Blood pressure and heart rate responses to centrally administered substance P are increased in spontaneously hypertensive rats

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Summary

1. The cardiovascular effects after intracerebroventricular injections of substance P were investigated in normotensive Wistar–Kyoto and in spontaneously hypertensive rats.

2. Substance P increased blood pressure in both rat strains. Wistar–Kyoto rats responded with moderate, dose-dependent blood pressure increases, and heart rate decreased; spontaneously hypertensive rats showed two- to three-fold increased pressor effects and, concomitantly, marked heart rate increases to intracerebroventricular injections of substance P.

3. Sino-aortic baroreceptor denervation rendered Wistar–Kyoto rats supersensitive to intracerebroventricular substance P to a similar degree as unoperated spontaneously hypertensive rats. Sino-aortic denervation had no effect on the blood pressure responses to the peptide in spontaneously hypertensive rats.

4. The central pressor actions of substance P could be markedly attenuated by intracerebroventricular pretreatment with the derivative of γ-aminobutyric acid, baclofen.

5. We conclude that the baroreceptor reflex is disturbed in spontaneously hypertensive rats. Substance P may contribute to the pathogenesis of hypertension. The effector pathways appear to be different from angiotensin.

Key words: baclofen, baroreceptor reflex, blood pressure, brain, substance P.

Introduction

The undecapeptide substance P has a broad spectrum of biological activities (von Euler & Pernow, 1977) and is found mainly in central and peripheral nervous tissue (Hökfelt, Elde, Johansson, Ljungdahl, Schultzberg, Fuxe, Goldstein, Nilsson, Pernow, Terenius, Ganten, Jeffcoate, Rehfeld & Said, 1978) as well as in the intestine (Polak & Pearse, 1976). Substance P has long been known for its hypotensive action after its peripheral administration (von Euler & Gaddum, 1931). Recent data demonstrate the localization of substance P in brain areas which are involved in blood pressure control (Hökfelt et al., 1978), and some central pressor activity of this peptide has been reported (Agnati, Fuxe, Bolme, Lundberg & Hökfelt, 1979). However, its brain-mediated effects on the cardiovascular system have not been investigated in any detail.

In this study we investigated the brain-mediated cardiovascular effects of substance P by injecting the peptide into the lateral brain ventricle of conscious normotensive and spontaneously hypertensive rats. The role of the baroreceptor reflex in these responses was studied in sino-aortic baroreceptor-denervated animals, and the involvement of pathways involving γ-aminobutyric acid was investigated by blockade of the central cardiovascular effects of substance P by the γ-aminobutyric acid derivative baclofen.

Material and methods

Animals

Adult male and female spontaneously hypertensive rats of the Wistar–Kyoto stroke-prone
strain (SH-sp rats), bred in Heidelberg since 1974, were used. Strictly age- and sex-matched normotensive Wistar-Kyoto (WK) rats served as controls. Body weight was 250–300 g.

**Test Procedures**

Cannulation of the lateral brain ventricle and arterial catheterization for direct blood pressure recording were performed as described elsewhere (Schaz, Stock, Simon, Schlör, Unger, Rockhold & Ganten, 1980). Arterial blood pressure and heart rate were monitored with a Statham P 23 Db transducer connected to a Gould Brush blood pressure computer and Brush 2400 polygraph, while the animals were conscious and freely moving in a wooden box (20 cm x 12 cm x 11 cm). Changes in mean arterial blood pressure were evaluated. Heart rate was calculated from the pulse pressure wave by the computer.

Four different experimental groups were studied.

**Group 1.** SH-sp rats (n = 8) and WK control rats (n = 9) received the following bolus injections of substance P into the lateral brain ventricle: O (saline control), 0-07, 0-7, 7 or 35 nmol dissolved in 0-9% sodium chloride solution (saline). Injection volumes were 1-5 µl, flushed with 3 µl of saline. The next injection was given only after return of blood pressure and heart rate to baseline levels.

**Group 2.** SH-sp rats (n = 8) and WK rats (n = 9) had bilateral sino-aortic denervation with procedure described by Krieger & Marseillan (1963). Control SH-sp rats (n = 6) and WK rats (n = 9) were sham-operated. After complete recovery (3-4 weeks after the operation) these groups underwent the same protocol as described for group 1.

**Group 3.** SH-sp rats (n = 13) received injections of 7 nmol of substance P into the lateral brain ventricle. After blood pressure had normalized, the rats were randomly injected intracerebroventricularly with either 0-5 nmol of β-(4-chlorophenyl)-γ-aminobutyric acid (baclofen) in 1 µl of saline (n = 6) or with the appropriate volume of the vehicle (n = 7). Five minutes later the first injection of substance P was repeated. The dose of 0-5 nmol of baclofen had previously been found to have no effects on blood pressure and heart rate by itself when injected into the brain ventricle.

**Group 4.** SH-sp rats (n = 6) underwent the same protocol as described for group 2, but angiotensin II (ANG II) (100 pmol) was administered instead of substance P.

**Drugs**

Substance P was purchased from Bachem Chemicals, Bubendorf, Switzerland. Baclofen was generously supplied by CIBA-GEIGY AG, Grenzach, F.R.G. ANG II was purchased from CIBA-GEIGY AG, Basle, Switzerland.

**Statistics**

Student’s two-tailed t-test was applied when appropriate, and a significance level of P < 0.05 was accepted. Results are reported as means ± SEM.

**Results**

**Intraventricular injections of substance P**

Injection of substance P into the lateral brain ventricle caused dose-dependent increases in mean arterial blood pressure in SH-sp and WK rats. These were three times higher in SH-sp rats (maximal responses 60 ± 3.6 mmHg) than in normotensive WK rats (18.1 ± 4.1 mmHg). In both strains, the rise in blood pressure after 7 nmol of substance P lasted for more than 10 min and up to 35 min after the highest dose, 35 nmol of substance P.

In WK rats, heart rate increased to the smallest dose (0.07 nmol), but then decreased dose-dependently with a maximal fall of 77.1 ± 9.4 beats/min after 35 nmol of substance P. In SH-sp rats, heart rate increased in response to all doses of substance P in a dose-independent manner.

**After sino-aortic denervation (Table 1).** The pressor effects of substance P were markedly increased in denervated WK rats, when compared with sham-operated WK rats. In contrast, the pressor responses to substance P were not different in denervated and sham-operated SH-sp rats. Denervated WK and SH-sp rats exhibited almost identical dose–response curves to intraventricular substance P.

**After pretreatment with baclofen.** The pressor responses to substance P in SH-sp rats were markedly attenuated by pretreatment with baclofen. In these rats, the increase in mean arterial blood pressure after 7 nmol of substance P was 31.8 ± 3.4 mmHg before, and 9.2 ± 1.1 mmHg after, administration of baclofen (P < 0.001). The heart rate responses were reversed from +139.2 ± 10.7 beats/min before to −31.7 ± 15.6 beats/min after baclofen treatment. When saline was injected instead of baclofen, the second blood pressure response to substance P was not different from the first one (30.6 ± 6.3 vs 29.7 ± 6.8 mmHg), indicating that no tachy-
physiological to repeated injections of substance P had occurred.

Baclofen (0.5 nmol) had no inhibitory effect on the pressor responses to ANG II injected into the lateral brain ventricle. Neither did a tenfold higher dose of the inhibitor (5 nmol), which by itself had marked blood pressure-increasing effects, alter the pressor responses to intraventricular ANG II.

Discussion

Our results demonstrate that substance P is a central pressor peptide. This is in agreement with a report by Agnati et al. (1979), who injected the peptide into the cisterna magna in chloralose-anaesthetized rats.

In contrast to the polyphasic pattern of blood pressure changes seen after intravenous injection of substance P (Unger, Rockhold, Schaz & Ganten, 1979), the blood pressure changes after intracerebroventricular application were unequivocal increases in normotensive as well as in spontaneously hypertensive rats.

SH-sp rats showed a marked supersensitivity to centrally applied substance P, as has previously been shown for angiotensin (Hoffman, Phillips & Schmid, 1977). Interactions of substance P with the sympathetic nervous system (Magnussen, Carlsson, Fischer, Chang & Folkers, 1976) or with ADH could account for this finding, since both systems have been reported to be stimulated in spontaneously hypertensive rats (Mohring, 1978; Schöning, Dietz, Rascher, Lüth, Mann, Schmidt & Weber, 1978) but altered baroreceptor function has to be considered as well.

The lack of a decrease in heart rate associated with the blood pressure increase suggests a change of baroreceptor reflexes in SH-sp rats. This is in contrast to normotensive WK rats, which responded with a fall of heart rate to blood pressure increases. Baroreceptor denervation rendered normotensive WK rats as supersensitive as SH-sp rats to the central pressor actions of substance P, whereas the hypertensive animals had unchanged responses to the peptide after sino-aortic denervation. This provides further evidence that there is altered baroreceptor function in the spontaneously hypertensive rats.

The \( \gamma \)-aminobutyric acid derivative baclofen has previously been reported to antagonize substance P effects on depolarization of spinal neurons (Saito, Konishi & Otsuka, 1975), on guinea-pig ileum contraction (Fotherby, Morrish & Ryall, 1976) and on excitation of cerebral neurons in the locus coeruleus (Guyenet & Aghajanian, 1979). In this study we have shown that baclofen also greatly diminishes the central pressor effects of substance P; the blood pressure increases to central angiotensin were unaffected by this inhibitor but can be antagonized by specific inhibitors of the renin-angiotensin system (Phillips, Felix, Hoffman & Ganten, 1977; Mann, Rascher, Dietz, Schöning & Ganten, 1979). Thus it appears that different pathways are involved in eliciting the central cardiovascular responses to angiotensin and substance P.

Acknowledgments

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References


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### Table 1. Effect of sino-aortic baroreceptor denervation on pressor effects of substance P injected into the lateral brain ventricles of WK and SH-sp rats

<table>
<thead>
<tr>
<th>Substance P(nmol)</th>
<th>0.07</th>
<th>0.7</th>
<th>7</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>WK rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>6.7 ± 1.9</td>
<td>11.0 ± 0.7</td>
<td>14.7 ± 1.8</td>
<td>21.7 ± 2.6</td>
</tr>
<tr>
<td>Denervated</td>
<td>8.0 ± 2.6</td>
<td>22.9 ± 2.3</td>
<td>36.8 ± 4.2</td>
<td>44.1 ± 5.0</td>
</tr>
<tr>
<td>SH-sp rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>5.2 ± 2.3</td>
<td>17.5 ± 2.6</td>
<td>27.3 ± 4.0</td>
<td>43.7 ± 2.3</td>
</tr>
<tr>
<td>Denervated</td>
<td>12.3 ± 2.6</td>
<td>22.4 ± 2.5</td>
<td>37.3 ± 4.2</td>
<td>42.8 ± 4.1</td>
</tr>
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