Structure activity studies on dopamine receptors; a comparison between rat striatal adenylate cyclase and *Helix aspersa* neurones

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We have previously shown that certain neurones of the snail *Helix aspersa* are inhibited by dopamine; this effect is mediated by specific dopamine receptors (Woodruff & Walker, 1969; Woodruff, 1971). These results were confirmed by Struyker Boudier, Gielien, Cools & Van Rossum (1974) who also compared the dopamine receptors mediating inhibition with those causing excitation of other *Helix* neurones. The present study compares the structural requirements of the dopamine sensitive striatal adenylate cyclase with those previously determined on snail neurones.

The potency of each agonist in increasing cyclic AMP production in rat striatal homogenates was determined by the method of Kebabian, Petzold & Greengard (1972) and the resulting cyclic AMP measured according to Gilman (1970). Potency was expressed as a percentage of the maximum response produced by 100 μM dopamine. A log dose/response curve was constructed for each agonist from which the ED_{50} values were obtained.

In the absence of dopamine the mean production of cyclic AMP by 50 μl striatal homogenate was 36.3 ± 2.08 (21) p moles/tube. This was increased to 100.5 ± 5.4 (23) by 100 μM dopamine. The potency of various phenylethylamine derivatives as agonists on the striatal adenyl cyclase and on snail neurones are shown in Table 1.

The dopamine analogue 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) mimicked both inhibitory and excitatory actions of dopamine in the snail brain and was equipotent with dopamine in increasing cyclic AMP production. Ergometrine, a potent antagonist on snail neurones, was a partial agonist on the adenylate cyclase system causing a maximal stimulation of 63% at 10 μM.

These results demonstrate that there is a close similarity between the structural requirements for dopamine-like activity in rat striatum and snail neurones.

Table 1 The activity of drugs on rat striatal adenylate cyclase and *Helix aspersa* neurones

	ADENYLATE CYCLASE		*HELIX NEURONES*
Agonist	ED_{50} (μM)	*Equipotent Molar Ratio* (ED_{50} *agonist*/ED_{50} *dopamine*)	*Equipotent Molar Ratio (from Woodruff & Walker, 1969)*
Dopamine	3.2 ± 1.0*	1	1
Epinine	3.4 ± 0.5	0.94*	1
(−)-Noradrenaline	76.0 ± 15.8	24*	25
3,4-dihydroxy-5-methoxy phenylethylamine	96.0 ± 13.9	30	17
(−)-Adrenaline	201.0 ± 14.1	63	92
(±)-Isoprenaline	inactive	inactive*	inactive
(−)-Phenylephrine	inactive	inactive	inactive
3,5-dihydroxy-4-methoxy phenylethylamine	inactive	inactive	inactive
3-hydroxy-4,5-dimethoxy phenylethylamine	inactive	inactive	inactive

Values are the mean ± s.e. mean obtained from 4–8 observations.
All active compounds gave 100% stimulation.
* Similar values were obtained by Miller, Horn, Iversen & Pinder (1974) for these compounds.

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Contractile properties of hypertrophied and normal rat hearts

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Conflicting reports of contractility changes associated with cardiac hypertrophy are found in the literature. An unchanged (Grimm, Kubota & Whitehorn, 1963) reduced (Spann, Buccino, Sonnenblick & Braunwald, 1967) or increased (Kerr, Winterberger & Giambattista, 1961) contractility has been observed. We have compared the performance *in vitro* of hearts from hypertensive and normal rats to establish whether or not cardiac hypertrophy is associated with reduced contractility.

Renal hypertension was induced in male Wistar rats ($n=40$) according to the method of Finch & Leach (1970). A control group ($n=40$) consisted of unilaterally nephrectomized and sham-operated rats. At 5 weeks the mean systolic blood pressures, as measured by the tail cuff technique, were: controls 142.1 ± 4.2 mmHg, hypertensives 226.9 ± 6.0 mmHg (1 mmHg $\simeq$ 133 Pa). Rats were designated 'hypertensive' and included in the study only if their blood pressures were $>$ control + 3 standard deviations. The animals were killed by cervical fracture, the hearts removed and perfused with McEwens (1951) solution at 37°C gassed with O_2/CO_2 (95:5) according to a modified Langendorff technique described by Broadley (1970). Recordings of isometric developed tension were made by the method of Beckett (1970) using a Grass FT03C force-displacement transducer in conjunction with a Devices M19 recorder. The S-A node was destroyed and the hearts paced using bipolar platinum electrodes delivering rectangular pulses of 2.0 ms duration and 2.5 V from a Devices stimulator.

Force-frequency relationships of the 2 groups were examined over heart rates of 270–500 bts/min at a diastolic tension of 2 grams. The relationship between diastolic tension (0.25–20 g) and developed systolic tension was studied in hearts paced at 275 bts/min and the sensitivity of each group to the positive inotropic effects of $CaCl_2$ were studied in hearts paced at 275 bts/min with a diastolic tension of 2 grams. Finally, the hearts were removed from the perfusion apparatus and weighed. Mean dry weights of each group were: controls, 0.189 ± 0.007 g; 'hypertensives' 0.300 ± 0.017 grams. Water content was 81% in each case.

In the above procedures, tension developed by the hypertrophied hearts was less ($P < 0.05$) than controls either per gram diastolic tension, per bt/min or per equivalent dose of $CaCl_2$. However, if in the force-tension experiments diastolic tension was expressed per gram heart weight and developed tensions in the remaining two procedures, expressed as a percentage initial control tension, there was no difference between the performances of the two groups.

To investigate further this apparent relationship between heart weight and contractile performance, the same procedures were repeated using hearts from normal rats ranging in weight from 70 to 550 grams. Dry heart weight range was 0.068 ± 0.003 g to 0.309 ± 0.012 grams. On this basis, the hypertrophied hearts did not show a reduced performance compared with hearts of similar weights derived from normotensive rats.

We conclude that pressure overload induced cardiac hypertrophy in rats need not be associated with reduced contractility, but that the apparently reduced cardiac performance is similar to that of hearts of similar size from normal animals and is related to heart weight.

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