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Potentiated Vasoconstrictor Response to Vasopressin following Meclofenamate in Conscious Rats (42649)

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Abstract. Experiments were performed to test the hypothesis that release of vasodilator cyclooxygenase products may attenuate the systemic and renal vasoconstrictor responses to arginine vasopressin (AVP) in the conscious, chronically instrumented rat. Four groups of animals were studied under the following conditions: (i) AVP infused iv at 2 ng/min for 40 min followed by a 15-min postcontrol; (ii) pretreatment with meclofenamate (3 mg/kg iv) followed by AVP infusion; (iii) meclofenamate pretreatment followed by saline vehicle infusion; and (iv) saline vehicle infusion alone (time control). AVP increased mean arterial blood pressure (MABP) in both meclofenamate-treated (n = 12) and untreated (n = 12) animals; however, the pressor response was significantly greater in animals with cyclooxygenase inhibition. Both heart rate (HR) and cardiac output (CO) (n = 6) fell during AVP infusion, but there were no differences between the meclofenamate-treated and the untreated groups. However, the total peripheral resistance response to AVP was significantly greater in animals treated with meclofenamate than the untreated group. Renal blood flow (RBF) was not affected by AVP infusion alone, but RBF fell significantly in animals given AVP after cyclooxygenase inhibition. The renal vascular resistance response to AVP was also enhanced by cyclooxygenase inhibition. There were no changes in any of the hemodynamic variables in either of the control protocols (i.e., meclofenamate alone or vehicle). These data demonstrate a consistent effect of cyclooxygenase inhibition to augment the systemic and renal vasoconstrictor responses to AVP, and suggest that endogenous vasodilator prostaglandins attenuate the potent vasoconstrictor action of this peptide *in vivo*.

Arginine vasopressin (AVP) is a potent vasoconstrictor which may contribute to maintenance of blood pressure in several pathophysiological settings such as hemorrhage (1), water deprivation (2–4), and some forms of experimental hypertension (5,6). Although the *in vitro* potency of AVP as a vasoconstrictor may exceed that of other pressor agents such as angiotensin II, a number of mechanisms appear to exist *in vivo* that attenuate the elevation in blood pressure and vascular resistance. These mechanisms include possible altered baroreflex function (7,8), vasodilation due to activation of V_2-like vasopressinergic receptors (9–11), and AVP-initiated endothelium-dependent relaxation (12).

Another possible mechanism which may reduce AVP-induced vasoconstriction is the release of vasodilator prostaglandins (13–19). *In vitro* experiments have documented that the potent vasodilator prostacyclin (PGI_2) is released by cultured vascular smooth muscle cells in response to AVP (14). In addition, *in vivo* renal synthesis of PGE is stimulated by exogenous AVP (20). Furthermore, administration of the cyclooxygenase inhibitor indomethacin delays the tachyphylaxis of the blood pressure response to continuous AVP infusion in humans (13). Studies on anesthetized animals have also demonstrated enhanced renal vasoconstriction in response to exogenous AVP following prostaglandin inhibition (15, 16, 18, 19). However, the physiological significance of these latter findings is uncertain, since anesthesia and acute surgical preparation greatly stimulate AVP release (21) and renal prostaglandin production (22), resulting in a reliance of renal blood flow (RBF) on vasodilator prostaglandins not typically observed in conscious animals (22). In order to avoid these complicating effects of anesthesia and acute preparation, a previous study from our laboratory examined the effect of cyclooxygenase inhibition on the blood pressure responses to bolus AVP in conscious rats (23). Although a greater and more prolonged rise in blood

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pressure was observed following cyclooxygenase inhibition in these studies, blood flow measurements were not performed so that the change in vascular resistance elicited by AVP under these conditions was not determined. Furthermore, only bolus AVP administration was employed in an attempt to observe the pressor effects of AVP prior to baroreflex activation. However, this form of administration does not mimic the normal release of AVP *in vivo*. Therefore, the present experiments were undertaken to test for the possible involvement of endogenous prostaglandins as modulators of the pressor effects of continuously infused AVP in conscious rats instrumented for determination of either cardiac output (CO) or renal blood flow. These experiments demonstrate that vasodilator prostaglandins likely attenuate the vasoconstrictor effect of AVP under conditions closely resembling situations of enhanced AVP release in conscious animals.

Materials and Methods. Experiments were performed using conscious, unrestrained, male Sprague–Dawley rats (body weight = 300–400 g).

Surgical preparation. Rats were pretreated with atropine (50 μg im) and anesthetized with a mixture of ketamine (110 mg/kg) and acepromazine (1 mg/kg) given intramuscularly. Four groups of rats ($n = 6$) were chronically instrumented for thermodilution cardiac output determinations. Using aseptic technique, a thermocouple probe (Sensortek, Inc.) was advanced through the left carotid artery to the aortic arch and secured. An injection catheter (PE-50) was advanced to the right atrium through either the right or the left jugular vein and tied in place. Polyvinyl catheters (PV-1, BOLAB, Inc.) were placed in the abdominal aorta and vena cava via the left femoral artery and vein. The catheters and thermocouple probe were routed subcutaneously to the dorsal aspect of the neck, exteriorized, and placed in a protective plastic container sutured to the skin. Experiments were performed after 2–3 days of recovery on animals that were afebrile and demonstrated normal food and water intake.

Another four groups of rats ($n = 6$) were chronically instrumented with pulsed Doppler blood flow probes for determination of renal blood flow. A midline abdominal incision was made and the left renal artery was exposed and isolated. Doppler probes were constructed in our laboratory using techniques described by Haywood *et al.* (24). Probes were placed on the renal artery and secured between the adrenal artery and the kidney with care not to damage the renal nerves. The insulated wire leads were passed through the abdominal wall and routed subcutaneously as previously described. One week later, the rats were reanesthetized and chronic femoral catheters were implanted and routed as outlined above. Experiments were performed after 2–3 days of recovery from catheter implant.

Experimental procedures. Animals were placed in a Plexiglas chamber of sufficient size (25 × 10 × 10 cm) to allow free movement, but small enough to discourage excessive exploration. The bottom of the chamber was covered with bedding for the comfort of the animal and air was continuously flushed through the chamber. The catheters were opened and flushed with sterile heparinized saline. The arterial catheter was connected to a Statham-Gould P23-Gb pressure transducer, the output from which was amplified by a Gould Universal amplifier. Pulsatile and mean arterial blood pressure (MABP) were recorded on separate channels of a Gould Brush 260 recorder. The pulsatile arterial pressure signal was further processed by a Gould Biotach amplifier to record heart rate (HR). In rats instrumented with thermocouple probes, CO was measured using the thermodilution technique with a Columbus Instruments cardiac output computer designed for use with small animals. The thermocouple probe output was recorded for inspection of proper waveform for each curve and stable baseline. In rats instrumented for RBF determination, the flow probe was connected to a pulsed Doppler blood flowmeter (Valpey-Fisher) and the mean signal was continuously recorded on one channel of the chart recorder. All rats were allowed 30–60 min to equilibrate, followed by one of the experimental protocols listed below.

AVP infusion. After control measurements, AVP was infused intravenously at a

rate of 2 ng/min for 40 min. Blood pressure and HR were continuously monitored in all animals (n = 12). In addition, RBF was measured continuously in six animals, whereas CO was determined at 10, 20, 30 and 40 min of AVP infusion in the other six rats. At 40 min, the intravenous infusion of AVP was terminated, and blood pressure, HR, and RBF were monitored for an additional 15 min. A final postinfusion CO determination was made at the end of this final 15-min period.

Meclofenamate pretreatment plus AVP infusion. Another group of rats (n = 12) was studied in a manner identical to that above, except that meclofenamate (3 mg/kg) was administered intravenously 30 min before the AVP infusion.

Time control. Another 12 rats received only an intravenous physiological saline infusion of equal volume (8 μl/min) to the above AVP infusion. All measurements and timing were identical to the other protocols.

Meclofenamate control. These rats (n = 12) were given meclofenamate intravenously 30 min before a saline vehicle infusion (8 μl/min). All measurements and timing were identical to the previous protocols.

Calculations and statistics. Total peripheral resistance (TPR) was calculated by dividing MABP by the corresponding CO. Renal vascular resistance (RVR) was calculated by dividing MABP by the corresponding RBF value. Because the Doppler signal is expressed in kilohertz and is a measure of velocity and not actual volume flow, renal blood flow and renal vascular resistance were expressed as percentages of control as described by others (24). MABP, HR, RBF, and RVR were assessed at 5-min intervals during the experimental manipulations and for 15 min afterwards. CO and TPR were determined at 10-min intervals during the experimental infusion period and 15 min afterward. The data from each group were compared by analysis of variance and if differences were indicated (i) the control pre-AVP infusion values were compared to the subsequent data using Dunnett's multiple comparison test, and (ii) the experimental groups were compared to one another at each time using Newman–Keul's multiple comparison test. Differences were assumed significant if $P < 0.05$.

Results. The initial control values for MABP, HR, CO, and TPR are presented in Table I. MABP and HR basal values and responses to the various stimuli were not different between the CO and the RBF preparations; thus data for those variables were combined (n = 12). In addition, no differences in any experimental parameter were observed between premeclofenamate and the 30-min postmeclofenamate values used for controls in Table I. RBF was also unaffected during this 30-min equilibration period.

MABP responses to the various experimental protocols are presented in Fig. 1. Both groups of rats administered AVP demonstrated a significant increase in MABP from control preinfusion values. However, the rise in MABP during AVP infusion in meclofenamate pretreated animals was significantly greater than in animals administered AVP alone. The groups which received meclofenamate or vehicle but no AVP were unchanged over time. Figure 2 presents the HR responses for each group. Both groups

TABLE I. PREINFUSION CONTROL VALUES FOR HEMODYNAMIC VARIABLES

	MABP (n = 12) (mm Hg)	HR (n = 12) (bpm)	Cardiac output (n = 6) ($ml \cdot min \cdot^{-1} \cdot kg^{-1}$)	TPR (n = 6) (units)
AVP infusion	106.9 ± 3.7	375 ± 15	285 ± 24	390 ± 24
Meclofenamate + AVP infusion	98.6 ± 2.9	368 ± 15	285 ± 18	346 ± 36
Meclofenamate + vehicle	101.1 ± 3.5	367 ± 14	285 ± 32	363 ± 46
Vehicle control	104.2 ± 4.2	375 ± 14	270 ± 25	381 ± 43

Note. MABP, mean arterial blood pressure; HR, heart rate; TPR, total peripheral resistance. Data are means ± SE.

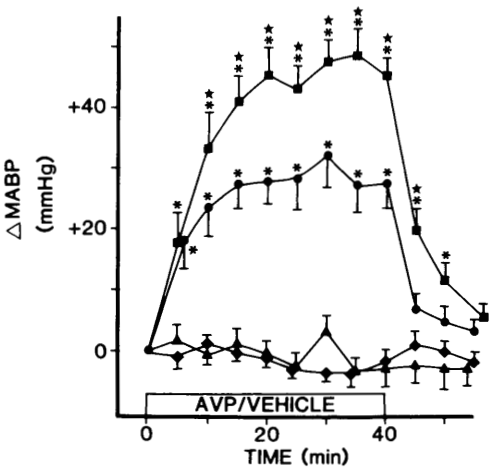

FIG. 1. Mean arterial blood pressure (MABP) responses to AVP or vehicle infusion. Circles, AVP infusion group (n = 12); squares, meclofenamate pretreatment plus AVP (n = 12); diamonds, meclofenamate plus vehicle (n = 12); triangles, vehicle control (n = 12). Data are means ± SE. Asterisks indicate significant difference from vehicle control; stars indicate differences between meclofenamate-treated and nontreated AVP groups ($P < 0.05$).

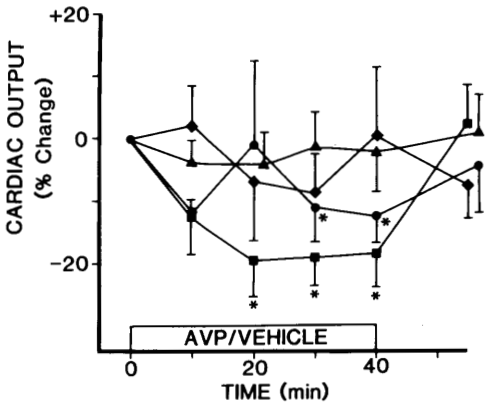

FIG. 3. Cardiac output responses to AVP or vehicle infusion. Symbols are identical to those in Fig. 1. Data are means ± SE; n = 6 in each group.

receiving AVP showed a marked reduction in HR; however, no significant difference was observed between the two groups. No significant HR response was observed in either control group. Consistent with the reduction in HR, CO decreased in the AVP-treated animals; however, no significant difference was observed between the meclofenamate-pretreated and the untreated groups (Fig. 3). Figure 4 illustrates the TPR responses for each protocol. TPR was significantly increased by AVP infusion, with the response in the meclofenamate-pretreated group significantly greater than that in the nonpretreated animals. TPR did not change

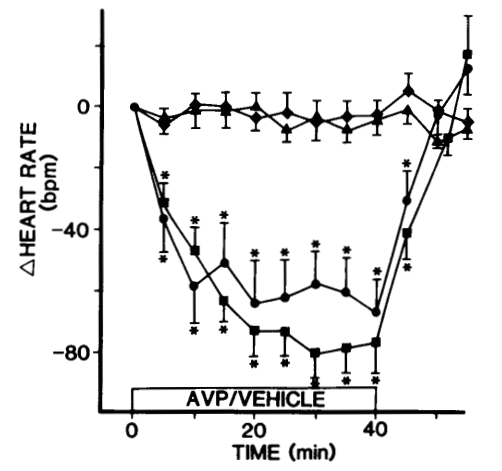

FIG. 2. Heart rate responses to AVP or vehicle infusion. Symbols are identical to those in Fig. 1. Data are means ± SE; n = 12 in each group.

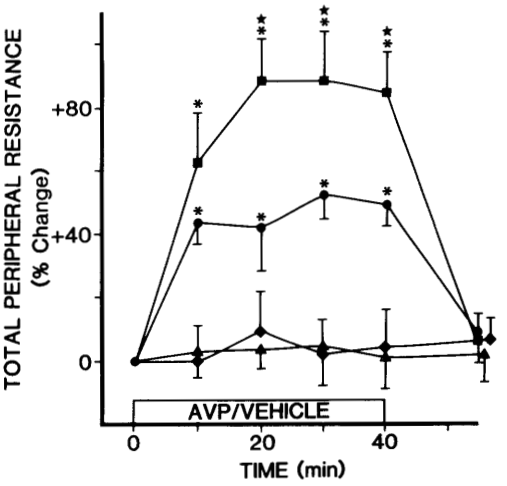

FIG. 4. Total peripheral resistance responses to AVP or vehicle infusion. Symbols are identical to those in Fig. 1. Data are means ± SE; n = 6 in each group.

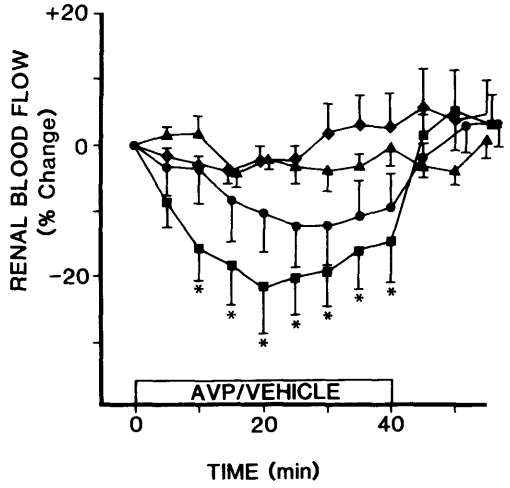

FIG. 5. Renal blood flow responses to AVP or vehicle infusion. Symbols are identical to those in Fig. 1. Data are means ± SE; n = 6 in each group.

in either control group. In animals instrumented with pulsed Doppler flow probes, RBF tended to decrease during AVP infusion; however, only the meclofenamate-pretreated group was significantly reduced when compared to the parallel time control (Fig. 5). There was no statistical difference, however, between the two groups administered AVP. In contrast, RVR rose significantly higher in meclofenamate-pretreated rats given AVP than in those given AVP alone. RVR was unaltered in either control group (Fig. 6).

Discussion. Results from our studies suggest that endogenous vasodilator prostaglandins modulate the systemic and renal vascular responses to pressor levels of circulating AVP. This conclusion is based upon the observation that both the TPR and the RVR responses to infused AVP are greater in conscious rats pretreated with the cyclooxygenase inhibitor meclofenamate than those in untreated controls. Furthermore, cyclooxygenase products appear to contribute toward maintenance of RBF under conditions of elevated plasma AVP, since RBF falls below control only in meclofenamate-treated animals. The rate of infusion for AVP used in these experiments results in an increase of plasma AVP concentration from a basal level of 2 pg/ml to about 35 pg/ml in the conscious rat (unpublished observation), which would correspond to observed AVP levels in a number of pathophysiological situations such as hemorrhage, hypotension, and nausea (25). Therefore, the present experiments document an apparent modulating effect of endogenous prostaglandins under well-controlled, physiologically relevant conditions in conscious rats.

Earlier experiments have documented stimulation of PGI_2 by AVP in cultured rat vascular smooth muscle cells *in vitro* (14). Although angiotensin II also caused enhanced PGI_2 synthesis in this system, the response to AVP was considerably greater. However, administration of an AVP analog devoid of vasoconstrictor properties was much less effective in stimulating PGI_2 release, suggesting that the pressor activity of AVP is important in releasing PGI_2. Studies on isolated rat kidneys have also documented stimulated PGI_2 release in response to AVP, but not to its nonpressor analog (26). In addition, earlier experiments have shown that other vasodilator cyclooxygenase products, notably PGE_2, may be released by the kidney in response to AVP both *in vitro* and *in vivo* (20, 27, 28). The present interpretations are based upon the assumption

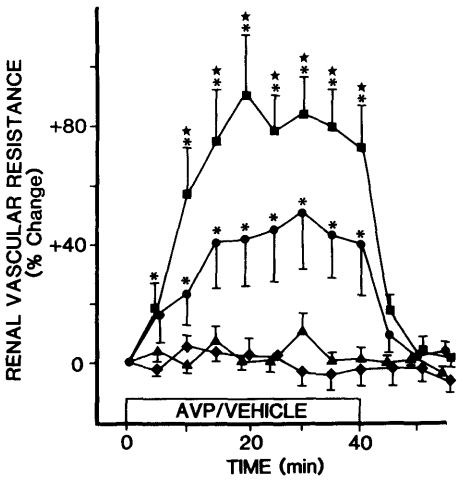

FIG. 6. Renal vascular resistance responses to AVP or vehicle infusion. Symbols are identical to those in Fig. 1. Data are means ± SE; n = 6 in each group.

that our dose of meclofenamate effectively blocks prostaglandin synthesis. Not only has this dose been previously shown to be effective in conscious animals (29), but these data are qualitatively similar to those previously reported from our laboratory assessing the pressor effects of bolus AVP administration in conscious rats (23). In these studies, both meclofenamate and ibuprofen, the structurally dissimilar cyclooxygenase inhibitor, showed comparable augmentation of the acute pressor response to AVP. Therefore, the current findings are most likely due to prostaglandin synthesis inhibition, and not some nonspecific action of meclofenamate.

The current studies clearly demonstrate an increased vasoconstrictor response to AVP following cyclooxygenase inhibition in the conscious rat. Both TPR and RVR were significantly greater in animals pretreated with meclofenamate than in untreated controls. These data are supportive of previous studies examining the renal vascular responses to AVP following cyclooxygenase inhibition (15, 16); however, the current experiments allow assessment of the vascular modulating effect of prostaglandins independent of several complicating factors associated with these earlier studies. Conflicting data exist from experiments involving administration of cyclooxygenase inhibitors to anesthetized, laparotomized animals. Cyclooxygenase inhibition dramatically reduced renal blood flow and increased resistance in the anesthetized dog, whereas similar drug administration has no effect in conscious animals (22). In contrast, meclofenamate and indomethacin were without effect on renal blood flow in the anesthetized rat (34). These data make conclusions regarding the role of prostaglandins on basal renal blood flow difficult. The former data suggest that basal vasodilator prostaglandin production is greatly enhanced under these acute conditions, leading to an abnormal reliance of renal blood flow on cyclooxygenase products. This interpretation is supported by measurements of stimulated renal prostaglandin production when compared to conscious animals (22). Furthermore, circulating levels of endogenous AVP are also greatly stimulated by acute preparation (21), so that the assessment of the interaction between prostaglandins and AVP in determining a final vascular response is questionable in anesthetized animals. The conscious rats in our studies showed no renal hemodynamic effect of meclofenamate alone. Additionally, previous experiments from our laboratory have demonstrated no effect of administration of a vascular AVP antagonist in identically prepared animals (11). Therefore, conclusions from the current experiments can be made without the uncertainties associated with prior studies.

Associated with the greater RVR response to AVP following cyclooxgenase inhibition was a reduction in RBF below control in animals treated with meclofenamate and AVP. This differed from animals treated with AVP alone, which showed no significant diminution of flow. These data suggest that endogenous vasodilator prostaglandins may protect RBF under conditions of increased circulating AVP. Since other investigators have shown that RBF is unaffected by a 1-hr infusion of AVP in conscious dogs (30), a physiological role for cyclooxygenase products as renal vasodilators maintaining RBF under conditions of elevated AVP is attractive.

Vasodilator prostaglandins have been proposed to be involved in modulating the responses to a number of pressor stimuli in addition to AVP. For example, prostaglandin synthesis inhibition potentiates vasoconstriction in mesenteric arteries following angiotensin II administration (31). Furthermore, meclofenamate may augment the renal vasoconstrictor response to norepinephrine or renal nerve stimulation in anesthetized rats (32). PGI_2 release has also been demonstrated in response to pulmonary vasoconstriction in isolated rat lungs (33). It therefore appears that vasodilator prostaglandins are important modulators of a variety of vasoconstrictor stimuli in several beds.

Conclusion. The present experiments demonstrate a consistent effect of cyclooxygenase inhibition to augment the systemic and renal vasoconstrictor responses to AVP, and suggest that endogenous vasodilator prostaglandins may attenuate the potent vasoconstrictor action of this peptide in the conscious rat.

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