Effects of Anterior Hypothalamic Disconnection on the Evolution of Goldblatt Renal Hypertension

A Dual Response

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SUMMARY The role of the central nervous system, in general, and of the hypothalamus, in particular, in the genesis of various forms of experimental hypertension has been the object of increased investigation. Lesions of the anteroventral area of the third ventricle (AV3V) in rats seem to block the development of various forms of hypertension. In the present experiments, AV3V was kept intact but its connections with the caudal neuroaxis were severed by means of a curved knife (2 mm radius), stereotaxically placed at the level of the arcuate nucleus. This disconnection, per se, induces polydipsia, and a reduction of the pressor effect of i.v.-infused angiotensin II. The interactions of simultaneously performed hypothalamic disconnection (HD) and Goldblatt one-kidney, one clip, (1K1C) or two-kidney, one clip (2K1C) hypertensions was studied. It was found that HD retards and attenuates the development of 1K1C hypertension but does not materially affect the evolution of the 2K1C model. Rats with established 1K1C or 2K1C hypertensions were not affected by HD, whereas rats with chronic HD (4 weeks) showed slight and slow developing hypertension in response to clipping. The possible significance of these results with respect to the neural connections of AV3V is discussed. (Hypertension 5 (supp V): V-85–V-89, 1983)

KEY WORDS • hypertension • central nervous system • hypothalamus • angiotensin II • brain disconnection

No sooner was it found that angiotensin exerts characteristic and specific actions upon the central nervous system than its role in the genesis of various forms of experimental hypertension became the object of increased investigation. The hypothalamus in particular has been in evidence for the past 10 years. Different methods have been used to study correlations between hypothalamic structures and the development of different forms of hypertension. Ablations, electrolytic lesions, and knife cuts are examples of techniques that have been employed. The anteroventral third ventricle region (AV3V) is of particular importance in the rat since its lesion seems to block the development of various forms of hypertension. In the present experiments AV3V was left intact but a disconnection was performed caudal to it, so that at least part of the pathways running to, or from the anterior hypothalamus were severed. This type of lesion reduces the pressor response to carotid occlusion and impairs the overall cardiovascular homeostatic defense to controlled bleeding. The former response seems to depend entirely upon the cut extending laterally to sever part of the medial forebrain bundle.

In the experiments to be described, the effects of this hypothalamic lesion on the pressor effect of angiotensin II and on water intake were studied. Interactions with two different forms of experimental renal hypertension were also examined.

Methods

All experiments were performed on male Wistar rats submitted to the following procedures:

Hypothalamic Disconnection

The method for hypothalamic disconnection has been previously described. Briefly it is achieved by means of a stereotaxically placed special double-edged knife of bayonet shape, 3 mm in length, 2 mm radius, lowered 1.5 mm caudal to the bregma along the midline down to the inner surface of the sphenoid. The
A bony surface was set horizontal by lowering the tooth-bar 5 mm with respect to the interaural line. The cut was achieved by rotating the knife 90° left and 90° right. Figure 1 is a diagram of the anatomical structures involved. Sham groups were made up of rats in which the knife was lowered into position but not rotated.

Renal Hypertension

Goldblatt one-kidney, one clip (1K1C) and two-kidney, one clip (2K1C) renal hypertension was produced in the standard manner using a 0.37 mm silver clip around the left renal artery of 200 g rats. For the Goldblatt 1K1C model, the right kidney was removed.

Pressor Tests

On the eve of pressor tests rats were implanted with indwelling catheters in the right femoral artery and vein. Each test consisted of dose response curves using three submaximal doses of angiotensin II and norepinephrine, given by i.v. infusion. Each value (steady plateau at 2 minutes of infusion) was determined in a randomized triplicate series. Rats were then anesthetized with althesin (Glaxo), 6 mg/kg i.v. and submitted to hypothalamic disconnection (or sham disconnection). Two hours after recovery from anesthesia the pressor tests were repeated.

Interaction of Renal Hypertension with Hypothalamic Disconnection

In the Goldblatt, 1K1C model, this interaction was tested in three different groups of rats: 1) kidney manipulation and disconnection performed on the same occasion; 2) kidney manipulation preceding disconnection by 4 weeks; 3) disconnection preceding kidney manipulation by 4 weeks. In each case, there was an associated sham-disconnection group.

In the Goldblatt, 2K1C model, the interaction was tested in two different groups of rats prepared as described under (1) and (2) above. Sham disconnection groups were performed in association.

In each animal, tail arterial pressure (tail occluding cuff and microphone) was recorded twice on the week preceding the kidney manipulation and twice a week for 7 weeks thereafter. Measurements for each week were averaged.

Water Intake Studies

Rats with hypothalamic disconnection were placed in individual cages and their daily water intake was measured.

Statistical Analysis

In most experiments, data were analyzed by analysis of variance followed by multiple pairwise comparisons between means (Tukey's test). In experiments where this procedure was unfeasible, (water intake) test values were compared with prelesion controls in each animal. The criterion for statistical significance was set at \( p < 0.05 \).

Results

Hypothalamic Disconnection

According to the diagram of figure 1, the cut separated the structures of the anterior hypothalamus from the arcuate, ventromedial, and dorsomedial nuclei.

![Diagram of hypothalamic disconnection](http://hyper.ahajournals.org)
The lateral extent of the cut (2 mm on each side of the midline) included the medial portion of the medial forebrain bundle. The ventral extent of the cut reached all neural structures down to the sphenoid; this of course meant that the supraoptichypophysial tracts were severed. Inherent to semicircular Halász-type knife cuts is the possibility that direct and indirect, polysynaptic pathways establishing connections between the structures lying rostrally and caudally to the cut may loop around the horizontal plane and be spared by the operation.

Interaction of Goldblatt 1K1C Hypertension and Hypothalamic Disconnection

When both procedures were performed simultaneously, (fig. 2 A), the hypothalamic cut strongly inhibited the development of arterial hypertension. In the lesioned rats, arterial pressure remained practically normal for 4 weeks; then it rose slightly, but was always significantly lower than in the sham-lesioned animals. Figure 2 B shows that a hypothalamic cut made 4 weeks after the onset of 1K1C hypertension did not interfere with the maintenance of high arterial pressure. Finally (fig. 2 C), when the procedure was reversed (i.e., hypothalamic disconnection preceding clipping by 4 weeks) arterial hypertension developed in both groups, but was slightly (but significantly) attenuated in the lesioned rats after the third week.

Interaction of Goldblatt 2K1C Hypertension and Hypothalamic Disconnection

When disconnection was performed simultaneously with Goldblatt 2K1C hypertension, it did not prevent the institution of hypertension; the only difference between the lesioned and sham rats occurred in the first week of observation (fig. 3 A) when lesioned animals were in fact significantly more hypertensive than sham controls. The delayed performance of the hypothalamic-
Hypothalamic Disconnection and the Pressor Effect of Angiotensin II Infusions

Although resting mean arterial blood pressure remained unaltered (119.8 ± 2.9 mm Hg before; 119.3 ± 2.3 mm Hg after disconnection), after the performance of the hypothalamic cut the pressor response to intravenous infusions of angiotensin II was attenuated over a range of doses. Figure 4 indicates that angiotensin II was 2.07 times more potent before the lesion. In three out of six rats, the pressor response to angiotensin II was retested 24 hours later and still found to be similarly attenuated (data not displayed). The pressor response to norepinephrine (fig. 4, right panel) was not affected by the lesion. No alterations of pressor response to angiotensin II was observed in sham-treated controls.

Hypothalamic Disconnection and Water Intake

By itself, the hypothalamic cut produced a triphasic pattern of water ingestion reminiscent of the onset of diabetes insipidus caused by section of the supraopticohypophysial tracts at the level of the median eminence; after an initial stage of polydipsia, a short near normal interphase was followed by the establishment of permanent polydipsia. It should be noted, however, that these rats are capable of producing relatively concentrated urine (1900 mosM/liter) after 72 hours of water deprivation.

Discussion

A very clear distinction between the evolution of two different types of renal hypertension has been established in the present experiments by the hypothalamic disconnection, which delays and attenuates the development of the Goldblatt 1K1C hypertension but actually accelerates the early development of hypertension in the Goldblatt 2K1C model. If, however, the hypothalamic disconnection is performed 4 weeks after either type of renal manipulation, no interference with the course of hypertension is revealed.

A number of alternative, or complementary explanations could account for those results. A simple line of thought would be to correlate the presence of a diabetes insipidus-like drinking pattern with the attenuated development of 1K1C hypertension. This would of course require proof that vasopressin is an essential co-factor only in this form of renal manipulation. But it is well established that neither form of Goldblatt hypertension is unequivocally affected by the presence or absence of vasopressin. Probably more pertinent to the point is the matter of salt metabolism. It has been frequently suggested that the 1K1C model is predominantly salt-and water-dependent, while the 2K1C variety is mainly renin-dependent. Preliminary experiments from our laboratory suggest that the hypothalamic disconnection by itself increases urinary salt excretion. This might be the cause of the attenuated rise in blood pressure of the 1K1C model. In this connection, it is interesting to note that sodium washout by peritoneal dialysis re-
duces blood pressure in the 1K1C, but not 2K1C, hypertensive rat. A more integrated way to explain our results is obviously through the action of the central nervous system, especially because it is highly likely that sodium and vasopressin may act through neural mechanisms. The hypothalamic disconnection interferes with vasoconstrictor activity: disconnected rats are more sensitive to hemorrhage and less responsive to carotid occlusion, a result that seems to be consequent to disconnection of the medial half of the medial forebrain bundle.

Electrolytic destruction of AV3V blocks the development of both forms of Goldblatt hypertension. Recently, Hartle and Brody showed that a midline dorsal hypothalamic lesion selectively blocks the development of a renin-dependent hypertensive model. They go on to suggest that: "The AV3V region must contain separate neural mechanisms that are involved in non-renin-dependent renal hypertension."

We have now found that a ventral disconnection affecting not only midline structures but also the medial forebrain bundle selectively affects the course of nonrenin-dependent 1K1C hypertension. This cut apparently leaves out the dorsal route described by Hartle and Brody and hence does not affect renin-dependent 2K1C hypertension.

The reduced pressor effect of angiotensin II following this hypothalamic disconnection agrees with the report of Johnson et al. concerning a ventromedial hypothalamic ablation, which also attenuates 1K Grollman hypertension. At first sight, these results do not appear to fit in with the idea of selective interference with salt- and water-dependent hypertension, or with the preservation of a renin-related pathway from AV3V. No explanation can at present be offered for this apparently puzzling observation, but it should be kept in mind that the administration of exogenous angiotensin II may be an inadequate substitute for the operation of the natural renin-related neural pathways.

References

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