Chronic lability of arterial pressure in the rat does not evolve into hypertension

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Summary
1. In rats, electrolytic lesions of the A2 group of catecholamine neurons result in lability of arterial pressure without hypertension.

2. To establish whether labile arterial pressure, when chronic, will lead to fixed hypertension, we placed lesions in the A2 area of adult male Sprague–Dawley rats and measured mean arterial pressure, heart rate and their variability (expressed as the standard deviation) 11 months later. Controls were age-matched, unoperated or sham-operated rats.

3. In rats with A2 lesions: (a) the mean arterial pressure was lower (103 ± 7.5 mmHg; n = 6; P < 0.05) than in sham-operated (123 ± 4.7 mmHg; n = 4) or unoperated (120 ± 3.1 mmHg; n = 9) controls; (b) the standard deviation of mean arterial pressure was higher (16 ± 1.8 mmHg; P < 0.001) than in sham-operated (5 ± 0.7 mmHg) or unoperated controls (7 ± 0.6 mmHg); (c) the mean and standard deviation of heart rate did not differ between groups. No histopathological changes were detected in the A2 group.

4. Chronic lability of arterial pressure does not evolve into sustained hypertension nor does it induce systemic lesions.

Key words: arterial pressure, baroreceptor, catecholamine neurons, hypertension, lability.

Introduction
Chronic lability of arterial pressure is a recognized clinical phenomenon in man (Eich, Cuddy, Smulyan & Lyons, 1966; Frohlich, Tarazi & Dushman, 1969) and may be a precursor of sustained hypertension. We have recently produced a model of chronic lability of arterial pressure in rats by making selective lesions (Snyder, Nathan & Reis, 1978; Talman, Snyder & Reis, 1980) of the noradrenergic innervation (Torack, Stranahan & Hartman, 1973) of the nucleus tractus solitarii, the primary site of termination of the afferent fibres of baroreceptor nerves (Miura & Reis, 1972). The noradrenergic cells of origin of much of that innervation comprise the A2 cell group (Dahlstrom & Fuxe, 1964), which is located in the medial and commissural portions of the nucleus tractus solitarii. Destruction of either the A2 neurons (Talman et al., 1980) (by electrolytic lesions) or the terminals of their axons in the nucleus tractus solitarii (Snyder et al., 1978) (by local injection of 6-hydroxydopamine) causes the arterial pressure to become extremely labile. The average of the arterial pressures chronically recorded for 1 h periods after A2 lesions is not elevated and there are no changes in heart rate. The lability of arterial pressure persists for at least 2 weeks (Talman et al., 1980).

In the present study we have sought to determine whether rats with A2 lesions will develop hypertension if they are allowed to survive for 1 year after the lesion.

Methods
These studies were performed in 32 male Sprague–Dawley rats aged 2–3 months at the time of surgery. Electolytic lesions were placed in the A2 area of 17 rats by methods described elsewhere (Talman et al., 1980). Five sham-operated control rats were prepared by exposing the brain stem and inserting an electrode into A2 without making an electrolytic lesion. The ten additional rats served as unoperated controls. The rats were housed four to five animals to a cage in thermostatically controlled rooms with cycled
lighting. They were fed standard laboratory chow ad libitum.

Eleven months after the placement of lesions, cannulae were inserted in a jugular vein for administering drugs and in the left carotid artery for the chronic recording of arterial pressure and heart rate as described previously (Snyder et al., 1978; Talman et al., 1980). The day after instrumentation mean arterial pressure and heart rate were measured for 1 h in the undisturbed animals. The data were fed into a computer for determination of the mean and variability, expressed as the standard deviation, of mean arterial pressure and heart rate. The cardiovagal component of the baroreflex was tested by administration of phenylephrine intravenously and the slope of the curve defining the relationship of the interbeat interval to the arterial pressure was calculated by computer.

After measurement of physiological variables, rats were anaesthetized and immediately killed by removal of the heart. The right superior cervical ganglion and the adrenal glands were removed, and the adrenal medulla was separated from the cortex. Tissues were frozen at -70°C and subsequently analysed for the activities of the enzymes tyrosine hydroxylase, dopamine-β-hydroxylase, phenylethanolamine-N-methyltransferase and choline acetyltransferase by methods established in this laboratory (Reis, Ross & Joh, 1977). The heart, lungs, kidneys, brain and the arch of the aorta were fixed in 10% formalin for subsequent histological examination.

Results

Seven of 17 rats with A2 lesions, four of five with sham lesions and nine of ten without lesions survived for 11 months. The total body weight of the A2 animals was significantly less (\( P < 0.02 \)) than that of control animals (control weight 659 ± 32.1 g; sham control weight 692 ± 1.7 g; A2 weight 440 ± 34.2 g, mean ± SEM). All rats with A2 lesions exhibited significantly (\( P < 0.001 \)) increased lability of mean arterial pressure (Fig. 1), exemplified by an increased standard deviation of the mean arterial pressure (control 6.7 ± 0.6 mmHg; sham 4.7 ± 0.7 mmHg; A2 15.7 ± 1.8 mmHg). The mean arterial pressure of A2 rats (103 ± 7.5 mmHg) was significantly lower (\( P < 0.05 \)) than that of control (120 ± 3.1 mmHg) or sham-operated rats (123 ± 4.7 mmHg). Heart rate and its variability were unchanged. In rats with A2 lesions the cardiovagal component of the baroreflex was reduced to 10% of control.

No histopathological changes were detected in the aorta, kidneys, renal arteries or hearts of rats with A2 lesions.

Since chronic sympathetic nerve activity can, over time, lead to an increase in the activities and the amounts of enzymes subserving neurotransmitter biosynthesis in the adrenals and sympathetic ganglia (Reis & Joh, 1978), we measured the activities of tyrosine hydroxylase, dopamine-β-hydroxylase and choline acetyltransferase in the superior cervical ganglion and these enzymes plus phenylethanolamine-N-methyltransferase in the adrenal medulla. There were no significant differences in the activities of any of these enzymes in animals with A2 lesions as compared with their controls.

Discussion

Previous investigations have indicated that the noradrenergic innervation of the nucleus tractus solitarii plays an important role in the modulation of baroreflexes and in the phasic control of arterial pressure (DeJong & Nijkamp, 1976; Snyder et al., 1978; Talman et al., 1980). The results of the current investigation confirm that electrolytic lesions of the A2 neurons in rats result in lability of arterial pressure without an elevation of the average arterial pressure or a change in the average heart rate or its variability. The lability of arterial pressure is apparently permanent and does not, over the course of 11 months, lead to established hypertension. A2 lesions virtually eliminate the cardiovagal component of baroreflexes but leave the vasodepressor component completely intact, thus centrally dissociating the integration of cardiovagal and sympatho-inhibitory baroreflex activity (Talman et al., 1980). The absence of an elevation of average blood pressure after nearly 1 year of persistent lability may relate to this preservation of vasodepressor reflex function. Another possible explanation for the lack of an elevation of blood pressure is that the pressure, though labile, never was sufficiently high to induce vascular changes which might perpetuate the hypertension (Folkow, 1971). Finally the animals with A2 lesions may have failed to develop hypertension because they did not maintain their nutrition or fluid balance. Against this possibility is the lack of evidence of malnutrition on pathological examination.

The study indicates that lability of arterial pressure by itself does not necessarily evolve into hypertension or lead to histological changes in the heart, kidneys or blood vessels.
Control

A2 lesion

Arterial pressure (mmHg)

Mean arterial pressure (mmHg)

Heart rate (beats/min)

FIG. 1. Chronic effects of A2 lesions on arterial pressure in the rat. The unoperated control rat and rat with A2 lesions of the same age were maintained for 11 months under identical conditions after placement of the lesion. Note the variability (lability) of arterial pressure with no appreciable change in heart rate.

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References


