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# Secretion of Pressor Amounts of Vasopressin in Experimentally Hypertensive Rats

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## ABSTRACT

Vasopressin secretion in pressor amounts was studied in one-clip, two-kidney and one-clip, one-kidney renovascular hypertensive rats as well as DOCA-salt hypertensive rats in various conditions in the conscious state. The characteristic, almost step-wise lowering of arterial pressure induced by intravenous injection of vasopressin antagonist was considered to indicate the presence of secretion of vasopressin in pressor amounts. Without any premedication and pretreatment, vasopressin antagonist was without effect on arterial pressure in any of the three kinds of hypertensive rats. After ganglion blockade with hexamethonium bromide, injection of vasopressin antagonist lowered arterial pressure only in DOCA-salt hypertensive rats. One hr after spinal cord transection at C8 performed under ether anesthesia, when the rats had recovered consciousness and arterial pressure had recovered partially from the spinal shock, injection of vasopressin antagonist lowered arterial pressure in all the three kinds of hypertensive rats. Since injection of vasopressin antagonist after spinal transection is without effect on arterial pressure in normotensive control rats but has a depressor effect in sponstaneously hypertensive rats (SHR), it may be said that vasopressin secretion in pressor amounts is facilitated in the three kinds of hypertensive rats as in SHR.

It is presumed that vasopressin is secreted in pressor amounts in normal rats when the sympathoadrenal system has failed, resulting in lowering of arterial pressure[4,5]. Such a state of emergency for the animal seems to be transmitted to the central vasopressin secreting mechanism as abolishment of both baro- and volume receptor impulses[8].

Plasma vasopressin concentration is elevated[2] in sponstaneously hypertensive rats (SHR)[11]. The resting secretion is insufficient in directly elevating arterial pressure but it exceeds the threshold for pressure elevation more easily in SHR, than in normal rats. For example, pressor amounts of vasopressin are secreted after spinal cord transection alone in SHR, but only after further ganglion blockade in normal rats[6]. It may be said that pressor vasopressin secretion is facilitated in SHR.

The question arises whether facilitation of secretion of pressor amounts of vasopressin is confined to SHR or shared by other experimentally hypertensive rats. The present study has shown that the latter is the case.

## METHODS

*Preparation of hypertensive rats*

Male Wistar rats about 10 weeks of age were anesthetized with thiamylal sodium (50 mg/kg, i.p.). After a left flank incision the left renal artery was reached and a clip made from a stainless steel tape, 1 mm wide and 0.1 mm thick with a gap of 0.3 mm, was placed on it. The contralateral kidney was left intact for one-clip, two-kidney hypertension and removed for one-clip, one-kidney hypertension. For DOCA-salt hypertension, rats were unilaterally nephrectomized and thereafter deoxycorticosterone ace-

tate was injected subcutaneously at a dose of 20 mg/kg per week and 1% sodium chloride was given in the drinking water.

*Arterial and venous catheterization*

Two to three weeks after clipping and/or nephrectomy when the pressure measured by the tail-cuff method exceeded 150 mmHg, rats were anesthetized again for chronic catheterization. A polyethylene catheter for recording arterial pressure was inserted from the right femoral artery to the terminal aorta. Another polyethylene catheter for intravenous injection was inserted into the right external jugular vein. The outer ends of these arterial and venous catheters, which were plugged with short stainless steel wires, were passed subcutaneousluy to the dorsal neck and exteriorized.

*Pressure measurement*

After catheterization, the rat was kept separately in a white polyethylene cage of 35 × 30 × 17 cm in size containing wood chips. Pressure measurement was started when more than 2 days had elapsed after catheterization and the rat had resumed to take ample amount of water and pellets. A polyethylene tube from a pressure transducer was connected to the arterial catheter in the rat remaining in the home cage. The tube was long enough to allow the rat to move almost freely in the cage during measurement.

*Vasopressin antagonist*

A vasopressin antagonist, [1-β-mercapto-β-, β-cyclopentamethylene propionic acid), 2-(O-methyl) tyrosine] arginine-vasopressin[9], was injected through the venous catheter at a dose of 0.01 mg/kg. The characteristic, slow step lowering of arterial pressure, which was completed in a few minutes, was considered to indicate secretion of vasopressin in pressor amounts.

*Ganglion blockage*

For this purpose, hexamethonium bromide was infused intravenously at a rate of 0.8 mg/min for a total dose of 25 mg/kg.

*Spinal cord transection*

This was performed under ether anesthesia, while arterial pressure was continuously observed. The spinal cord was transected between the vertebrae C7 and Th 1[7]. A local anesthetic xylocaine jelly was applied to the wound made for transection and thereafter ether anesthesia was terminated. Arterial pressure dropped abruptly on spinal cord transection, but it gradually recovered partially. Further experiments were performed after the rat had recovered consciousness and the arterial pressure had reached a new plateau level in about one hr.

## RESULTS

*Effect of vasopressin antagonist on arterial pressure*

As in all normal rats[8] and almost all SHRs[6], in the conscious state without any premedication and pretreatment other than catheterization, vasopressin antagonist (0.01 mg/kg, i.v.) induced no consistent lowering of arterial pressure in any of the three kinds of experimentally hypertensive rats. As for DOCA-salt rats, this is a confirmation of the results of Burnier et al[1].

*Effect of vasopressin antagonist after ganglion blockade*

Even after ganglion blockade with hexamethonium, as in normal rats and most SHRs, vasopressin antagonist was without appreciable effect in both kinds of renovascular hypertensive rats. However, it did lower arterial pressure significantly ($p < 0.001$ by the paired t-test) in DOCA-salt hypertensive rats (Figs. 1 and 2), indicating secretion of vasopressin in pressor

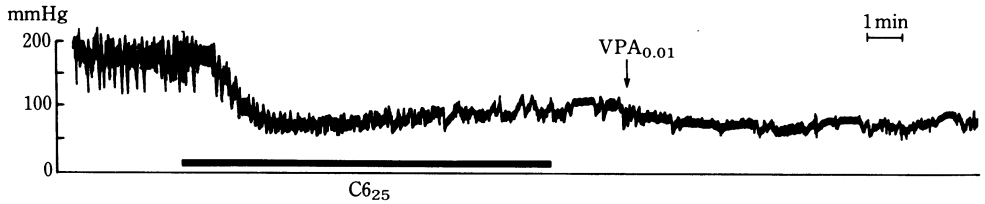


**Fig. 1.** Lowering of arterial pressure in a conscious DOCA-salt hypertensive rat on bolus injection of vasopressin antagonist (VPA, 0.01 mg/kg), indicating secretion of a pressor amount of vasopressin, induced by preceding ganglion blockade with hexamethonium bromide (C6, 25 mg/kg), infused for the underlined period.

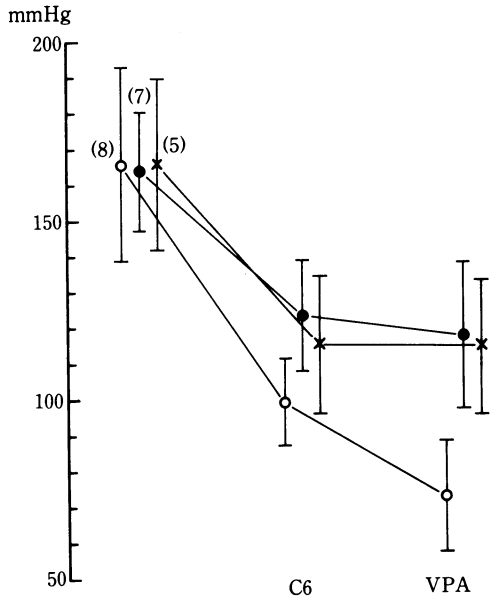


**Fig. 2.** Successive changes in arterial pressure in one-clip, two-kidney renovascular hypertensive rats (crosses), one-clip, one-kidney renovascular hypertensive rats (filled circles) and DOCA-salt hypertensive rats (open circles) in the conscious state on intravenous infusion of hexamethonium bromide (C6, 25 mg/kg) and bolus injection of vasopressin antagonist (VPA, 0.01 mg/kg). Mean ± SD. The number in parentheses represents the number of rats. Pressure was noted immediately before and after C6 infusion, and 5 min after VPA injection.

amounts.

*Effect of vasopressin antagonist after spinal cord transection*

This experiment was performed in 8 one-clip, two-kidney renovascular hypertensive rats, 5 one-clip, one-kidney renovascular hypertensive rats, and 2 DOCA-salt hypertensive rats. In each rat vasopressin antagonist was injected as a bolus one hr after spinal transection when the rat had recovered consciousness and the arterial pressure had recovered partially to a new plateau level. One example of this experiment in a one-clip, two-kidney renovascular hypertensive rat is presented in Fig. 3. The mean arterial pressure ± SD from the 8 one-clip, two-kidney rats was 143 ± 26.8 mmHg before vasopressin injection and 122 ± 26.6 mmHg 5 min after it. The decrease was significant at $p<0.005$. The corresponding values from the 5 one-clip, one-kidney rats were 133 ± 15.6 and 113 ± 18.9 mmHg, respectively, the decrease being significant at $p<0.005$. In the 2 DOCA-salt rats, the arterial pressure was 134 and 77 mmHg before vasopressin antagonist and 112 and 57 mmHg, respectively, 5 min after it. These results indicate that vasopressin was secreted in pressor amounts in all of the three kinds of experimentally hypertensive rats one hr after spinal cord transection at C8.

## DISCUSSION

Because injection of vasopressin antagonist, without any premedication or pretreatment, did not lower arterial pressure, secretion of vasopressin does not seem to take a direct part in elevating arterial pressure in any of the three kinds of hypertensive rats investigated in this study. This is consistent with the reports of other workers[1,12].

Among the three kinds of experimental hypertension, DOCA-salt hypertension is unique in that hypersecretion of vasopressin within nonpressor amounts has been reported[1,2,10,14]. In fact, in also the present study it was in DOCA-salt hypertensive rats only that ganglion block-

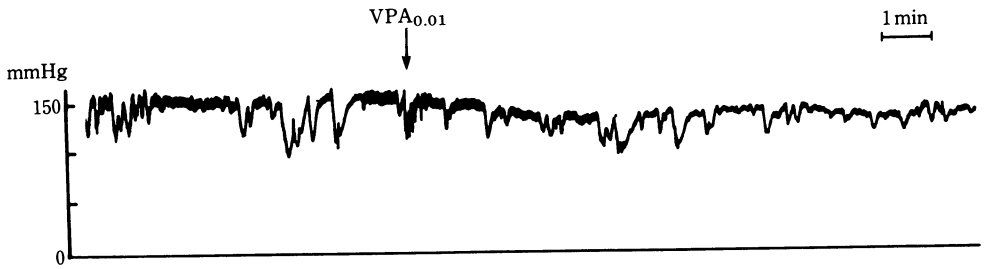


**Fig. 3.** Lowering of arterial pressure in a one-clip, two-kidney renovascular hypertensive rats on bolus injection of vasopressin antagonist (VPA, 0.01 mg/kg) one hr after spinal cord transection at C8.

age induced secretion of vasopressin in pressor amounts. At least phenomenologically, DOCA-salt hypertensive rat is the rat in which pressor vasopressin secretion is most easily induced. This could be a reflection of the presumably centrally determined hypersecreting tendency of this hormone in this kind of experimental hypertension. However, since ganglion blockade induced the largest fall in arterial pressure in DOCA-salt hypertensive rats (Fig. 2), the silencing effect of the highly reset baroreceptors, which leads to secretion of pressor amounts of vasopressin, should also be the largest among them.

In a previous study it was concluded that vasopressin secretion in pressor amounts is facilitated in SHR because it occurred after spinal transection alone in this hypertensive rat, while spinal transection plus ganglion blockage was necessary for secretion in normotensive control rats[6]. The present study indicated that vasopressin secretion in pressor amounts was similarly facilitated in all of the three kinds of experimentally hypertensive rats investigated. It is possible that the facilitated state of vasopressin secretion in pressor amounts is a common phenomenon in all hypertensions.

In SHR it is assumed that the facilitated state of vasopressin secretion in pressor amounts is in such a way that elimination of baroreceptor impulses alone is sufficient for pressor vasopressin secretion, while elimination of both baro- and volume receptor impulses is required in normal rats[6]. As one of the possible causes for the above, mention may be made of the decreased distensibility of the left atrial wall in SHR, leading to reduced volume receptor impulses[13]. Whether the reduced atrial distensibility is shared by other experimentally hypertensive rats is an insteresting question to challenge. It is also possible that this phenomenon, facilitated secretion of pressor amounts of vasopressin, holds a key to understanding some other facets of hypertension in general.

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