Hiroshima J. Med. Sci.
Vol.42, No.2, 83~88, June, 1993
HIJM 42-10

Vasoconstricting Effect of Vasopressin on Regional Vascular Beds in Conscious Rats After Ganglionic Blockade

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ABSTRACT

We analyzed the vasoconstrictor effects of arginine vasopressin (AVP) on regional arteries before and after ganglionic blockade with hexamethonium. Simultaneous measurements of mean arterial pressure and regional flows were obtained in conscious rats, using chronically implanted electromagnetic flow probes. Regional vascular resistance was calculated as mean arterial pressure divided by regional flow. AVP was applied intravenously as a bolus, at doses ranging from 5×10^{-11} to 5×10^{-8} g/kg. AVP increased mean arterial pressure, decreased superior mesenteric, renal and terminal aortic flows (supplied mainly for the hindquarter vascular area), and increased superior mesenteric, renal and terminal aortic (hindquarter) resistances in a dose-dependent manner. Ganglionic blockade decreased mean arterial pressure and renal resistance significantly, whereas there were no significant differences between changes in resistance before and after ganglionic blockade in superior mesenteric or terminal aortic areas. This suggested the presence of basal sympathetic vasoconstrictor tone in the renal area. After ganglionic blockade, the pressor effect of AVP was enhanced significantly. The increase in renal resistance induced by AVP was augmented after ganglionic blockade, whereas increases in superior mesenteric or terminal aortic resistance remained unchanged following ganglionic blockade. Our data suggest that the vasoconstrictor effect of AVP on renal vascular area is reduced by a mechanism which inhibits renal sympathetic basal tone.

Key words: *Vasopressin, Regional blood flow, Peripheral resistance, Ganglionic blockade, Rat*

Two main physiological roles of arginine vasopressin (AVP) are the antidiuretic and vasoconstrictor effects. AVP, infused so as to approximate physiological secretion, can significantly affect systemic resistance vessels in conscious dogs and furthermore, baroreceptor denervation enhances greatly pressor effects of AVP[2,3)]. Augmented pressor effects of AVP were also induced by ablation of the central nervous system[1,13,16)] or by ganglionic blockade[6,12,14,15)].

The pressor resonse to AVP is mainly caused by prominent vasoconstrictions on regional vascular beds[10)]. Although AVP increases total peripheral resistance and decreases cardiac output in conscious dogs, this change in cardiac output disappears after barorecepor denervation, resulting in enhancement of the pressor response. However, it is still obscure whether or not the autonomic nervous system also affects the vasoconstricting capacity of AVP acting regional vascular beds. Therefore, in order to assess the interacton of AVP with the sympathetic nervous system on regional hemodynamics, attempts were made to characterize the vasoconstrictor effects of AVP in regional vascular areas before and after ganglionic brockade with hexamethonium bromide (C6).

MATERIALS AND METHODS

Implantation of flow probes and catheters

Male Wistar rats at 12-15 weeks of age were employed in the present study. The mean value of body weight of the rats was 351 ± 56.3g (n=34). The rats were anesthetized with thiamylal sodium (50mg/kg i.p.). An electromagnetic flow probe (Nihon Kohden, Tokyo) one per rat was placed either around the superior mesenteric artery (internal diameter of probe: 1.5 mm), the renal artery (1.0 mm) or the terminal aorta (2.0 mm) in each rat. The lead wire to the plug from the probe passed under the skin and led to the dorsal neck to exteriorize the plug through a skin incision. The technical details of implantation procedure have been reported previously[8)]. When probes were applied to the superior mesenteric or renal artery, a catheter was inserted via the right femoral artery into the terminal aorta for direct

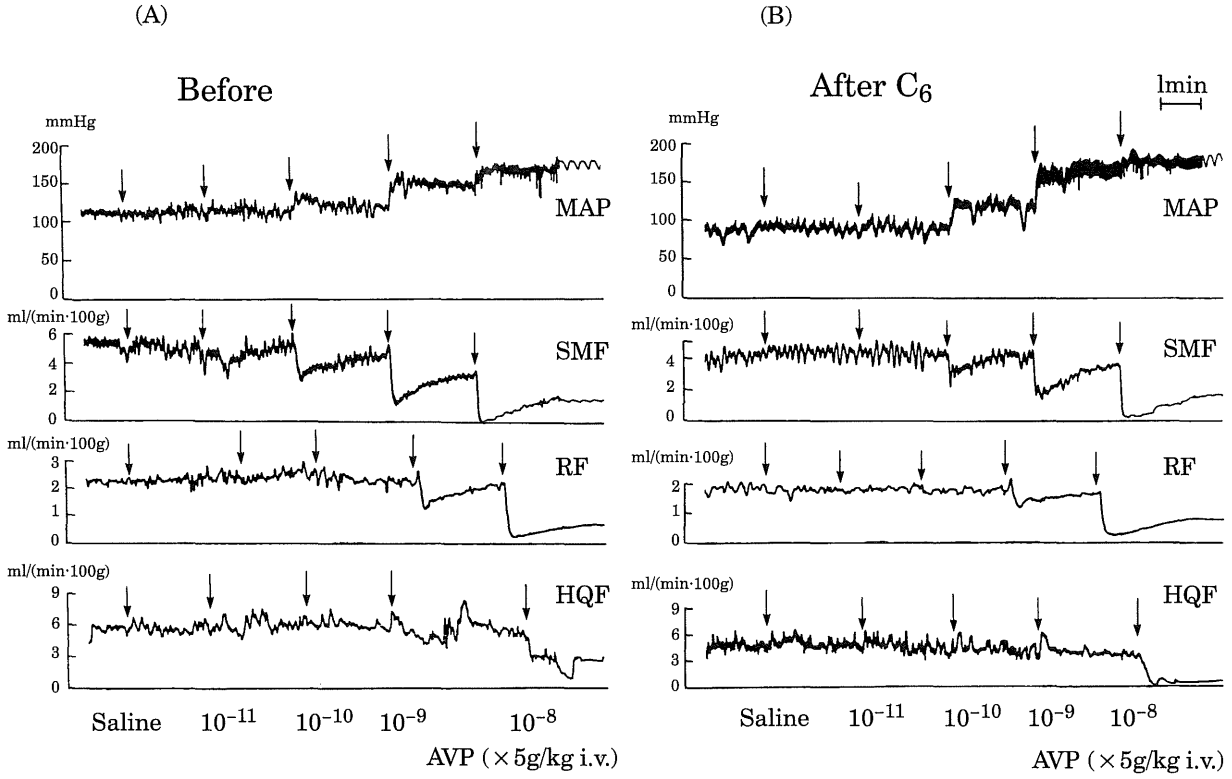

Fig. 1. Typical recordings of effect of arginine vasopressin in conscious rats. From top to bottom, mean arterial pressure (MAP) and superior mesenteric flow (SMF) were recorded in a rat, renal flow (RF) in a different rat and hindquarter flow (HQF) in a third rat. A: at arrows from left to right, saline (1 ml/kg) and successively increasing amounts of arginine vasopressin were injected intravenously. B: the same procedure was repeated after ganglionic blockade with hexamethonium bromide (C6).

measurement of arterial pressure. Since arterial pressure was not measured in the rats with a flow probe around the terminal aorta, the mean hindquarter resistance was calculated as follows: mean hindquarter resistance = mean arterial pressure / mean hindquarter flow, where the mean arterial pressure was calculated from the data obtained in both the superior mesenteric and renal flow measurements. A catheter for intravenous injection was inserted into the right jugular vein.

Measurement

After probe implantation, each rat was placed in a white polyethylene cage of 35 × 30 × 17 cm in size containing wood chips, and was provided with ample pellets and drinking water. Measurements of arterial pressure and regional blood flow were performed 3 days after implantation. The zero flow level was defined by digital compression of the artery. All regional flows were normalized for 100 g of body weight.

AVP (Sankyo, Tokyo) was applied intraveously as a bolus at doses ranging from 5×10^{-11} to 5×10^{-8} g/kg at intervals of about 2 minutes. Hexamethonium bromide (25mg/ml; Yamanouchi, Tokyo) was infused at 0.03 ml/min for a total dose of 25 mg/kg for ganglionic blockade. AVP injection was repeated again after administration of C6.

Statistical analysis

We performed Kolmogorov-Smirnov's tests to check the normality of the samples, and assumed normality because the results did not reject the normality hypothesis. Statistical analysis was performed with the paired or the unpaired t-test. P values of <0.05 were considered to be statistically significant.

RESULTS

The effects of AVP on hemodynamics

AVP increased mean arterial pressure and decreased regional blood flows in a cumulative fashion (Fig. 1). Mean arterial pressure increased significantly at a dose of AVP 5×10^{-10} g/kg (Fig.2-A). AVP also increased superior mesenteric and renal resistances significantly (Fig. 3-A).

The effects of AVP on hemodynamics after ganglionic blockade

Mean arterial pressure in the presence of C6 was lower than that in the absence of C6 (presence of C6; 95 ± 8.4 mmHg, absence of C6; 117

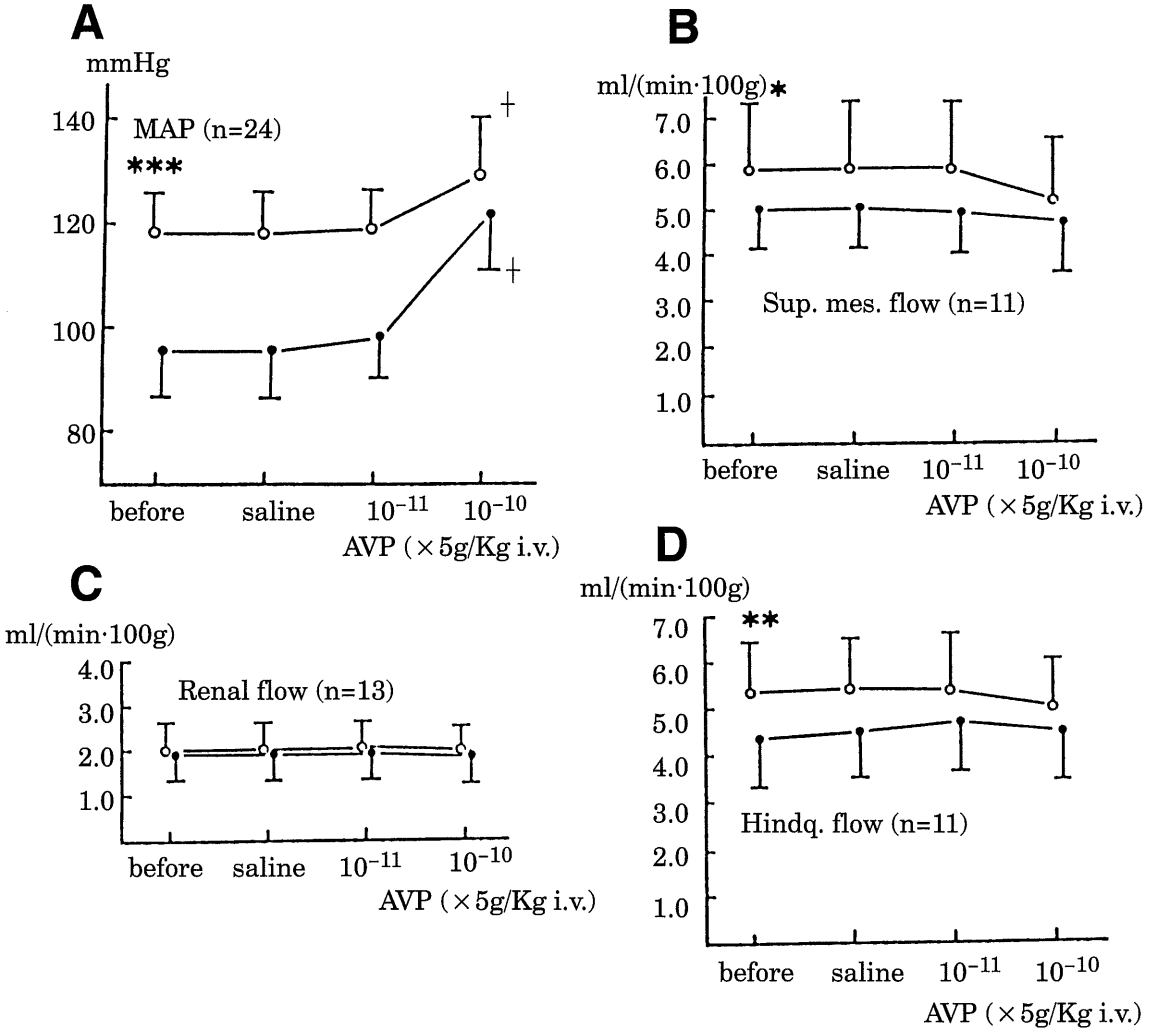

Fig. 2. Effects of arginine vasopressin (AVP) infusions on the mean arterial pressure and regional blood flows in conscious rats before (○) and after (●) ganglionic blockade. (A) mean arterial pressure (MAP), (B) superior mesenteric flow (Sup. mes. flow), (C) renal flow, (D) hindquarter flows (Hindq. flow). Each value is mean ± SD. *p<0.05, **p<0.01 and ***p<0.001 compared to value before injection of ganglionic blockade. + p<0.001 compared to value before AVP injection.

± 7.9 mmHg, p<0.001). But, there was no significant difference between mean arterial pressures before and after ganglionic blockade at a dose of AVP 5 × 10^{-10} g/kg (before blockade; 130 ± 11.0 mmHg; after blockade; 122 ± 11.4 mmHg). The increase in mean arterial pressure induced by AVP after ganglionic blockade was significantly greater than that before ganglionic blockade at a dose of AVP 5×10^{-10} g/kg (before; +12.8 ± 8.8 mmHg; after; +26.7 ± 9.3 mmHg, p<0.001) but there was no significant difference between increments before and after, at a dose of 5 x 10^{-11} g/kg (before; +0.92 ± 3.43 mmHg, after; +2.78 ± 4.03 mmHg, N.S).

AVP decreased regional blood flows in these three vascular beds in a dose-dependent manner (Fig. 1). Superior mesenteric and hindquarter flows in the presence of C6 were also lower than those in the absence of C6. There was no significant difference between these flows before and after C6 at a dose of AVP 5×10^{-10} g/kg (Fig. 2-B, D). In contrast, there was no significant difference between renal flows before and after ganglionic blockade throughout all concentrations of AVP applied (Fig. 2-C).

AVP increased regional vascular resistances in these three vascular beds dose-dependently (Fig. 3-A). The percentage increase in renal resistance induced by a dose of AVP 5×10^{-10} g/kg after ganglionic blockade was significantly higher than that before ganglionic blockade, whereas the percentage increases in superior mesenteric or hindquarter resistance in the presence of hexamethonium were similar to those in the absence of hexamethonium (Fig. 3-B).

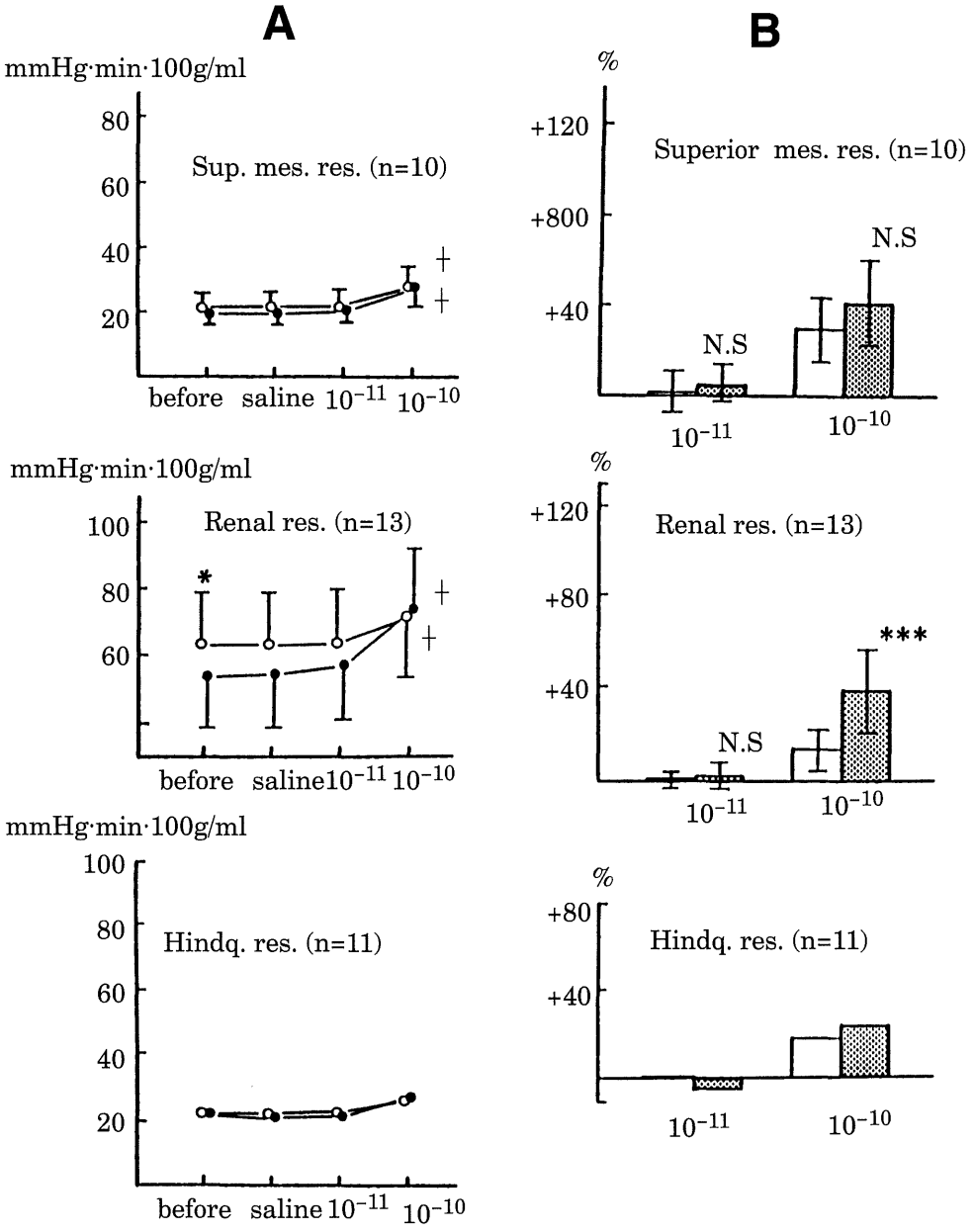

Fig. 3. (A) Effcts of arginine vasopressin (AVP) infusions on the superior mesenteric (top), renal (middle), and hindquarter (bottom) resistance before (○) and after ganglionic blockade with C6 (●). Note that renal resistance decreased as a result of ganglionic blockade. Each value was mean ± SD for superior mesenteric and renal resistances. Hindquarter resistance was calculated as mean arterial pressure divided by mean hindquarter flow. (B) Percent changes in regional vascular resistances by AVP infusions were calculated before (open columns) and after ganglionic blockade (dotted columns).
† $p<0.001$, statistical significant difference before and after AVP infusion (5×10^{-10} g/kg); *$p<0.05$ and ***$p<0.001$, statistical by significant difference before and after C6. N.S.: not significant. Note that the increase in renal resistance by AVP infusion was significantly enhanced after ganglionic blockade.

DISCUSSION

Hemodynamic response to AVP before ganglionic blockade

In the present study, AVP increased mean arterial pressure and regional vascular resistances in a dose-dependent manner in conscious rats. The vasoconstricting effects of AVP (5×10^{-10} g/kg) were greater in the superior mesenteric area than in the renal vascular area (superior mesenteric; +29.7 ± 14.2%, renal; +14.0 ± 9.07%, $p<0.001$, see Fig. 3-B). It has already been reported that AVP has a prominant effect on resis-

tance vessels in skeletal muscle and skin in unanesthetized rats[5], but no effect on the renal area[9]. Schmid et al[11] have reported that the vasoconstricting effect of AVP is the most prominent in skeletal muscle followed by mesenteric and renal vascular beds. This is partially in agreement with our results.

Hemodynamic response to AVP after ganglionic blockade

The pressor action of AVP was enhanced after ganglionic blockade (see Fig. 2-A). According to Montani et al[10], AVP induces a decrease in cardiac output and an increase in total peripheral resistance in conscious dogs. The decrease in cardiac output disappears after baroreceptor denervation, resulting in enhancement of the pressor response. This observation indicates that the augmented pressor effects of AVP after ganglionic blockade is mainly due to a failure of the decrease in cardiac output. However, our results showed that the vasoconstrictor effect of AVP was enhanced in the renal vascular area in the presence of hexamethonium (see Fig. 3-B). Thus, the vasoconstricting effects of AVP on regional hemodynamics may also result from the interaction with the autonomic nervous system.

Several reports relate to our study. AVP administered intravenously inhibited the sympathetic renal nerve activity in conscious rabbit instrumented with a chronic nerve electrode on the renal nerve[13] and in the anesthetized rabbit with vagotomy[6]. Sharabi et al12) have observed in rats that AVP caused a smaller increase in arterial pressure and a greater inhibition of lumbar sympathetic nerve activity. It remains controversial, however, whether or not the inhibition of the sympathetic activity induced by AVP is produced by a baroreceptor-mediated mechanism[6,12,13]. Thus, our data suggest that elevated blood pressure induced by AVP might inhibit sympathetic activity, leading to a decrease particularly in renal vascular resistance. In fact, mean arterial pressure decreased after ganglionic blockade with hexamethonium. Ganglionic blockade decreased renal resistance significantly, whereas superior mesenteric and hindquarter resistances remained unchanged after ganglionic blockade. These data suggest that a sympathetic tonic discharge was present only in the renal area in conscious rats, which is consistent with one previous report[7].

The potentiated pressor effects of AVP by ganglionic blockade reported here are generally consistent with data reported by Hoffman[5] using the microsphere method. He suggested that accentuated pressor effects in response to AVP infusions in sympathetic blocked rats may be due to the abolition of reflex inhibitory action of the central cardiovascular system. However, our data on regional hemodynamics are inconsistent with the results of Hoffman[5]. In our study, vascular resistance changes in both superior mesenteric and hindquarter areas induced by AVP infusions were similar before and after ganglionic blockade, except in the renal vascular bed where ganglionic blockade enhanced vascular responsiveness to AVP. On the contrary, Hoffman[5] showed that, in sympathetic blocked rats, AVP infusions decreased changes in renal and intestinal vascular resistances compared to the changes seen in normal rats. We cannnot account for these differences in regional hemodynamics. Therefore, mechanisms of regional vasoconstriction induced by AVP require further evalution.

Hiwatari et al[4] have reported that after autonomic blockade, the decrease in arterial pressure in Brattleboro rats (which are genetically deficient in endogenous AVP) was greater than that in Long-Evans rats (normal control rats). Furthermore, administration of an antagonist to AVP vascular receptor decreased arterial pressure only in Long-Evans rats, resulting in no difference in arterial pressure between these two strain rats. Following autonomic blockade, plasma concentration of AVP increased significantly only in Long-Evans rats. These observations indicated that sympathetic nerve blockade might enhance vasoconstrictor capacity of AVP acting on vascular receptors of the regional vascular beds. Furthermore, there is another possibility that enhanced sensitivity to AVP vascular receptor after ganglionic blockade in the renal area might be greater than that in the superior mesenteric or hindquarter area, leading to regional differences in the vasoconstrictor effect of AVP in the presence of hexamethonium.

It is well known that the renal flow is kept constant by the autoregulation, irrespective of changes in blood pressure. In our study, the renal flow remained unchanged after ganglionic blockade and AVP decreased renal flow, to the same extent, before and after blockade. Therefore, it still remains a possibility that the autoregulation may decrease the vasoconstrictor capacity of AVP acting on the renal vascular bed.

In summary, the present data suggest that the pressor response to AVP is due mainly to prominent vasoconstrictions on resistance vessels in skeletal muscle, skin and mesenteric areas, so that the elevated arterial pressure may reflexly inhibit sympathetic nervous activity, resulting in a decrease in the vasoconstrictor capacity of AVP acting on the renal vascular area in which sympathetic tonic discharge was observed.

ACKNOWLEDGEMENT

The authors are very grateful to Dr. M. Kakehashi of Department of Public Health, Hiroshima University School of Medicine for his guidance on the statistical tests.

(Received October 2, 1992)
(Accepted March 17, 1993)

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