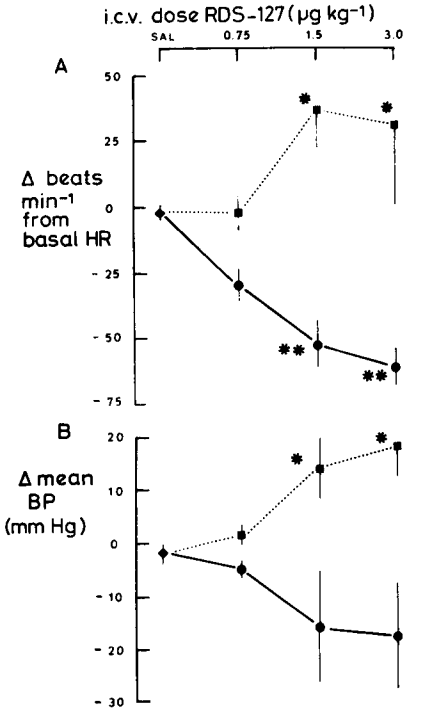

FIG. 3. A. Heart rate responses to RDS-127 given i.c.v. (●) and to RDS-127 after pretreatment with haloperidol (10 μg kg^{-1}, i.c.v.) 15 min before, n = 3–4 (■). B. mean arterial blood pressure responses to RDS-127 given i.c.v. (●) and to RDS-127 after pretreatment with haloperidol, n = 3–4 (■). ** Indicates the value is statistically decreased from the basal value, $P < 0·05$. * Statistically different from the saline + RDS-127 treated groups $P < 0·05$.

at central sites to inhibit sympathetic outflow and enhance efferent vagal activity to the heart (Cavero et al 1981; Dutta et al 1975; Finch & Haeusler 1973). Cavero and co-workers have suggested that the bradycardia produced by DPDA in the rat involves DA receptors which are located outside the blood-brain barrier since the effects were blocked by domperidone. Dutta et al (1975) have demonstrated that in the cat microinjections of apomorphine into the ventral medial hypothalamus or dorsal motor nucleus of the vagus produces a depressor response and bradycardia; an effect which was abolished by haloperidol pretreatment or by midcollicular transection. In contrast to the previous reports, Finch & Haeusler (1973) did not find haloperidol effective in blocking the cardiovascular effects of apomorphine in the rat. At the present time an explanation for these differences in results is not clear.

The weak hypotensive actions of RDS-127 could occur through interactions with pre- or postganglionic nerve ending to blood vessels (Buylaert et al 1977; Cavero et al 1981). However, if the hypotension was of central origin, phentolamine would be expected to block it by eliminating the influence of sympathetic vasoconstrictor tone. An alternative explanation of the mechanism by which RDS-127 could produce hypotension is reported for another DA receptor agonist, bromocriptine. Bromocriptine facilitates the release of adrenaline from the adrenal gland of rats to stimulate vascular β-adrenoceptors which produces vasodilation (Hamilton 1981). RDS-127 could also work through this mechanism since it has been shown to increase the release of adrenaline from the adrenal gland by interacting with DA receptors located in the hindbrain (Arnerić et al 1982a). The weak hypotensive action of RDS-127 in chloral hydrate anaesthetized animals may be due to the generally low baseline blood pressure produced by this anaesthetic. However, similar qualitative and quantitative effects are produced in urethane anaesthetized rats (unpublished). Interestingly, the hypotensive action of RDS-127 in barbitone anaesthetized dogs is much more pronounced (i.e. $10\,\mu g\,kg^{-1}$ i.v., lowers mean blood pressure 38 ± 5 mmHg, N = 4; unpublished) and of longer duration (30–60 min). Despite this marked depressor action in the dog, renal blood flow is decreased (unpublished) and on in-vitro preparations RDS-127 has a vasoconstrictor action which is equipotent to methoxamine (Arnerić et al 1982b). Therefore, the hypotensive action of RDS-127 requires further investigation.

The therapeutic application of DA analogues to treat cardiovascular disturbances is increasing (Lokhandwala & Barrett 1982). Compounds like bromocriptine, which have been suggested to act centrally to decrease sympathetic neurotransmission, are also useful for the treatment of essential hypertension in man (Kolloch et al 1980). The ability of RDS-127 to lower blood pressure and heart rate in various models of hypertension remains to be established.

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