Central α₂-receptor mechanisms contribute to enhanced renal responses during ketamine-xylazine anesthesia

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Renal responses during ketamine-xylazine anesthesia

This study examined the contribution of central and peripheral mechanisms to enhanced renal responses during ketamine-anesthetized rats. The model system uses the intravenous infusion of the α₂-agonist xylazine to enhance basal levels of urine flow rate and increase diuresis in ketamine-anesthetized rats. This study examined the contribution of central and peripheral α₂-adrenergic receptor mechanisms in mediating the enhanced renal excretory responses produced by xylazine. In ketamine-anesthetized rats, the enhanced levels of urine flow rate and urinary sodium excretion produced by the intravenous infusion of xylazine were reversed by the intravenous bolus injection of the α₂-adrenoceptor antagonist yohimbine but not by the α₁-adrenoceptor antagonist terazosin. In separate animals, the intracerebroventricular administration of yohimbine only reduced urine flow rate by ∼50% but did not alter urinary sodium excretion. The decrease in urine flow rate produced by intracerebroventricular yohimbine was reversed by the intravenous injection of a selective V₂-vasopressin receptor antagonist. In a separate group of ketamine- and xylazine-anesthetized rats, the bilateral microinjection of yohimbine into the hypothalamic paraventricular nucleus (PVN) also significantly decreased urine flow rate by 54% without altering urinary sodium excretion. The microinjection of the β-adrenoceptor antagonist propranolol into the PVN did not alter either renal excretory parameter. These results suggest that during intravenous infusion, xylazine enhances urine flow rate by activating α₂-adrenergic receptors in the PVN, which in turn decrease vasopressin release. The ability of α-adrenergic mechanisms in the PVN to selectively influence the renal handling of water but not sodium, may contribute to the reported dissociation of the natriuretic and diuretic responses of α₂-adrenoceptor agonists.

hypothalamic paraventricular nucleus; yohimbine; urine flow rate; urinary sodium excretion; renal excretory function

WE HAVE RECENTLY demonstrated that the intravenous infusion of the α₂-adrenergic agonist xylazine significantly enhances basal levels of urine flow rate and urinary sodium excretion in ketamine-anesthetized rats (7). The enhanced and sustained renal responses attained in ketamine-anesthetized rats receiving xylazine infusion were in marked contrast to the low renal excretory levels of water and sodium observed in rats anesthetized with ketamine or pentobarbital alone (7). Similar to these findings, a number of studies have shown that other α₂-agonists (e.g., clonidine, guanabenz, BHT-933, rilmenidine, etc.) also produce a diuretic and natriuretic response in anesthetized (and conscious) animals and humans (13, 17, 18, 31). Despite these findings, the mechanisms by which these compounds change the renal excretion of water and sodium have not been completely elucidated.

Reduced renal excretory responses occur in surgically operated animals and humans anesthetized with different anesthetic agents (4, 10, 32, 45). Because surgery and anesthesia are potent stimuli for vasopressin release, α₂-agonists may produce diuretic and natriuretic responses during anesthesia and surgery by inhibiting the central nervous system (CNS) secretion and/or renal tubular action(s) of vasopressin. In regard to this latter possibility, considerable evidence indicates that the activation of renal α₂-adrenoceptors is a predominant mechanism by which selective α₂-agonists produce diuretic and natriuretic responses in several mammalian species (14, 15, 40, 41, 43). Stimulation of renal α₂-adrenoceptors inhibits vasopressin-mediated cAMP formation and the subsequent effects on water and sodium excretion (28, 40). Based on these findings, the intravenous infusion of xylazine may enhance renal excretory function in ketamine-anesthetized rats by stimulating α₂-adrenoceptors in the collecting duct and thus modulating the antidiuretic effect of vasopressin in this nephron segment.

In addition to a direct renal action, it is possible that a portion of the diuretic and/or natriuretic response elicited by the intravenous infusion of xylazine in ketamine-anesthetized rats is mediated by a pathway involving α₂-adrenoceptors located in the CNS. More specifically, the increase in urine flow rate produced by intravenous xylazine may result, at least in part, from a central action of the drug to inhibit the secretion of vasopressin. Such a mechanism would be consistent with the results of a number of studies showing that the activation of central α₂-adrenergic receptors, in particular the α₂-receptor subtype, inhibits the release of vasopressin in conscious and anesthetized animals (6, 20, 21, 38, 39). Although changes in circulating vasopressin levels may also contribute, it appears that the natriuretic response produced by α₂-adrenoceptor agonists is mediated by an alternative mechanism(s) independent of this hormone (3, 9, 22, 24, 39, 43).
The purpose of the present study was to examine the contribution of central α₂-adrenergic receptor mechanisms in mediating the enhanced renal excretory responses produced by the intravenous infusion of xylazine in ketamine-anesthetized rats. For this purpose, we compared the changes in renal function produced by the intravenous and intracerebroventricular injection of the α₂-adrenergic receptor antagonyst yohimbine in ketamine- and xylazine-anesthetized rats. Microinjection techniques were then used to determine whether α₂-adrenoceptors in the hypothalamic paraventricular nucleus (PVN) play a role in mediating the enhanced renal responses to xylazine. The PVN was chosen as the focus of these studies because the PVN contains neurons that synthesize and release vasopressin in the posterior pituitary (44). Vasopressin secretion is known to be markedly enhanced under conditions of anesthesia and surgery (8, 11, 30, 35). In addition, the vasopressinergic neurons in the PVN receive dense catecholaminergic projections from the A1 and other nuclei (44) and contain large numbers of α₂-adrenoceptors (1, 34, 37).

**METHODS**

**Subjects**

Experiments were performed using male Sprague-Dawley rats (275–325 g, Harlan). All procedures were done in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Care and Use Committee at Louisiana State University Medical Center. The rats were housed in groups in a temperature- and humidity-controlled room with a 12:12-h light-dark cycle. Standard rat chow (Na⁺ content 163 meq/kg) and tap water were available ad libitum.

**Surgical Procedures**

Intracerebroventricular cannula implantation. Five to seven days before the experiment, certain rats were anesthetized (ketamine 30 mg/kg im in combination with xylazine 3 mg/kg im) and a stainless steel cannula was implanted into the right lateral cerebral ventricle. The cannula was implanted 0.3 mm posterior to the bregma, 1.3 mm lateral to the midline, and 4.5 mm below the skull surface (36). The cannula was fixed into position by using jewelers’ screws and cranioplastic cement. Verification of the cannula position in the lateral ventricle was made by observing the leakage of cerebrospinal fluid from the cannula after removal of the obturator (7).

Catheter implantation. On the day of the experiment, rats were anesthetized with sodium methohexital (Brevital, 35 mg/kg ip, supplemented with 10 mg/kg iv as needed; Lilly, Indianapolis, IN). Catheters (PE-50 fused to PE-10) were placed in the femoral artery and vein for the recording of arterial pressure and administration of drugs, respectively. The catheters were tunneled subcutaneously to the back of the neck, flushed, and plugged. A suprapubic incision was then made, and a bladder catheter (flanged PE-240) was inserted and sutured into the urinary bladder. The bladder catheter was then exteriorized and secured by suturing it to adjacent muscle and skin. After surgical preparation, the rat was placed in a rat holder, which permitted the collection of urine. Rats then received ketamine (40 mg/kg iv) or xylazine (50 µg·kg⁻¹·min⁻¹) and xylazine (50 µg·kg⁻¹·min⁻¹) was then started and continued throughout the experiment. The arterial and venous catheters were connected to a pressure transducer (model P23 Db, Statham, Oxnard, CA) and an infusion pump (model 944, Harvard Apparatus, South Natick, MA), respectively. Mean and pulsatile arterial pressures were recorded on a Grass 7D polygraph (Grass Instruments, Quincy, MA). Heart rate was determined from the arterial pressure signal by a Grass model 7P4 tachograph. During surgery and experimental procedures body temperature was maintained at 37 ± 1°C using a water-filled heating pad and/or a heat lamp.

**Microinjection procedures.** Certain studies were performed in ketamine- and xylazine-anesthetized rats in which drugs were microinjected into the PVN of the hypothalamus. For these studies rats were anesthetized (Brevital, 35 mg/kg ip, supplemented with 10 mg/kg iv as needed) and chronically implanted with catheters in the bladder and the femoral artery and vein as described previously. After the catheters were implanted, the rats were administered ketamine (40 mg/kg iv) over a 5-min period. An intravenous infusion (55 µl/min) of isotonic saline containing ketamine (1.0 mg·kg⁻¹·min⁻¹) and xylazine (50 µg·kg⁻¹·min⁻¹) was then started and continued throughout the experiment. In ketamine- and xylazine-anesthetized rats the intravenous infusion of xylazine significantly increases urine flow rate and urinary sodium excretion (7). Therefore, in the experimental protocols described, rats were allowed to stabilize for at least 2 h after starting the intravenous ketamine and xylazine infusion before starting the experiment.

**Experimental Protocols**

In previous studies we have shown that in ketamine-anesthetized rats the intravenous infusion of xylazine significantly increases urine flow rate and urinary sodium excretion (7). The enhanced levels of these renal excretory parameters tended to stabilize — 120 min after the start of drug infusion and remained relatively constant for an additional 90 min (longer time control periods not studied) (7). Therefore, in the experimental protocols described, rats were allowed to stabilize for at least 2 h after starting the intravenous ketamine and xylazine infusion before starting the experiment.

Effects of intravenous yohimbine or terazosin administration on renal excretory function. Experiments were performed to determine the role of α₂- and/or α₁-adrenergic receptor mechanisms in the renal responses produced by intravenous xylazine infusion in ketamine-anesthetized rats. After equilibration and stabilization of renal excretory responses, two consecutive control urine samples were collected (10 min each). The selective α₂-adrenoceptor antagonist yohimbine (0.5 mg/kg, n = 6) or the α₁-adrenoceptor antagonist terazosin (0.5 mg/kg, n = 5) was then administered as an intravenous bolus. After waiting 15 min for drug distribution, five consecutive experimental urine samples (10 min each) were collected.

Effects of intravenous V₂-vasopressin receptor antagonist administration on renal excretory function. Studies were performed to examine the role of vasopressin in mediating the changes in renal excretory function produced by the intrave-
nous infusion of xylazine in ketamine-anesthetized rats. After stabilization of urine flow rate and urinary sodium excretion, two consecutive 10-min control urine samples were collected. Yohimbine (0.5 mg/kg iv) was then administered and allowed to distribute for 15 min. Urine was then collected during four consecutive experimental yohimbine periods. After the fourth experimental yohimbine urine sample was collected, the V2-vasopressin receptor antagonist [d(CH2)5,D-Ile2,Ile4,Arg8]-vasopressin (1 nmol/kg) was injected intravenously. Immediately after injection of the vasopressin antagonist, three consecutive 10-min urine samples were collected.

Effects of intracerebroventricular yohimbine administration on renal excretory function. Experiments were performed to examine the contribution of central α2-adrenoceptor mechanisms to the diuretic and/or natriuretic response elicited by the intravenous infusion of xylazine in ketamine-anesthetized rats. After stabilization of urine flow rate and urinary sodium excretion, two consecutive 10-min control urine samples were collected. After these control periods the α2-adrenoceptor antagonist yohimbine was injected (20 µg/kg icv, n = 6) and allowed to distribute for 15 min. Five consecutive experimental urine samples (10 min each) were then collected. In control experiments the study was repeated with the exception that the same dose of yohimbine (20 µg/kg, n = 4) was administered as an intravenous bolus.

Renal excretory responses elicited by the microinjection of yohimbine into PVN. Studies were performed to determine whether activation of α2-adrenoceptor mechanisms in the PVN contribute to the enhanced diuretic and natriuretic responses produced by xylazine infusion in ketamine-anesthetized rats. After the ketamine and xylazine infusion was started and steady-state renal excretory responses were obtained, urine samples were collected during two consecutive 10-min control periods. After these control collections, the α2-adrenergic receptor antagonist yohimbine (60 ng in 60 nl) was bilaterally microinjected into the PVN. The drug was then allowed 10 min for distribution. The experimental protocol was then completed by collecting five consecutive 10-min experimental urine samples. Preliminary experiments using 30, 60, and 90 ng of yohimbine showed that the 60-ng dose of yohimbine produced maximal changes in renal excretory function in ketamine- and xylazine-anesthetized rats. At the end of the experiment, injection sites in PVN were marked bilaterally by microinjecting Pontamine sky-blue dye through the third barrel of the pipette.

Two types of control groups were used in the microinjection studies. In the first, yohimbine (60 ng, n = 6) was bilaterally microinjected into sites superior, dorsal, or caudal to PVN. In a separate group of rats the mixed β-adrenergic receptor antagonist propranolol (60 ng, n = 7) was bilaterally microinjected into the PVN.

Histological Processing

At the end of the microinjection experiments the rats were deeply anesthetized and perfused transcardially with normal saline followed by 4% phosphate-buffered Formalin. The brains were removed and stored at 4°C for at least 2 days in the Formalin solution and an additional 2 days in a 4% sucrose solution. The brains were then frozen and sectioned (40 µm) using a cryostat microtome. The sections were then placed on glass slides and stained with neutral red. Microinjection sites were identified microscopically from the stained sections using the atlas of Paxinos and Watson (36) as a reference.

Data Analysis

Changes in mean arterial pressure and heart rate, before and after drug administration, were calculated directly from the polygraph records. The kidneys were removed, decapsulated, and weighed for normalization of renal excretory data. In microinjection studies the kidneys were removed before the rats were perfused. Urine volume was determined gravimetrically. Urine sodium concentration was measured by flame photometry (Instrumentation Laboratories, model 943).

All data are expressed as means ± SE. The data were statistically analyzed using repeated measures analysis of variance for the main effects and interactions and Scheffé’s test for pairwise comparisons among the means (46). Statistical significance was defined as P < 0.05.

Drugs Used

The drugs used in this study were yohimbine hydrochloride (Sigma Chemical, St. Louis, MO), terazosin (generous gift from Abbott Laboratories, Abbott Park, IL), propranolol hydrochloride (Sigma), sodium methohexitol (Brewital, Lilly, Indianapolis, IN), ketamine hydrochloride (Ketaset, Fort Dodge Laboratories, Fort Dodge, IA), and xylazine (Butler, Columbus, OH). Yohimbine, terazosin, and propranolol were dissolved in normal saline (0.9%).

RESULTS

The cardiovascular and renal responses produced by the intravenous bolus administration of the α2-receptor antagonist yohimbine (0.5 mg/kg, n = 6) or the α1-receptor antagonist terazosin (0.5 mg/kg, n = 5) in Sprague-Dawley rats receiving continuous infusion (55 µl/min iv) of ketamine (1 mg·kg⁻¹·min⁻¹) and xylazine (50 µg·kg⁻¹·min⁻¹) are shown in Fig. 1. Mean data ± SE are shown for each cardiovascular and renal excretory parameter during two consecutive 10-min control periods (C1 and C2) and during five consecutive experimental periods (10 min each) beginning 15 min after intravenous bolus drug administration (25–65 min). The injection of yohimbine produced an immediate and profound decrease in urine flow rate and urinary sodium excretion. Intravenous yohimbine significantly reversed the enhanced renal excretory levels of water for ~55 min (time points 25–55 min). Concurrent with the changes in urine flow rate, intravenous yohimbine significantly decreased urinary sodium excretion at the 25- and 35-min time points before returning to control levels. In addition, intravenous yohimbine tended to reduce mean arterial pressure and increase heart rate, although these changes were not statistically significant. In contrast the intravenous injection of the α1-receptor antagonist terazosin failed to alter either renal excretory parameter at any time. Terazosin did, however, produce a slight, but insignificant, decrease in mean arterial pressure and increase in heart rate.

The changes in cardiovascular and renal excretory function produced by the sequential intravenous administration of yohimbine and the V2-vasopressin receptor antagonist [d(CH2)5,D-Ile2,Ile4,Arg8]-vasopressin in ketamine- and xylazine-anesthetized rats are shown in Fig. 2. Mean data are shown for each parameter during consecutive 10-min urine collection periods during control (C1 and C2), 15 min after intravenous administration of yohimbine (time points 25–55), and the subsequent intravenous bolus administration of the V2-vasopressin receptor antagonist (time points 65–85).
Similar to that shown in Fig. 1, the intravenous bolus administration of yohimbine produced a significant reduction in urine flow rate (25–55 min) and urinary sodium excretion (Fig. 2, 25–35 min). Subsequent administration of the V2-vasopressin receptor antagonist immediately reversed the yohimbine-induced antidiuresis to levels significantly above those observed during control (time points 65 and 75 min). Despite the effects on urine flow rate, the V2-vasopressin receptor antagonist did not alter urinary sodium excretion (65–85 min). Neither yohimbine nor the V2-vasopressin receptor antagonist significantly altered heart rate or mean arterial pressure.

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The cardiovascular and renal responses produced by the intracerebroventricular injection of yohimbine (20 µg/kg), in 6 ketamine- and xylazine-anesthetized rats are shown in Fig. 3. Mean data are depicted for each parameter during two consecutive control periods (C1 and C2, 10 min each) and during five consecutive experimental periods (10 min each) beginning 15 min after the intracerebroventricular injection of yohimbine (25–65 min). The intracerebroventricular administration of yohimbine produced a significant decrease in urine flow rate that was rapid in onset and persisted for 45 min (experimental periods 25–45) before returning to control levels. Although intracerebroventricular yohimbine tended to decrease urinary sodium excretion, these changes were not statistically significant. Concurrent with the renal excretory changes, yohimbine increased mean arterial pressure 25 and 35 min after intracerebroventricular injection, but did not significantly change heart rate. The intravenous bolus administration of the same dose of yohimbine (20 µg/kg) failed to alter any cardiovascular or renal excretory parameter (Fig. 3).

The cardiovascular and renal responses produced by the bilateral microinjection of the α2-receptor antagonist yohimbine (60 ng, n = 8) into PVN are shown in Fig. 4. After stabilization of renal excretory function, two consecutive 10-min urine samples (C1 and C2) were collected. Compared with control levels the microinjection of yohimbine into PVN produced an immediate and significant decrease (54%) in urine flow rate by the first experimental collection (compare C2 vs. the 20-min time point). The decrease in urine flow rate was maximal within 20 min after injection and returned to control levels by the fourth experimental period (time point 50 min). In contrast, microinjection of yohimbine into PVN did not alter urinary sodium excretion at any
time period. Yohimbine failed to alter any cardiovascular parameter. The microinjection of yohimbine (60 ng, n = 5) into sites dorsal or caudal to PVN did not significantly change heart rate, mean arterial pressure, or renal excretory function (Fig. 4). The histologically identified sites into which yohimbine was microinjected are shown in Fig. 6.

Figure 5 demonstrates the cardiovascular and renal excretory responses produced by the bilateral microinjection of propranolol (60 ng, n = 7) into PVN. Compared with control periods (C1 and C2, 10 min each), the microinjection of propranolol into PVN did not significantly alter any cardiovascular or renal excretory parameter.

**DISCUSSION**

We have previously shown that the intravenous infusion of the a2-adrenergic agonist xylazine increases urine flow rate and urinary sodium excretion in ketamine-anesthetized rats (7). The results of the present studies demonstrate that these renal excretory responses are mediated, at least in part, by the activation of a2-receptors in the CNS. Moreover, it appears that the diuretic, but not the natriuretic, response produced by the intravenous infusion of xylazine was mediated by a2-receptors located in the PVN. The magnitude of the decrease in urine flow rate produced by bilateral microinjection of yohimbine (60 ng) into PVN was comparable to that observed when this antagonist was administered intracerebroventricularly (20 µg/kg; compare Figs. 4 and 3, respectively). The diuretic and natriuretic responses produced by xylazine infusion were not affected by microinjection of propranolol into PVN, thus excluding the possibility that β-adrenoceptor mechanisms in this nucleus contributed to the xylazine-induced renal excretory responses.

The results of the present studies suggest that the diuretic response elicited by xylazine in ketamine-anesthetized rats involves a central pathway in which xylazine inhibits vasopressin secretion. Although not tested directly, our findings are consistent with such a mechanism since the enhanced basal level of urine flow rate produced by intravenous infusion of xylazine was significantly decreased by the microinjection of yohim-
bine into the PVN. The PVN is a brain nucleus that is dense in \(\alpha_2\)-receptors and that is known to participate in the control of vasopressin secretion (1, 37, 44). These findings suggest that xylazine activates \(\alpha_2\)-adrenergic receptors in the PVN and thereby inhibit vasopressin secretion. The subsequent microinjection of yohimbine into the PVN reduced urine flow rate by \(\sim 50\%\) by preventing the inhibitory action of xylazine on vasopressin secretion and thus increasing circulating levels of this hormone. This later premise is supported by our observation that the reduction in urine flow rate produced by yohimbine administration was reversed by the subsequent intravenous administration of a \(V_2\)-vasopressin receptor antagonist (see Fig. 2).

As suggested previously, the PVN is at least one brain site that is involved in mediating the enhanced urine flow rate response produced by xylazine infusion. In light of previously published findings regarding the role of the PVN in vasopressin synthesis, storage, and release, these results were not entirely unforeseen. Whether other CNS sites are also involved has not been determined. It is apparent that there is also a peripheral component by which xylazine infusion augments urine flow rate. This was made apparent by the observation that both the intracerebroventricular and PVN injection of yohimbine only reduced urine flow rate by \(\sim 50\%\). This was in contrast to the profound reduction of urine flow rate (and urinary sodium excretion) that was produced when yohimbine was injected intravenously (Fig. 1). Thus both central (i.e., PVN) and peripheral \(\alpha_2\)-adrenergic mechanisms appear to contribute to the enhanced diuretic response produced by the intravenous infusion of xylazine in ketamine-anesthetized animal models.

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**Fig. 5.** Effects of microinjection of propranolol into PVN on cardiovascular and renal excretory function in ketamine- and xylazine-anesthetized Sprague-Dawley rats. Values are means ± SE, illustrating systemic cardiovascular and renal excretory responses produced by bilateral microinjection of nonselective \(\beta\)-adrenoceptor antagonist propranolol (60 ng/60 nl) into PVN (n = 7) in ketamine- and xylazine-anesthetized rats. Experiments were performed during continuous intravenous infusion of isotonic saline (35 µl/min) containing ketamine (1 mg·kg\(^{-1}\)·min\(^{-1}\)) and xylazine (50 µg·kg\(^{-1}\)·min\(^{-1}\)). Consecutive 10-min urine samples were collected during control (C\(_1\), C\(_2\)) and 10 min after microinjection of propranolol (time points 20–60). Abbreviations as in Fig. 1.

**Fig. 6.** Histologically verified sites into which yohimbine and propranolol were microinjected into PVN and into adjacent control sites; ● Sites of yohimbine microinjection; ○ control injections of yohimbine; ■ site of propranolol microinjection. Horizontal calibration is 1 mm.
rats. Note, however, that because these studies did not establish whether all CNS \(\alpha_2\)-receptors were blocked by intracerebroventricular yohimbine, these results only estimate the extent to which central vs. peripheral \(\alpha_2\)-receptor mechanisms contribute to the diuretic response produced by xylazine infusion. Therefore, it is possible that this treatment only reduced but did not abolish the CNS component of the diuresis. In this manner, intracerebroventricular yohimbine may not have affected \(\alpha_2\)-receptor mechanisms in other brain regions (i.e., the supraoptic nucleus) to the same extent as in the PVN. Despite these possibilities, it is important to consider that while the peripheral (19, 38, 39, 42, 43) and central (5, 6, 20, 21) administration of \(\alpha_2\)-agonists reduce vasopressin secretion, the majority of studies in rats indicate that \(\alpha_2\)-agonists have a direct renal action to produce a diuresis by modulating the hydrosmotic effect of vasopressin (3, 12, 14–16, 33, 40). Thus it appears that the diuretic response produced by intravenous xylazine infusion may involve integration of complex peripheral, direct renal, and CNS mechanisms of action. This premise is in accord with proposed mechanisms by which other \(\alpha_2\)-receptor agonists (e.g., donidone, BHT-933, guanabenz, rilmenidine) affect the renal handling of water after their peripheral administration (3, 39, 43).

In contrast to activation of \(\alpha_2\)- or \(\beta\)-adrenergic receptor mechanisms in the PVN, the present studies suggest that xylazine utilizes an alternative pathway(s) and/or CNS site of action(s) to produce natriuresis. It has been proposed that the natriuretic action of peripherally administered \(\alpha_2\)-agonists may involve both central inhibition of vasopressin release in combination with a second action of the compound that leads to inhibition of the renal tubular reabsorption of sodium (2, 9, 39, 43). More specifically, it has been proposed that the natriuretic action of \(\alpha_2\)-agonists is independent of an action of vasopressin (9, 29). For example, \(\alpha_2\)-agonists inhibit efferent renal sympathetic nerve activity (22–25), with sympathetic withdrawal resulting in natriuresis due to attenuation of the neural release and postsynaptic tubular action of norepinephrine on sodium transport in the kidneys (26). Although we have shown that intravenous infusion of xylazine produces a decrease in directly recorded renal sympathetic nerve activity (unpublished observation), it remains to be established whether renal sympatho-inhibition contributes to the natriuresis observed in ketamine- and xylazine-anesthetized rats. It is apparent, however, that during intravenous infusion xylazine does not act within the PVN to affect sodium excretion because the microinjection of yohimbine into this nucleus failed to alter urinary sodium excretion (see Fig. 4). It should be noted that in addition to a CNS action, it is clear that \(\alpha_2\)-agonists can inhibit renal tubular sodium reabsorption by modulating sodium (and water) transport in the renal nephron (2, 5, 14, 16, 39, 40).

Perspectives

The hypotension and reduction in glomerular perfusion pressure during anesthesia and surgery (a major stimulus to vasopressin secretion) substantially reduce urine flow rate and urinary sodium excretion. The impaired renal function during anesthesia and surgery may result, at least in part, from the ability of these stressors to attenuate tonic \(\alpha_2\)-adrenergic receptor-mediated inhibition of vasopressin secretion in PVN or other areas such as supraoptic nucleus. The administration of xylazine appears to counteract the disinhibitory action of these stressors. Whether xylazine attenuates vasopressin release by presynaptically inhibiting excitatory inputs to the PVN or by activating inhibitory postsynaptic \(\alpha_2\)-receptor on vasopressinergic neurons remains to be determined. At the level of the kidneys, it is likely that xylazine physiologically antagonizes the hydrosmotic effect of vasopressin by stimulating \(\alpha_2\)-receptors in the collecting duct. Together, the maintenance of a continuous \(\alpha_2\)-agonist influence on renal function produced by the intravenous infusion of xylazine may restore the ability of the kidneys to excrete water and sodium by reinstating these inhibitory actions on vasopressin mechanisms.

In summary, we have previously demonstrated that intravenous infusion of the \(\alpha_2\)-agonist xylazine produces a marked increase in urine flow rate and urinary sodium excretion in ketamine-anesthetized rats. The present study extends these findings and indicates that the enhanced renal excretory responses produced by xylazine are mediated via activation of complex peripheral and CNS \(\alpha_2\)-adrenergic receptor systems. In regard to central mechanisms, the findings of these studies also demonstrate that xylazine activates \(\alpha_2\)-adrenergic receptors in the PVN of the hypothalamus to contribute to the decrease in urine flow rate, but not urinary sodium excretion. The diuretic response produced by xylazine is presumably caused by a decrease in vasopressin release subsequent to PVN \(\alpha_2\)-receptor stimulation. The inability of the microinjection of propranolol into PVN to alter either renal excretory response indicates that \(\beta\)-adrenergic receptors in this brain nucleus are not involved in mediating the renal responses produced by intravenous xylazine. The action of \(\alpha_2\)-adrenergic mechanisms in the PVN to selectively influence the renal handling of water, but not sodium, may contribute to the reported dissociation of the natriuretic and diuretic responses of \(\alpha_2\)-adrenoceptor agonists.

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