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[1-Deaminopenicillamine, 4-Valine, 8-D-Arginine]-Vasopressin Antagonizes the Mesenteric Vasoconstrictor Response to Arginine Vasopressin in Cats[1] (40485)

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[1-Deaminopenicillamine, 4-valine, 8-D-arginine]-vasopressin (dPVDAVP) has been reported to inhibit the vasopressor response to arginine vasopressin (AVP) in anesthetized rats (1). However neither antagonism of AVP by dPVDAVP in other species nor the effects of dPVDAVP on the resistance vessels of a major vascular bed have been studied. The mesenteric resistance vessels are highly sensitive to vasopressin (2, 3) and a role for circulating vasopressin in the control of these vessels has been postulated (see discussion). Thus the mesenteric bed of cats was used to determine if dPVDAVP was an antagonist of resistance vessel responses to arginine vasopressin. The effect of dPVDAVP on the mesenteric vasoconstrictor responses to vasopressin was compared to its effect on responses to another peptide, angiotensin II.

Materials and methods. Six cats (2.1–3.5 kg) were anesthetized by intraperitoneal injection of 30 mg/kg of sodium pentobarbital (Nembutal, Abbott Lab.). Superior mesenteric arterial flow was recorded from a noncannulating electromagnetic flow probe (Statham Instr. Co. Oxnard, CA) and arterial pressure was recorded from a cannula advanced into the femoral artery. Hypophysectomy was performed by a transpalatal approach. The details of these methods have been described elsewhere (4).

Arginine vasopressin (Sigma) or angiotensin II (Sigma) was infused through a cutaneous forelimb vein in four cats at rates sufficient to reduce superior mesenteric arterial flow to values which were approximately 50–70% of the corresponding preinfusion control values. dPVDAVP was infused on two occasions, once during the plateau phase of the response of the mesenteric resistance vessels to arginine vasopressin and again later. During the second infusion of dPVDAVP, the infusion of angiotensin II was repeated.

The responses of the mesenteric resistance vessels were calculated in conductance units (ml/min/kg/mmHg) and the values recorded during the responses were expressed as a percentage of the control conductance values recorded immediately before each infusion period. Analysis of variance for repeated measures or paired t test was used for statistical analysis. All values are expressed as the mean ± SE.

Results. Infusion of AVP (2.2 ± 0.1 mU/min/kg) in hypophysectomized cats caused a fall in superior mesenteric arterial conductance and an increase in arterial pressure (Fig. 1). Both conductance and pressure reached relatively stable new levels 6–12 min after beginning the infusion. Before infusion of the peptide, conductance was 0.212 ± 0.043 ml/min.kg.mmHg and arterial pressure was 135 ± 10 mmHg and the values for conductance and pressure recorded 3 min after beginning the infusion were significantly different from these control values ($p < .05$). Infusions of 2.4 ± 0.3 and 5.4 ± 0.7 μg/min/kg of dPVDAVP during the response to AVP caused increases in conductance towards the control values (Fig. 1). The values for conductance recorded during the final minutes of 5.4 μg/min/kg of dPVDAVP were only slightly less than and not significantly different from control values ($p > .05$). Associated with the vasodilatation was a fall in arterial pressure and the values for pressure recorded during the final minutes of 2.4 and 5.4 μg/

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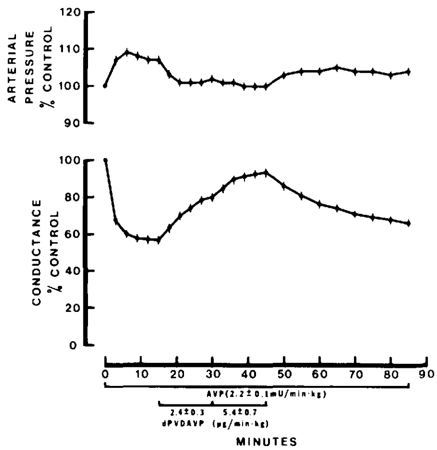

FIG. 1. Effect of intravenous infusion of dPVDAVP on the response of superior mesenteric arterial conductance and femoral arterial pressure to a prolonged infusion of AVP in four hypophysectomized cats.

min/kg of dPVDAVP were not significantly different from control values ($p > .8$). When the infusion of dPVDAVP was stopped, the mesenteric vasoconstrictor and pressor responses to AVP recovered slowly. Thus dPVDAVP antagonized the mesenteric vasoconstrictor response to AVP and the effect was at least partially reversible with time.

Infusion of angiotensin II (0.047 ± .004 μg/min/kg) both before and during a prolonged infusion of 4.0 ± 0.3 μg/min. kg of dPVDAVP caused a decrease in mesenteric conductance and an increase in arterial pressure (Fig. 2). Control values for the initial infusion of angiotensin II were 0.209 ± 0.032 ml/min. kg mmHg and 138 ± 9 mmHg and those for the second infusion were 0.206 ± 0.035 ml/min. kg.mmHg and 132 ± 10 mmHg. The responses to the two infusions of angiotensin were quite similar. The conductance values (% control, Fig. 2) recorded during the second infusion of angiotensin II when dPVDAVP was being administered simultaneously were not significantly different from those recorded during the first infusion of angiotensin II when the animal had not been exposed to dPVDAVP ($p > .1$). The pressure values recorded during the second infusion of angiotensin II were slightly larger ($p < .02$) than those of the first infusion but the difference was small. Thus a dose of dPVDAVP that antagonized the mesenteric vasoconstrictor response to AVP had little effect on the mesenteric vasoconstrictor response to angiotensin II.

In 6 hypophysectomized cats, infusion of 4.2 ± 0.3 μg/min/kg of dPVDAVP for periods of from 5 to 8 min caused little change in mesenteric conductance and arterial pressure (Table I). In 3 of these animals, increasing the dose of dPVDAVP to 16.2 ± 2.6 μg/min/kg for 1–8 min caused little further change in conductance or pressure (Table I). Thus infusion of dPVDAVP in doses which antagonize the mesenteric vasoconstrictor response to AVP caused little change in conductance or pressure under conditions when circulating levels of vasopressin are likely to be negligible.

Discussion. dPVDAVP appears to be an antagonist of the vasoconstrictor activity of AVP in cats as well as in rats. The compound inhibited the mesenteric vasoconstrictor response in cats to AVP; it initiated little or no vasodilatation when administered alone to hypophysectomized animals; it failed to inhibit the mesenteric vasoconstrictor response to another peptide, angiotensin II. In preliminary experiments it also failed to inhibit the response to the α-agonist phenylephrine. Recently Manning et al. (1) reported that dPVDAVP inhibited the pressor response to AVP but not to norepinephrine or angiotensin II. Thus, our studies on the effects of infusions of dPVDAVP on the resistance ves-

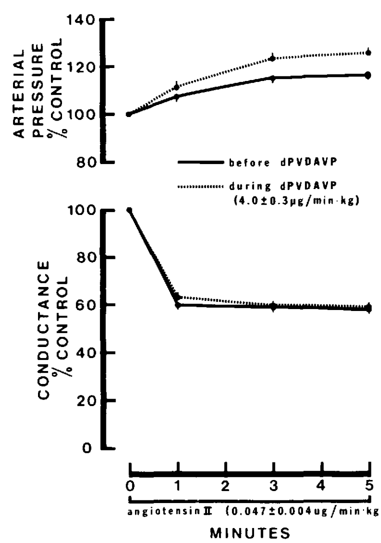

FIG. 2. Effect of intravenous infusion of angiotensin II before and during a prolonged infusion of dPVDAVP.

TABLE I. EFFECT OF dPVDAVP ON SUPERIOR MESENTERIC ARTERIAL CONDUCTANCE AND FEMORAL ARTERIAL PRESSURE IN HYPOPHYSECTOMIZED CATS.

	Control	dPVDAVP (4.2 ± 0.3 μg/min/kg, n = 6)	Control	dPVDAVP (16.2 ± 2.6 μg/min/kg, n = 3)
Conductance[a]				
ml/min·kg·mmHg	0.189 ± 0.027	0.192 ± 0.027	0.160 ± 0.019	0.167 ± 0.023
% control		103 ± 2.0		104 ± 2.0
		(94–109)		(99–107)
Pressure[a]				
mmHg	130 ± 8.0	129 ± 7.3	133 ± 9.7	128 ± 4.9
% control		99 ± 0.9		97 ± 3.5
		(96–103)		(89–104)

[a] Values are the means ± SE except for those in parentheses which represent the range of individual values.

sels of a major vascular bed in the cat are in agreement with the earlier observations of Manning et al. who studied the effects of injections of dPVDAVP on the blood pressure responses of the rat.

The lack of an antagonist to the vasoconstrictor properties of AVP has hindered research into the role this hormone might play in the control of resistance vessels in conscious animals although other evidence suggests such a role for the peptide may exist. A role for vasopressin in the control of the mesenteric resistance vessels is suggested by several observations on the effects of acute hypophysectomy. Removal of the gland caused mesenteric vasodilatation in normovolemic anesthetized cats (5); it abolished the intestinal vasoconstrictor response to volume-depletion induced by hemorrhage (4) or by administration of diuretic agents (6) providing that the renin-angiotensin system was not allowed to compensate; it caused the mesenteric resistance vessels to respond to doses of exogenous AVP which previously were inactive in the intact animal (2). Unfortunately these studies on the effects of acute hypophysectomy were performed in anesthetized surgically-stressed animals, conditions which elevate markedly the circulating levels of vasopressin (7). The discovery of dPVDAVP should permit comparable studies on the mesenteric resistance vessels of conscious animal.

Summary. Intravenous infusion of [1-Deaminopenicillamine, 4-valine, 8-D-arginine]-vasopressin (dPVDAVP) inhibited the mesenteric vasoconstrictor response to arginine vasopressin in cats but the compound initiated little or no vasodilatation when administered alone in hypophysectomized cats and it failed to inhibit the mesenteric vasoconstrictor response to angiotensin II. The results are consistent with the interpretation that dPVDAVP is an antagonist of the vasoconstrictor activity of arginine vasopressin.

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