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

Juro IRIUCHIJIMA

Department of Physiology, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan

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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 faciliated 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 lowered[3]. It has been suggested that catecholamine concentrations are signaled by cardiac volume receptors[5]. 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 hypothalamus[8,10].

It is known that secretion of vasopressin is elevated in spontaneously hypertensive rats (SHR)[11] within the antidiuretic range[1]. Although the pressor dose of vasopressin is one to two orders of magnitude greater than the antidiuretic dose[9], 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バゾ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 poylethylene 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-mercapto-β, β-cyclopentamethylene propionic acid), 2-(O-methyl) tyrosine] arginine-vasopressin[7], was injected through the venous catheter at a dose of 0.01 mg/kg to observe whether the characteristic 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 continuously, 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 anesthesia was terminated. Arterial pressure dropped abruptly on spinal transection but it gradually recovered. Further experiments were performed after the rat had recovered consciousness and the arterial pressure had reached a new plateau level in about one hr[4].

Ganglion blockade

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

Sinoaortic denervation

This was performed acutely under ether anesthesia according to the method of Kriegar[6]. In this preparation all the surgical wounds were painted with xylocaine jelly.

Statistical analysis

Student's t-test was used throughout.

RESULTS

Effect of vasopressin antagonist on arterial pressure in conscious SHR

When 0.01 mg/kg of vasopressin antagonist was injected as a bolus to SHRs in which arterial pressure was being recorded continuously with a chronically implanted catheter, it usually had no appreciable effect on arterial pressure as in normal rats[3]. In only one out of the 6 SHRs tested, the injection lowered arterial pressure which might be ascribable to the effect of the antagonist. Even in this rat the effect was quite obscure when the same injection was performed 3 days earlier.

Effect of vasopressin antagonist after ganglion blockade

After ganglion blockade with 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 antagonist 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 consciousness and the arterial pressure had recovered partially and reached a new plateau level, injection of vasopressin antagonist invariably induced a slight but distinct decrease in arterial pressure (Fig. 1). The mean arterial pressure±SD from 8 SHRs (6 males and 2

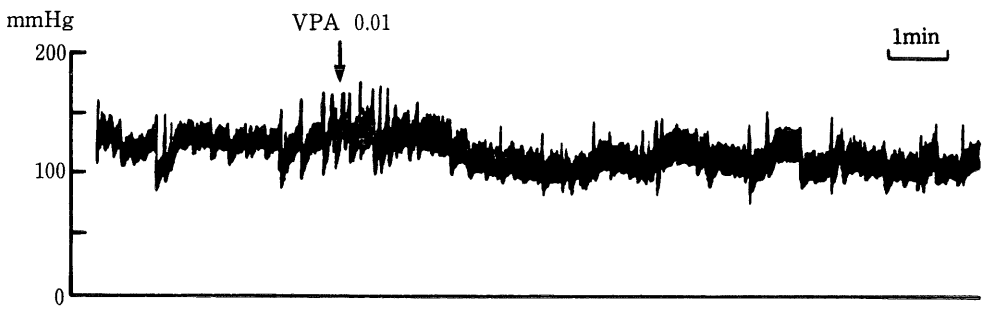

Fig. 1. Lowering of arterial pressure on intravenous injettion (arrow) of vasopressin antagonist (VPA) at a dose of 0.01 mg/kg in a conscious SHR about 1 hr after spinal transection.

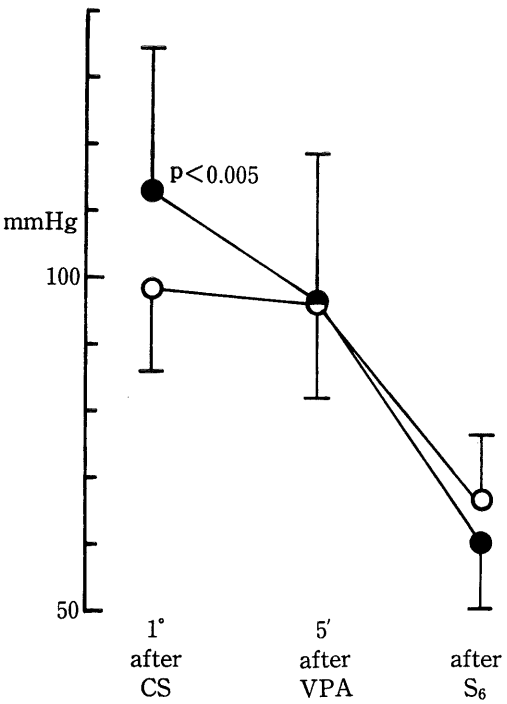

Fig. 2. Changes in arterial pressure in conscious SHRs (filled circles) and normal rats (open circles) 1 hr after spinal transection (CS: cord section) on intravenous injection of vasopressin antagonist (VPA, 0.01 mg/kg) followed by hexamethonium bromide (C6, 25 mg/kg). C6 injection at a rate of 0.8 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[3]. 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[3]. 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[4], the pressure

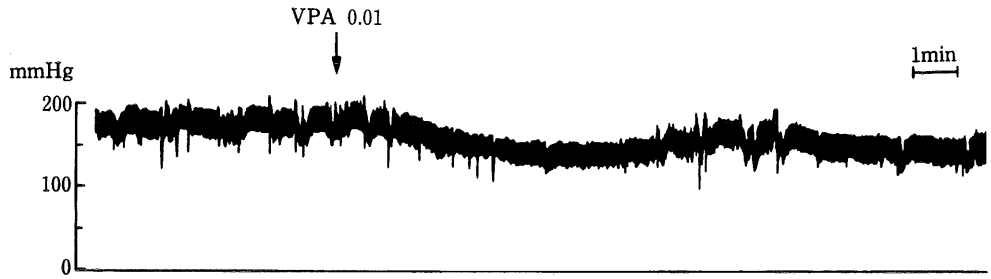

Fig. 3. Lowering of arterial pressure on intravenous injection (arrow) of vaspressin antagonist (VPA) at a dose of 0.01 mg/kg in a conscious SHR about 30 min after acute sinoaortic denervation under ether anesthesia.

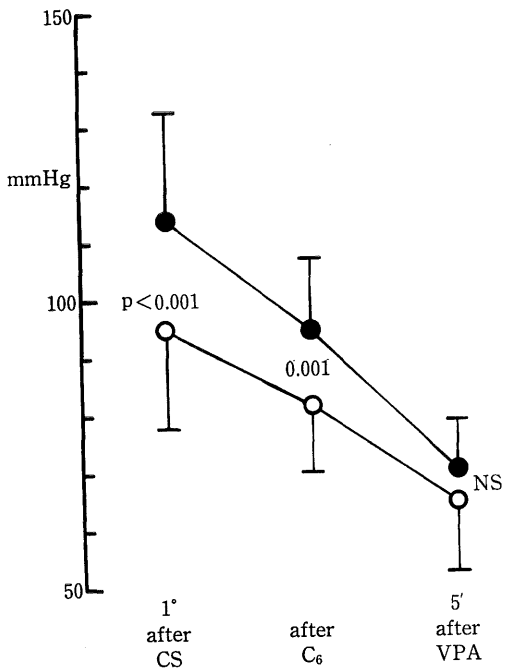

Fig. 4. Changes in arterial pressure in conscious SHRs (filled circles) and normal rats (open circles) 1 hr after spinal transection (CS) on intravenous injection of first hexamethonium bromide (C6, 25 mg/kg) and then vasopressin antagonist (VPA, 0.01 mg/kg).
Mean±SD. n=12 for SHRs and n=18 for controls. Note that the difference in pressure between the rat groups persisted until VPA was finally given.

had been significantly higher in the hypertensive rats than in the normal rats until vasopressin antagonist was finally administered.

DISCUSSION

In agreement with previous authors[1], 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[3]. 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 thnesholds of most baroreceptors. On the other hand, ganglion blockade, being replaceable with cervical vagotomy or α or β adrenoceptor blockade, is considered to markedly diminish cardiac volume receptor impulses through relaxation of cardiac muscle and dilation of capacitance vessels[5]. 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.[14], 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 ascriable to the decreased distensibility of the left atrial wall[12,13]. This finding suggests a scarcity of volume receptor impulese 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[4]. 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[4] or after pithing the whole central nervous system[2]. Pentobarbital is inhibitory on vasopressin secretion[3] and pithing the entire central nervous system does not spare the hypothalamo-hypophyseal system like cord section and cord pithing.

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