A circulating humoral pressor agent in Dahl S rats with salt hypertension

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Summary

1. In Dahl S rats becoming hypertensive while on a diet of high NaCl content there appears to be a blood-borne humoral agent which produces vasoconstriction in a bioassay using the isolated hindquarters of rats.

2. This vasoconstrictor effect strongly suggests the presence of a humoral pressor agent or the lack of a vasodilator agent in the blood of hypertensive S rats.

3. The vasoconstrictor effect is not due to high renin concentrations.

4. This humoral vasoconstrictor action could partly account for the high vascular resistance in the hypertensive S rat.

Key words: humoral pressor agent, vasoconstriction.

Introduction

Human essential hypertension appears to have a definite relationship to NaCl in the diet. For instance, a life-long low intake of NaCl, with less than 60 mmol/day, is associated with a virtual absence of essential hypertension even among human subjects susceptible to it (Kean, 1944; Lowenstein, 1961; Maddocks, 1967; Prior, Evans, Harvey, Davidson & Lindsey, 1968; Shaper, 1972; Page, Danion & Moellering, 1974; Sinnett & Whyte, 1973; Oliver, Cohen & Neel, 1975). In established essential hypertension, a diet very low in Na⁺ or the use of natriuretic drugs often brings blood pressure into the normal range. Moreover, a very high intake of NaCl, 800 mmol/day, will cause a rise of blood pressure even in normotensive subjects (Murray, Luft, Block & Weyman, 1978). In essential hypertension a combination of genetic susceptibility and a reasonably high salt intake is needed to bring about the abnormal rise in blood pressure. The mechanism of this pressure rise is only partly understood. There is ultimately an increase of peripheral vascular resistance to account for most of the hypertension. In young human hypertensive subjects there is often a transient increase in resting cardiac output to account for part of the hypertension. In order to study the manner in which a high salt intake produces hypertension in a susceptible subject, we utilized the Dahl S rat, which has great sensitivity to NaCl hypertension (Dahl, Heine & Tassinari, 1962). For comparison, the Dahl R rat was also studied, since it has a very great resistance to NaCl hypertension (Dahl et al., 1962). Takeshita & Mark (1978) have indicated that the sympathetic nervous system can account for half of the increase in peripheral vascular resistance in the hypertensive S rat. We have searched for humoral vasoconstrictor agents which could possibly account for the other half of the increase in peripheral vascular resistance in these hypertensive S rats.

Methods

We fed both S and R rats, at 8–12 weeks of age, a high (8%) NaCl diet for 4 weeks to bring out their essential difference. After 4 weeks of the high salt diet, the S rats were already developing hypertension with an average blood pressure of 176 mmHg. After 4 weeks of the same high salt diet the R rats remained normotensive with an average blood pressure of 142 mmHg.
To search for vasoconstrictor agents, we used for bioassay the isolated hindquarters from R rats that had been on an high salt (8%) diet for 1 month. The hindquarters of the bioassay rat were connected to the circulation of the perfusing rat artery-to-artery and vein-to-vein, without any transient ischaemia. A constant-flow pump was used to supply arterial blood to the hindquarters. Venous blood returning from the hindquarters was pumped back to the perfusing rat. Once the connections had been made, a large alligator clamp was applied, to separate and isolate the hindquarters from the rest of the rat. This clamp prevented any leakage of blood and lymph from the hindquarters, and also prevented the transmission of any nerve impulses along the spinal cord to the hindquarters. The sympathetic nerves to the hindquarters were also severed to provide complete hindquarters. The vascular resistance in the hindquarters. The sympathetic nerves to the hindquarters were also severed to provide complete sympathetic denervation. A Sigmamotor pump kept flow to the weighted hindquarters constant at 4 ml/min. This constancy was verified by flow measurements every 5 min. Since flow was constant, the measurement of arterial pressure downstream from the pump provided an accurate index of vascular resistance per 100 g of hindquarters.

**Results**

In 14 studies in which R rats perfused R hindquarters for 30 min, the vascular resistance in the hindquarters averaged 30.8 resistance units (Table 1). In 14 other studies in which S rats perfused R rat hindquarters, vascular resistance in the hindquarters averaged 35.9 resistance units. Thus the blood of hypertensive S rats caused the resistance in the hindquarters of normotensive R rats to increase by 17%, compared with similar perfusions with R blood. This difference was significant (P < 0.001). This result strongly suggests the presence of a humoral pressor agent or the lack of a vasodilator agent in the blood of S rats.

The pressor agent is not likely to be renin since the S rat characteristically has low renin concentrations. Moreover, plasma renin activity averaged 28 ng 20 min⁻¹ 10 ml⁻¹ of plasma in incubation at 37°C in 16 R perfusions, compared with 17 ng/20 min⁻¹ 10 ml⁻¹ in nine S perfusions. The renin activity was 39% lower in the S perfusions. Thus the circulating pressor agent in S rats is not likely to be renin.

In 15 similar perfusions in which hypertensive S rats perfused hypertensive S hindquarters, the vascular resistance in the hindquarters averaged 35.8 resistance units (Table 1). Thus the humoral pressor effect in S blood had induced a degree of vasoconstriction in normotensive R hindquarters that was equal to the vasoconstriction it produced in hypertensive S hindquarters. Table 1 also shows the contrasting types of perfusion into hypertensive S hindquarters. The vascular resistance was similar when these S hindquarters were perfused with either S blood or R blood. This would suggest that the vasoconstrictive effects in the hypertensive S hindquarters cannot be undone during 30 min of perfusion with R blood with its relative absence of a pressor effect.

One might think that R blood was not able to vasodilate hypertensive S hindquarters because structural changes in the arterioles of S rats might prevent full vasodilation. This was tested at the end of each study by giving maximally vasodilating doses of papaverine into the arterial line to the hindquarters. With only 2-5 weeks of hypertension, the hypertensive S hindquarters vasodilated with papaverine to the same extent as the normotensive R hindquarters. Thus there appears to be an insignificant degree of structural thickening in the arterioles of the S rats.

Takeshita & Mark (1978) found that stimulation of the sympathetic nerves in the salt-fed S rat produced an inordinately large increase in vascular resistance of the hindquarters, much more than was produced in the salt-fed R rats. We had fairly similar conditions when salt-fed hypertensive S rats perfused salt-fed hypertensive S hindquarters, and when salt-fed normotensive R rats perfused salt-fed normotensive R hindquarters. To our surprise, we were unable to find any exaggerated rise in vascular resistance in the hypertensive S hindquarters during sympathetic nerve stimulation. We used three strengths of stimulation (1.5 Hz, 3 Hz and 9 Hz), each for 30 s duration. The rise in vascular resistance at all three strengths of stimulation was almost identical in the S hindquarters with that in the R hindquarters. The actual set-up of our study

**Table 1. Vascular resistance in the rat-hindquarters bioassay of blood from resistant (R) and susceptible (S) strains of rat**

<table>
<thead>
<tr>
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<th>Vascular resistance (units/100 g of hindquarter)</th>
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<tbody>
<tr>
<td>14 R rats perfusing R hindquarters</td>
<td>30.8 ± 0.6</td>
</tr>
<tr>
<td>14 S rats perfusing R hindquarters</td>
<td>35.9 ± 0.9</td>
</tr>
<tr>
<td>15 S rats perfusing S hindquarters</td>
<td>35.8 ± 0.8</td>
</tr>
<tr>
<td>16 R rats perfusing S hindquarters</td>
<td>34.4 ± 0.9</td>
</tr>
</tbody>
</table>
Humoral pressor agent

is different from that of Takeshita & Mark (1978). However, with our method, we could not detect any excessive vasoconstriction of hypertensive S hindquarters with sympathetic nerve stimulation.

Discussion

The mechanism by which high salt feeding brings on hypertension in susceptible subjects is still uncertain. The participation of the sympathetic nerves is definitely suspected. The results here indicate that a blood-borne humoral vasoconstrictor agent is present or a vasodilator agent is absent in hypertensive S rats on a high NaCl diet.

Such agents could partly account for the high vascular resistance in these hypertensive rats. The origin and identity of these agents is uncertain, obviously requiring many additional studies. This agent may or may not be similar to the humoral agent detected by Dahl and his coworkers in these same S rats (Dahl, Knudsen, Heine & Leitl, 1967; Iwai, Knudsen, Dahl, Heine & Leitl, 1969; Knudsen, Iwai, Heine, Leitl & Dahl, 1969).

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References


