Time-course of the reduction of baroreceptor sensitivity in experimental hypertensive rabbits

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Summary

1. Hypertension was produced experimentally in three groups of rabbits by atherosclerosis, medial sclerosis and renal encapsulation.

2. The sensitivity of afferent baroreceptor fibre recordings, obtained from an isolated perfused aortic arch preparation, was reduced in all three treated groups.

3. The reduction of baroreceptor sensitivity was directly related to the increase in the lability of the blood pressure in the intact animal and to the reduction of the distensibility of the perfused region.

4. There was a closer relationship between the length of time the rabbits had been hypertensive and the reduction in the baroreceptor sensitivity, than to the level of their blood pressure.

5. The reduction of baroreflex sensitivity obtained by the infusion of phenylephrine was also directly correlated with the period of the hypertension.

6. Baroreceptor resetting occurred to a higher pressure in the renal hypertensive group.

Key words: atherosclerosis, baroreceptors, baroreflex, distensibility, hypertension.

Introduction

Baroreceptor resetting to a higher pressure occurs within hours in rats (Krieger, 1970), or days in dogs (McCubbin, 1958; Liard, Cowley, McCaa & Guyton, 1974) and rabbits (Aars, 1968) of the production of hypertension and is still present in chronically hypertensive rabbits (Angell-James, 1973).

Since the resetting lags behind the rise of pressure (McCubbin, 1958) the probability remains that baroreceptor dysfunction occurs as a result of the hypertension rather than being the cause of it, and that it may be modified by the length of time the animal has been hypertensive.

The time-course of baroreceptor resetting was investigated by studying single baroreceptor fibre activity in an isolated aortic arch preparation (Angell-James, 1971) and the reflex changes in pulse interval by the pressor test (Bristow, Honour, Pickering, Sleight & Smyth, 1969).

Methods

Rabbits

Four groups of New Zealand white rabbits were used: group 1, control; group 2, atherosclerotic; group 3, medial sclerotic; group 4, renal hypertensive (one encapsulated kidney). Their blood pressure was measured weekly with a Grant-Rothschild capsule. At the terminal experiment and at 4-weekly intervals it was measured directly from the central ear artery with an electromanometer.

Series 1

The rabbits were anaesthetized with urethane (17.5 mmol/kg body weight) 7–41 weeks after the commencement of their treatment. The aortic arch was isolated and perfused with Krebs–Henseleit solution (37–39°C) and single baroreceptor fibre activity was amplified and recorded during stepwise increases and decreases in perfusion pressure. Pressure–volume curves were obtained for the perfused region. Correlation coefficients were weighted to include the number of fibres studied.
in each rabbit. Full details of the method have been described previously (Angell-James, 1971, 1973, 1974a, b).

Series II

Twenty-one rabbits of group 1, thirteen of group 3 and eight of group 4 were given an injection of 5 and 10 µg/kg of phenylephrine at intervals of 4 weeks after their initial treatment. The elevation of the mean blood pressure this produced was plotted against the succeeding pulse interval, which was obtained from ECG recordings.

Results

Afferent baroreceptor experiments

The blood pressure became elevated in all the three treated groups of rabbits (Table 1). It was found that the amount of lability of the blood pressure observed during small body movements before the anaesthetic was directly related to the degree of the reduction of the sensitivity of the single baroreceptor fibres studied in the isolated perfused preparation (Table 1). The reduction of baroreceptor sensitivity was also directly related to the reduction in distensibility of the arterial wall.

Table 1. Results from rabbits of series I in which the aortic arch was isolated and perfused

<table>
<thead>
<tr>
<th>No. of rabbits</th>
<th>Group 1 (control)</th>
<th>Group 2 (atherosclerotic)</th>
<th>Group 3 (medical sclerotic)</th>
<th>Group 4 (renal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>2.2±0.12</td>
<td>3.4±0.2</td>
<td>3.5±0.3</td>
<td>3.3±0.22</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>85</td>
<td>87.9±6.5</td>
<td>87.2±3.7</td>
<td>87.5±5.6</td>
</tr>
<tr>
<td>Experimental lability</td>
<td>114.7±4.3</td>
<td>137.8±5.7</td>
<td>160.3±7.9</td>
<td></td>
</tr>
<tr>
<td>Experimental week</td>
<td>0–25</td>
<td>30–65</td>
<td>20–45</td>
<td></td>
</tr>
<tr>
<td>Baroreceptor fibres</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>29</td>
<td>70</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>Threshold pressure (mmHg)</td>
<td>52.5±5.5</td>
<td>57.9±5.1</td>
<td>37.8±3.8</td>
<td>106.5±5.8</td>
</tr>
<tr>
<td>Sensitivity (gradient: impulses s⁻¹ mmHg⁻¹)</td>
<td>1.19±0.14</td>
<td>0.73±0.07</td>
<td>0.61±0.05</td>
<td>0.64±0.06</td>
</tr>
<tr>
<td>Point of inflexion (mmHg)</td>
<td>112.4±4.6</td>
<td>109.6±4.6</td>
<td>95.0±4.6</td>
<td>163.4±5.1</td>
</tr>
<tr>
<td>Correlation coefficients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP/sensitivity</td>
<td>—</td>
<td>0.71</td>
<td>0.76</td>
<td>0.78</td>
</tr>
<tr>
<td>Time/sensitivity</td>
<td>—</td>
<td>0.96</td>
<td>0.95</td>
<td>0.91</td>
</tr>
<tr>
<td>Hysteresis (difference in frequency: impulses/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mmHg(1)</td>
<td>12.4±2.4 P&lt;0.01</td>
<td>19.1±4.2 P&lt;0.001</td>
<td>25.3±8.8 P&lt;0.02</td>
<td>22.4±5.3 P&lt;0.001</td>
</tr>
<tr>
<td>40 mmHg(1)</td>
<td>7.0±2.6 P&lt;0.02</td>
<td>11.5±2.9 P&lt;0.05</td>
<td>14.8±5.4 P&lt;0.05</td>
<td>9.6±4.2 P&lt;0.02</td>
</tr>
<tr>
<td>60 mmHg(1)</td>
<td>4.2±3.2 P&gt;0.2</td>
<td>8.1±2.9</td>
<td>20.4±8.0 P&lt;0.05</td>
<td>8.7±2.7 P&lt;0.02</td>
</tr>
<tr>
<td>80 mmHg(1)</td>
<td>—</td>
<td>6.2±2.7 P&gt;0.2</td>
<td>18.8±7.1 P&lt;0.05</td>
<td>7.7±2.7 P&lt;0.02</td>
</tr>
<tr>
<td>Pressure–volume curves</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Initial volume (ml)</td>
<td>0.7±0.07</td>
<td>1.18±1.9</td>
<td>1.34±0.16</td>
<td>0.86±0.9</td>
</tr>
<tr>
<td>Point of inflexion (% of initial volume)</td>
<td>350%</td>
<td>300%</td>
<td>125%</td>
<td>200%</td>
</tr>
<tr>
<td>Gradient of linear part of p-v curve (% Δvolume/mmHg)</td>
<td>4:1</td>
<td>2:1</td>
<td>1:4</td>
<td>1:7</td>
</tr>
</tbody>
</table>

(1) Pressures above original threshold.
in which the receptors were situated. Thus the sensitivity of the baroreceptors was least in group 3 and greatest in group 2, compared with the normal. The separation of the impulse frequency-pressure curves obtained when the perfusion pressure was first elevated and then lowered in steps was also most pronounced in group 3 and less obvious in group 2.

The threshold pressure of the aortic baroreceptors was found to be elevated in group 4. The amount of the resetting was related to the degree of the hypertension ($\chi = 0.93$). In all three treated groups there was a closer correlation between the reduction of the sensitivity of the receptors and the length of time since their initial treatment than to the actual level of their blood pressure (Table 1).

**Baroreflex experiments**

The sensitivity of the baroreflex obtained after injection of 5 $\mu$g/kg of phenylephrine in group 3 rabbits fell from a control value of 4.1 ± 0.28 ms/mmHg to 1.75 ± 0.26 ms/mmHg 16 weeks after the cessation of the treatment, and with 10 $\mu$g of phenylephrine it fell from a control value of 4.0 ± 0.31 ms/mmHg to 1.5 ± 0.15 ms/mmHg. Both doses of phenylephrine demonstrated a linear relationship between the reduction of the baroreflex sensitivity with time (correlation coefficients 0.97 and 0.99).

The correlation coefficients relating the change in blood pressure to the change in baroreflex sensitivity were 0.62 and 0.46. There was no resetting of this reflex to a higher heart rate.

In group 4, in which the blood pressure had increased from 84 mmHg (± 0.5) to 166 mmHg (± 6.3), the infusion of phenylephrine produced reductions in the baroreflex sensitivity from 4.5 ± 0.32 ms/mmHg to 2.0 ± 0.34 ms/mmHg with the lower dose, and from 4.3 ± 0.29 ms/mmHg to 2.2 ± 0.47 ms/mmHg with the higher dose during 16 weeks of hypertension. The correlation coefficient between baroreflex sensitivity and time was 0.85 and 0.84 for the two doses of phenylephrine in this group. The correlation coefficient relating the change of blood pressure to the reduction of baroreflex sensitivity was 0.80 and 0.72 for the two doses. This reflex was reset to a higher heart rate.

**Discussion**

Baroreceptor-denervated rabbits have abnormally labile blood pressures (Alexander & De Cuir, 1967), and the reduced baroreceptor sensitivity could account for the lability of the blood pressure in the present series of rabbits. This reduced baroreceptor sensitivity would explain, at least in part, the reduced reflex effects observed in groups 3 and 4 after the injection of phenylephrine, as in the aged hypertensive man (Gribbin, Peto, Pickering & Sleight, 1971).

The direct correlation found between the change in the characteristics of single baroreceptor fibre activity and the reduction in the distensibility of the aortic arch in these four groups of rabbits provides additional evidence for the close association between the receptors and the mechanics of the region in which they are situated (Aars, 1969; Angell-James, 1971; Koushanpour & Kelso, 1972). It has been shown (Kedzi, 1962) that it is the local effect of the high blood pressure that in some way resets the carotid sinus baroreceptors; even after 6 months the carotid sinus baroreceptors did not reset in the carotid sinuses which were protected from the high pressure in hypertensive dogs.

Baroreceptors are reset to a higher pressure after a short period of hypertension (Aars, 1968; Liard et al., 1974), and the reflex responses of group 4 had reset in 4 weeks. The explanation for the early resetting could be a combination of the direct effects of the high blood pressure and the early retention of sodium and water (Ledingham & Cohen, 1964; Tobian & Redlead, 1957; Conway, 1968; Swales, Thurston, Queiroz & Medina, 1972; Liard et al., 1974).

Prolonged hypertension results in the formation of pathological lesions (Pickering, 1968; Wolinsky, 1970; Angell-James, 1973, 1974a, b), which in association with the local electrolyte changes would explain the long-term baroreceptor resetting and reduction in sensitivity in the renal hypertensive group.

The explanation for the closer relationship between the reduction of baroreceptor activity and baroreflex sensitivity to the period of hypertension than to the level of the hypertension must lie in the progressive nature of the arterial lesions.

In experimental situations reduction of the hypertension resets the baroreceptors in a short period of time (1–6 h; Salgedo & Krieger, 1973) but there is also evidence that the longer the animals have been hypertensive the longer it takes them to reset (Blackett & Sellers, 1951; McCubbin, 1967). Such
evidence is an additional reason for controlling the level of hypertension in man.

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References


