Brain-stem structures and catecholamines in the control of arterial blood pressure in the rat

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Summary
1. Noradrenaline, adrenaline and α-methylnoradrenaline administration into the nucleus tractus solitarii (NTS) of anaesthetized rats decreased blood pressure and heart rate in a dose-dependent fashion.
2. Bilateral injections were effective in lower doses than unilateral administration. α-Methylnoradrenaline given bilaterally produced hypotension in a dose of 0.08 nmol whereas after unilateral injection a dose of 0.32 nmol was needed to obtain the same degree of hypotension.
3. Electrical stimulation of the NTS caused hypotension and bradycardia. Conversely, bilateral electrolytic lesions or deafferentation of the NTS led to acute hypertension. Chronically such lesions caused neurogenic hypertension.
4. In spontaneously hypertensive rats increased concentrations of noradrenaline, adrenaline and dopamine were measured in the part of the NTS located just caudal to the obex (A2 region).

Key words: adrenaline, brain stem, central control of blood pressure, α-methylnoradrenaline, noradrenaline, nucleus tractus solitarii.

Introduction
It has been demonstrated that the nucleus tractus solitarii of the medulla oblongata plays an important role in the control of arterial blood pressure (Miura & Reis, 1969; Doba & Reis, 1973; Reis, Nathan & Doba, 1975). Reflex regulation and a tonic inhibitory control of blood pressure appear to be mediated via the NTS(1) to a substantial degree. Since central hypotensive drugs like α-methyldopa and clonidine may exert their action on the NTS (for review see Van Zwieten, 1973, 1975), we investigated the effects of local application of catecholamines in the area of the NTS. The effect of ablation of parts of the NTS was studied acutely as well as in a chronic experiment. In addition, the catecholamine content of different parts of the NTS was assessed by a sensitive radiochemical method which enabled the simultaneous assay of noradrenaline, adrenaline and dopamine.

Methods
Normotensive male rats of an inbred Wistar strain (Wi/CPb), spontaneously hypertensive rats and the normotensive Wistar/Kyoto control strain were used (de Jong, Nijkamp & Bohus, 1975a). Local application of the catecholamines in the area of the NTS of normotensive Wi/CPb rats was performed through a stereotaxically inserted stainless-steel needle (outer diameter 200 μm) or a glass cannula (outer diameter 60 μm) in a volume of 0.4–1.0 μl. All these experiments were performed under urethane anaesthesia (de Jong, 1974; Nijkamp & de Jong, 1975).

For the lesion and transection experiments normotensive Wi/CPb rats were anaesthetized with ether and placed in a stereotaxic apparatus. Bilateral lesions of selected regions were made as described previously (de Jong, Zandberg & Bohus, 1975b). Bilateral transections were performed with a glass microknife (de Jong & Palkovits, 1976). Immediately after the operation the wound was closed and the anaesthesia was ended. Blood pressure in the conscious rats was recorded from a permanent indwelling iliac cannula implanted under ether anaesthesia 20–24 h before the experiment (Nijkamp, Ezer & de Jong, 1975). Rats in which the effect of the lesion

(1) Abbreviation: NTS, nucleus tractus solitarii.

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was assessed chronically were pretreated with reserpine to prevent the acute fulminating hypertensive phase. A tail sphygmographic method was employed to measure blood pressure chronically.

For the catecholamine assays brains were taken out immediately after decapitation and were frozen on solid carbon dioxide. Sections (300 μm) were cut in a cryostat and the individual brain regions were removed with small punches. Catecholamines were assayed by an enzymatic-isotopic method for the simultaneous assay of noradrenaline, adrenaline and dopamine with a sensitivity of approximately 10 pg (Van der Gugten, Palkovits, Wijnen & Versteeg, 1976).

Results

Microinjections of (−)-noradrenaline, (−)-adrenaline and (−)α-methylnoradrenaline bilaterally into the NTS decreased blood pressure and heart rate. Maximal effects were reached within 5–10 min and lasted 20–60 min. The effects were dose-dependent. α-Methylnoradrenaline was more potent than noradrenaline and adrenaline (de Jong et al., 1975a). Bilateral application was more effective than unilateral administration. The lowest dose of α-methylnoradrenaline which caused a significant decrease in blood pressure after bilateral administration was 0.08 nmol. Bradycardia occurred with a dose of 1.25 nmol. After unilateral administration these doses were respectively 0.32 nmol and 20 nmol. The effect of the catecholamines on cardiovascular functions were stereospecific, since the (+)-stereoisomers of noradrenaline and α-methylnoradrenaline were without effect (Fig. 1).

Electrical stimulation of the NTS caused hypotension and bradycardia (de Jong et al., 1975a, b). The most effective site appeared to be just caudal to the obex at the location where microinjection of α-methylnoradrenaline also showed a maximal effect. This area corresponds to the A2 region at the level of the caudal tip of the area postrema. The more caudal structures of the NTS (nucleus commissuralis) were not sensitive to α-methylnoradrenaline.

Bilateral lesions of the NTS caused an acute elevation of mean blood pressure to 160–180 mmHg compared with a control value of 100–110 mmHg. This acute hypertension was prevented by anaesthesia. The lesions were located just rostral from the A2 region. Deafferentation of the NTS by bilateral transections in the dorsal medulla just lateral to the NTS resulted in a similar degree of hypertension to that caused by the lesions. Chronically, bilateral lesions of the NTS caused hypertension with a slight increase of heart rate. No increase in heart weight was observed.

Discussion

The present data again provide evidence for the important role of the NTS in cardiovascular regulation. Bilateral lesions of the NTS or deafferentation
elicits severe acute hypertension. Chronically, lesions of the NTS also caused hypertension. This hypertension may be neurogenic because there was no increase in heart weight. In contrast, electrical stimulation or local injection of (−)-noradrenaline, (−)-adrenaline or (−)-α-methylnoradrenaline caused hypotension and bradycardia. The most effective area appeared to be the A2 region. The (+)-stereoisomers of noradrenaline and α-methylnoradrenaline were ineffective. These data may indicate that the central inhibitory control of blood pressure may be funnelled in this region and also that stereospecific catecholaminergic inhibition of cardiovascular functions may be mediated in this part of the NTS. The A2 region of the NTS contains noradrenergic cell bodies and terminals but it also appears to contain a relatively high content of adrenaline (Van der Gugten et al., 1976). Although convincing evidence for a selective role of brain adrenaline in cardiovascular control is lacking, and our microinjection data also do not show a great difference between the effects of noradrenaline and adrenaline, the elevation of the adrenaline level in the A2 region of spontaneously hypertensive rats in combination with that of noradrenaline and dopamine is interesting. Elevations in noradrenaline concentration were not restricted to the A2 region but also occur in other medullary areas. Further studies will be necessary to evaluate the importance of these observations for central cardiovascular control. Preferably, catecholamine metabolism in individual brain nuclei in the medulla and other brain areas should be studied during the development of hypertension.

References


