Facilitated Secretion of Pressor Amounts of Vasopressin in Spontaneously Hypertensive Rats*)

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ABSTRACT

Vasopressin antagonist, which antagonizes pressor effect of vasopressin, was injected to spontaneously hypertensive rats under various conditions to observe whether arterial pressure was decreased to indicate secretion of pressor amounts of vasopressin. Vasopressin was secreted in pressor amounts in spontaneously hypertensive rats after acute spinal transection or sinoaortic denervation. This is in sharp contrast to normal rats in which ganglion blockade with hexamethonium bromide is necessary in addition to spinal transection or sinoaortic denervation for secretion of pressor amounts of vasopressin. This indicates that vasopressin secretion in pressor amounts is facilitated in spontaneously hypertensive rats.

INTRODUCTION

We have previously reported that, in normal water replete rats, vasopressin in amounts sufficient to elevate arterial pressure is secreted when baroreceptor impulses are interrupted and catecholamine concentrations in the blood are lowered8. It has been suggested that catecholamine concentrations are signaled by cardiac volume receptors5. It is further suggested that catecholamines increase volume receptor impulses by increasing their sensitivity by making the cardiac wall tenser through inotropic action and by increasing blood volume through constriction of capacitance vessels. It is also assumed that both baroreceptor and volume receptor impulses inhibit vasopressin secretion by inhibiting the structures in the lower medulla oblongata, which send exciting impulses to the vasopressin releasing system in the hypothalamus8,10.

It is known that secretion of vasopressin is elevated in spontaneously hypertensive rats (SHR)11 within the antidiuretic range11. Although the pressor dose of vasopressin is one to two orders of magnitude greater than the antidiuretic dose9, it is expected that the conditions for vasopressin secretion in pressor amounts are also somewhat different in SHR. The present study undertaken to investigate the difference showed that vasopressin was released in pressor amounts more readily in SHR than in normal rats.

METHODS

Rats

SHRs and normal Wistar rats of both sexes, 10-20 week-old, were employed in the present study.

Catheterization

For observation of arterial pressure in the conscious state, under anesthesia with thiamylal sodium (50 mg/kg, i. p.) a polyethylene tube was inserted from a femoral artery to the terminal aorta and the other end was led under the skin to the dorsal neck to exteriorize. For intravenous injection, another polyethylene tube was inserted into the external jugular vein and

*) 入内島十郎：高血圧自然発症ラットにおける昇圧量パプレシン分泌の促進
the other end was also exteriorized in the dorsal
neck. After the operation the rat was kept
separately in a white polyethylene cage of 35 ×
30 × 17 cm in size containing wood chips. Water
and pellets were given ad libitum. Measurement
of pressure was commenced when more than
2 days had passed after catheterization and the
rats had started to drink and eat normally.

Vasopressin antagonist

A vasopressin antagonist, [1-β-mercaptopo-β,
β-cyclopentamethylene propionic acid], 2-(O-
 methyl) tyrosine] arginine-vasopressin, was
injected through the venous catheter at a dose
of 0.01 mg/kg to observe whether the charac-
teristic almost step-wise lowering of arterial
pressure was induced to indicate secretion of
vasopressin in pressor amounts.

Spinal transection

Intact rats or catheterized rats were
anesthetized with ether. In intact rats a femoral
artery and vein were cannulated to begin with. While
the arterial pressure was being observed con-
tinuously, the spinal cord was transected between
the vertebrae C7 and Th 1. A local anesthetic
xylocaine jelly was applied to the wound made
for spinal transection and thereafter ether anes-
thesia was terminated. Arterial pressure drop-
ped abruptly on spinal transection but it
gradually recovered. Further experiments were
performed after the rat had recovered conscious-
ness and the arterial pressure had reached a
new plateau level in about one hr.

Ganglion blockade

For ganglion blockage, hexamethonium bromide (25 mg/kg, i.v.) in SHRs in the
conscious state, injection of vasopressin antagonist
induced a marked lowering of arterial pressure in
only 2 of 6 rats. One of the two was the
foregoing rat in which injection of the antago-
nist seemed to lower arterial pressure without
ganglion blockade.

Effect of vasopressin antagonist on arterial
pressure in spinal-transected SHR

One hour after acute spinal transection under
ether anesthesia, when the rat had recovered conscious-
ness and the arterial pressure had reached a
new plateau level, injection of vasopressin antagonist
invari-
ably induced a slight but distinct decrease in
arterial pressure (Fig. 1). The mean arterial
pressure ±SD from 8 SHRs (6 males and 2

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\[ \text{Fig. 1. Lowering of arterial pressure on intravenous injection (arrow) of vasopressin antagonist (VPA) at a dose of 0.01 mg/kg in a conscious SHR about 1 hr after spinal transection.} \]
Vasopressin in Rat Spontaneous Hypertension

Fig. 2. Changes in arterial pressure in conscious SHRs (filled circles) and normal rats (open circles) 1 hr after spinal transection (CS: cord section) on intravenous injection of vasopressin antagonist (VPA, 0.01 mg/kg) followed by hexamethonium bromide (C6, 25 mg/kg). C6 injection at a rate of 0.8 mg/min was started 10 min after bolus injection of VPA. Arterial pressure level on completion of the injection was noted as that after C6. Mean±SD, n=8 for SHRs and n=7 for controls. Note that VPA significantly (p<0.005) decreased arterial pressure in SHRs alone and abolished the difference in pressure between the groups.

Females, aged 11.0±3.1 weeks) before and 5 min after vasopressin antagonist is presented in Fig. 2 as filled circles. The mean decrease in pressure±SD was 16.5±9.4 mmHg and significant at p<0.005 by the paired t-test. Although this sample of SHRs was not balanced by sex, it did not seem to present any obstacle in drawing a conclusion on this kind of rat model in general: the arterial pressure was no longer different between the sexes after spinal transection.

In normal rats under the same condition vasopressin antagonist had no appreciable effect on arterial pressure. The open circles in Fig. 2 represent the mean arterial pressure±SD from 7 normal rats (5 males and 2 females, aged 11.1±2.1 weeks). There was no difference in pressure between SHRs and normal rats after vasopressin antagonist. After further ganglion blockade with hexamethonium bromide (25 mg/kg, i.v.), arterial pressure further decreased similarly in both rat groups.

Effect of vasopressin antagonist after acute sinoaortic denervation

In normal rats, sinoaortic denervation alone like spinal transection is not sufficient in inducing secretion of pressor amounts of vasopressin. In two SHRs, however, injection of vasopressin antagonist induced a marked lowering of arterial pressure after acute sinoaortic denervation (Fig. 3).

Effect of vasopressin antagonist on arterial pressure after spinal transection and ganglion blockade

Fig. 4 summarizes the observations of arterial pressure in which hexamethonium was first given to spinal-transected normal and hypertensive rats and vasopressin antagonist was then administered. In other words, the order of administration of these two drugs was reversed as compared with the experiments presented in Fig. 2. As reported previously, the pressure...
Changes in arterial pressure in conscious SHRs (filled circles) and normal rats (open circles) 1 hr after spinal transection (CS) on intravenous injection of first hexamethonium bromide (C6, 25 mg/kg) and then vasopressin antagonist (VPA, 0.01 mg/kg).

Mean ± SD. n = 12 for SHRs and n = 18 for controls. Note that the difference in pressure between the rat groups persisted until VPA was finally given.

Fig. 4. Changes in arterial pressure in conscious SHRs (filled circles) and normal rats (open circles) 1 hr after spinal transection (CS) on intravenous injection of first hexamethonium bromide (C6, 25 mg/kg) and then vasopressin antagonist (VPA, 0.01 mg/kg).

DISCUSSION

In agreement with previous authors, vasopressin does not seem to play a role in maintaining hypertension in SHR, because vasopressin antagonist was rarely effective in lowering arterial pressure in intact SHRs. To constantly induce secretion of pressor amounts of vasopressin, acute spinal transection or sinoaortic denervation plus ganglion blockade was required in normal rats. However, the present study demonstrated that only spinal transection or sinoaortic denervation was sufficient for secretion of pressor amounts of vasopressin in SHRs. Spinal transection and sinoaortic denervation are interchangeable presumably because the former lowers arterial pressure below the thresholds of most baroreceptors. On the other hand, ganglion blockade, being replaceable with cervical vagotomy or α or β adrenocceptor blockade, is considered to markedly diminish cardiac volume receptor impulses through relaxation of cardiac muscle and dilation of capacitance vessels. Thus, in normal rats, for secretion of vasopressin in pressor amounts, it is suggested that both baro- and volume receptor impulses should be eliminated, while in SHRs elimination of baroreceptor impulses seems to be sufficient.

In normal rats, baro- and volume receptor impulses are considered to converge upon and inhibit the structures in the lower medulla oblongata, which send excitatory impulses to the vasopressin secreting system in the hypothalamus when released from the inhibitory influence of baro- and volume receptor impulses. In SHRs, it is assumed either that cardiac volume receptor impulses are scarce or that the medullary structures are so excitable that their activity for vasopressin secretion can be released by eliminating baroreceptor impulses alone, leaving volume receptor impulses intact. In either way, secretion of pressor amounts of vasopressin may be said to be in a facilitated state in SHR.

According to Thoren et al., the cardiopulmonary receptors are reset in SHR so that a greater atrial pressure is needed to activate these receptors compared to normotensive controls. The resetting is at least partly ascribable to the decreased distensibility of the left atrial wall. This finding suggests a scarcity of volume receptor impulses in SHR.

We have observed previously that after cord section (C7-Th 1) or cord pithing (below Th 1) the arterial pressure was significantly higher in SHRs than in normal rats 1–2 hr after the operation under ether. The present study has indicated that the difference is due to the facilitated secretion of vasopressin in pressor amounts in SHR. Consistent with this there is no appreciable difference in pressure between SHRs and normal rats even after cord section and pithing plus further pentobarbital anesthesia or after pithing the entire central nervous system. Pentobarbital is inhibitory on vasopressin secretion and pithing the entire central nervous system does not spare the hypothalamohypophyseal system like cord section and cord pithing.
REFERENCES


