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Role of Cholinergic and Adrenergic Pathways of the Medial Septal Area in the Control of Water Intake and Renal Excretion in Rats

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LEITE, D. F., L. A. A. CAMARGO, W. A. SAAD, A. RENZI, S. FÓGLIA, L. A. DE LUCA, JR. AND J. V. MENANI. *Role of cholinergic and adrenergic pathways of the medial septal area in the control of water intake and renal excretion in rats.* PHARMACOL BIOCHEM BEHAV **42**(1) 1-8, 1992.—In this study, we investigated an interaction between noradrenergic and cholinergic pathways of the medial septal area (MSA) on the control of water intake and urinary electrolyte excretion by means of injection of their respective agonists. Noradrenaline (a nonspecific α-adrenergic agonist) and clonidine (an α_2-adrenergic agonist), but not phenylephrine (an α_1-adrenergic agonist), induced natriuresis and kaliuresis. α-Adrenergic activation had no effect on the natriuresis and kaliuresis induced by carbachol (a cholinergic agonist) and it inhibited the antinatriuresis and antikaliuresis induced by isoproterenol (a β-adrenergic agonist). Interactions related to volume excretion are complex. α-Adrenergic activation induced a mild diuresis and inhibited the antidiuresis induced by isoproterenol, but phenylephrine combined with carbachol induced antidiuresis. The water intake induced by carbachol was inhibited by clonidine and noradrenaline, but not phenylephrine. These results show an asymmetry in the interaction between α-adrenergic and cholinergic receptors concerning water intake and electrolyte excretion.

Cholinergic receptors Adrenergic receptors Thirst Water intake Natriuresis Kaliuresis Diuresis

ELECTRICAL stimulation of the septal area (SA) of the rabbit brain induces natriuresis and kaliuresis (11). The same responses plus a concomitant antidiuresis were obtained with the injection of cholinergic agonists (20). Noradrenaline injection into the SA also induces an increase in urinary Na^+ and K^+ excretion with no change in urinary volume. Central administration of α-adrenergic antagonists reduced the natriuresis and kaliuresis induced by noradrenaline (3).

Opposite effects in sodium excretion can be obtained by activating either β-adrenergic or cholinergic receptors in the SA (2,20). Isoproterenol inhibits the sodium excretion that follows a water load (2) while the opposite happens when carbachol (20) is injected into the SA.

Water intake is induced by injection of cholinergic (27), but not β-adrenergic, agonists (22) into the SA. Interactions between central cholinergic and noradrenergic pathways in the control of water intake have been previously reported to occur in rats (17,21).

Several lines of evidence suggest that the central noradrenergic system presents facilitatory and inhibitory components that participate in the central control of fluid-electrolyte balance. Activation of central α-adrenergic pathways have a natriuretic effect (3), but in some areas it has an inhibitory effect on water intake induced by water deprivation, angiotensin II, or carbachol (6-10,13-15,18,20,22,25). The receptors involved are probably α_1- and α_2-adrenergic since both clonidine and phenylephrine inhibit that behavior depending on the area into which they are injected. To our knowledge, no study has compared the effects of these two drugs on water intake and natriuresis induced by carbachol with those of noradrenaline, the endogenous ligand.

The natriuretic effect of α-adrenergic activation by noradrenaline suggests that it can antagonize the antinatriuresis induced by isoproterenol. Moreover, the opposite effects of α-adrenergic activation on water intake (inhibition) and sodium excretion (stimulation) suggests that their interaction with cholinergic receptors should also follow the same rule, that is, α-agonists, including noradrenaline, should inhibit the dipsogenic, but not the natriuretic, effect of carbachol. However, the effect of clonidine or phenylephrine injection into

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the septal area on sodium excretion and water intake and their interaction with carbachol effects is not known.

In the present experiments, we investigated the role of the α-adrenergic receptors of the medial septal area (MSA) in the control of water intake and renal water and electrolyte excretion in rats. A possible interaction between α-adrenergic receptors and β-adrenergic receptors or cholinergic receptors of the MSA in the control of water ingestion and Na^+, K^+, and urine excretion was also studied.

METHOD

Animals

Male Holtzmann rats weighing 250–280 g were housed in metabolic cages with free access to food pellets and tapwater.

Brain Surgery

Rats were anesthetized with ether and restrained in a stereotaxic apparatus (Kopf model). A longitudinal incision was made on the skin of the animal's head, the subcutaneous tissue was pulled back, and the skull was drilled with a spherical drill. A stainless steel cannula (12 × 0.7 mm o.d.) was introduced into the MSA. The skull was positioned by placing bregma and lambda on the same level. The coordinates for approaching the MSA were obtained from the Konig and Klippel atlas (12): 0.8 mm anterior to the bregma in the midline to a depth of 3.0 mm below the duramater. The cannulae were fixed to the skull with screws and acrylic resin. A prophylactic dose of penicillin (Pentabiótico Fontoura Wyeth) was injected after brain surgery.

Drug Injection

The drugs were dissolved in 0.15 M NaCl and injected into the MSA using a Hamilton microsyringe (10 μl) connected by PE 10 polyethylene tubing (25 cm) to a needle (0.3 mm o.d.) that was introduced into the brain through the cannula previously fixed to the animal's head. The needle for injection into the MSA was 2 mm longer than the cannula fixed to the animal's head. The volume of injection was always 1 μl injected over a period of 30–60 s.

Drugs

Drugs used were carbachol hydrochloride (Merck Sharp & Dohme), *dl*-isoproterenol hydrochloride (Sigma Chem. Co.), clonidine hydrochloride (Boehringer-Ingelheim), L-phenylephrine hydrochloride (Sigma Chem. Co.), and *l*-norepinephrine bitartrate (Sigma Chem. Co.).

Histology

After experiments, animals were anesthetized with ether and perfused through the heart with saline and 10% formalin. The brain was removed and stored in 10% formalin for at least 1 week. The brain was then frozen and transversal sections (20–30 μm) were cut and stained with hematoxylin-eosin for examination by light microscopy. Only the results of rats whose MSA was reached by injection were used. Figure 1 shows the site of injection into the MSA.

Statistical Analysis

The results are reported as mean ± SEM. The Student's (paired and unpaired) *t*-test and analysis of variance (ANOVA) were used to determine significance. Values were considered statistically significant when $p < 0.05$.

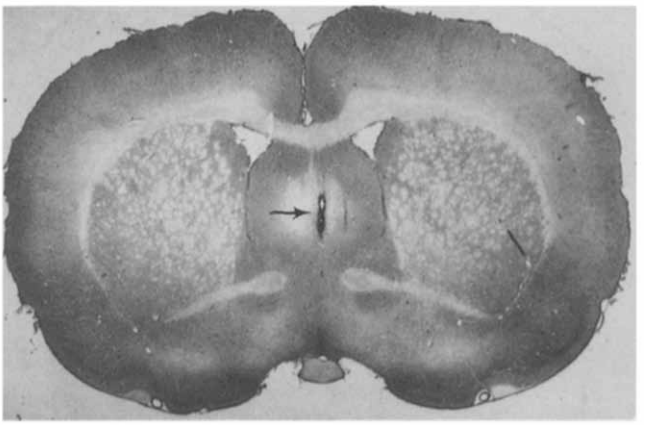

FIG. 1. Photomicrograph of site of injection into the MSA (arrow).

Experimental Protocol

Water ingestion. Five days after brain surgery, animals were submitted to the experimental session. Each animal was submitted to four or five experimental sessions at 3-day intervals. An α-adrenergic agonist (noradrenaline, clonidine, or phenylephrine) was injected into the MSA 20 min before injection of carbachol into the same area. Recording of water intake started immediately after carbachol injection and continued for 1 h. The volume of water ingested was measured with graduated (0.1-mm marks) tubes adapted with metal spouts for drinking. No solid food was offered during these experiments.

Water intake was studied in different experimental sessions and in several groups of animals after injection of the following drugs into the MSA of satiated rats:

- control (0.15 M NaCl)
- carbachol (2 nmol)
- noradrenaline (40, 80, and 160 nmol) + carbachol (2 nmol)
- clonidine (10, 20, and 40 nmol) + carbachol (2 nmol)
- phenylephrine (80 and 160 nmol) + carbachol (2 nmol).

Sodium, potassium, and urine excretion. After 12 h of food, but not water, deprivation, a water load of 5% body weight was performed through an intragastric cannula. One hour later, a second water load of the same volume was administered. Thirty minutes later, 1 μl control (0.15 M NaCl), carbachol (2 nmol), or isoproterenol (80 nmol) was injected into the MSA. Urine was then collected at 30, 60, and 120 min. The α-adrenergic agonists were injected 20 min before carbachol or isoproterenol. Sodium and potassium concentrations in urine were determined with a flame photometer (Model 143, Instrumentation Labs.). The cumulative value of the samples following injections was used for statistical evaluation of the results and expressed as μEq/120 min. The urine volume during the same period was measured and expressed as ml/120 min.

Sodium, potassium, and urine excretions were studied in different experimental sessions and in several groups of animals after injection of the following drugs into the MSA:

- control (0.15 M NaCl)
- carbachol (2 nmol)
- noradrenaline (40, 80, and 160 nmol) + carbachol (2 nmol)
- clonidine (10, 20, and 40 nmol) + carbachol (2 nmol)
- phenylephrine (40, 80, and 160 nmol) + carbachol (2 nmol)

- isoproterenol (80 nmol)
- noradrenaline (40, 80, and 160 nmol) + isoproterenol (80 nmol)
- clonidine (10, 20, and 40 nmol) + isoproterenol (80 nmol)
- phenylephrine (160 nmol) + isoproterenol (80 nmol).

RESULTS

Effect of Pretreatment with Noradrenaline, Clonidine, or Phenylephrine on the Dipsogenic Action of Carbachol

The water ingestion observed after 1 h in the control experiment (injection of 0.15 M NaCl into the MSA) was 0.1 ± 0.04 ml/h. Injection of carbachol (2 nmol) into the MSA produced a dipsogenic response (9.6 ± 0.8 ml/h) (Fig. 2A). Previous injection of noradrenaline (80 and 160 nmol) into the MSA decreased the water ingestion produced by carbachol (6.1 ± 0.8 and 3.0 ± 0.8 ml/h, respectively). No change in the dipsogenic effect of carbachol was observed after previous administration of the 40-nmol dose of noradrenaline.

Pretreatment with clonidine (10, 20, and 40 nmol) into the MSA also reduced the water ingestion produced by carbachol (4.5 ± 0.8, 2.5 ± 0.7, and 2.1 ± 0.5 ml/h, respectively) (Fig. 2B). No change in the dipsogenic effect of carbachol was observed after previous treatment with phenylephrine (80 and 160 nmol). Water ingestion after phenylephrine and carbachol was 7.9 ± 1.9 and 8.6 ± 1.8 ml/h, respectively.

Injection of only the α-adrenoceptor agonists produced no effect on water ingestion.

Effect of Pretreatment with Noradrenaline, Clonidine, or Phenylephrine on Sodium and Potassium Urinary Excretion and Urinary Volume

Injection of carbachol into the MSA. Figure 3 shows Na^+ and K^+ excretion and urinary volume after intraseptal injection of 0.15 M NaCl (control), carbachol (2 nmol), noradrenaline (40, 80, and 160 nmol), and noradrenaline + carbachol.

Urinary Na^+ and K^+ excretion but not urinary volume increased after carbachol injection. Noradrenaline (80 and 160 mnol) alone also induced a significant increase in Na^+ excretion, and the dose of 160 nmol significantly increased K^+ excretion and urinary volume. No change in the natriuretic and kaliuretic effect of carbachol and diuresis was observed after previous treatment with noradrenaline.

Previous injection of clonidine (10, 20, and 40 nmol) into the MSA also produced no change in the natriuresis, kaliuresis, and diuresis observed after carbachol. Clonidine alone caused significant increases in urinary Na^+ excretion. The doses of 10 and 40 nmol caused an increase in urine excretion and the dose of 10 nmol increased urinary K^+ excretion (Fig. 4).

No changes in the natriuretic and kaliuretic effects of carbachol were observed after previous treatment with phenylephrine (40, 80, and 160 nmol), but urinary volume was significantly reduced when compared with the control group (NaCl 0.15 M). Phenylephrine alone increased urinary volume at all doses, but Na^+ and K^+ excretion was not changed (Fig. 5).

Injection of isoproterenol. Urinary Na^+ and K^+ excretion and urinary volume decreased following injection of isoproterenol (80 nmol) into the MSA (Fig. 6). Pretreatment with noradrenaline (40, 80, and 160 nmol) reduced the antinatriuretic and antidiuretic effect of isoproterenol, but only the 80-nmol dose of noradrenaline reduced the antikaliuretic effect (Fig. 6).

Clonidine produced no change in the antinatriuretic and antikaliuretic effects of isoproterenol. The 10- and 20-nmol doses of clonidine, but not the 40-nmol dose, blocked the antidiuretic effect of isoproterenol (Fig. 7). Phenylephrine

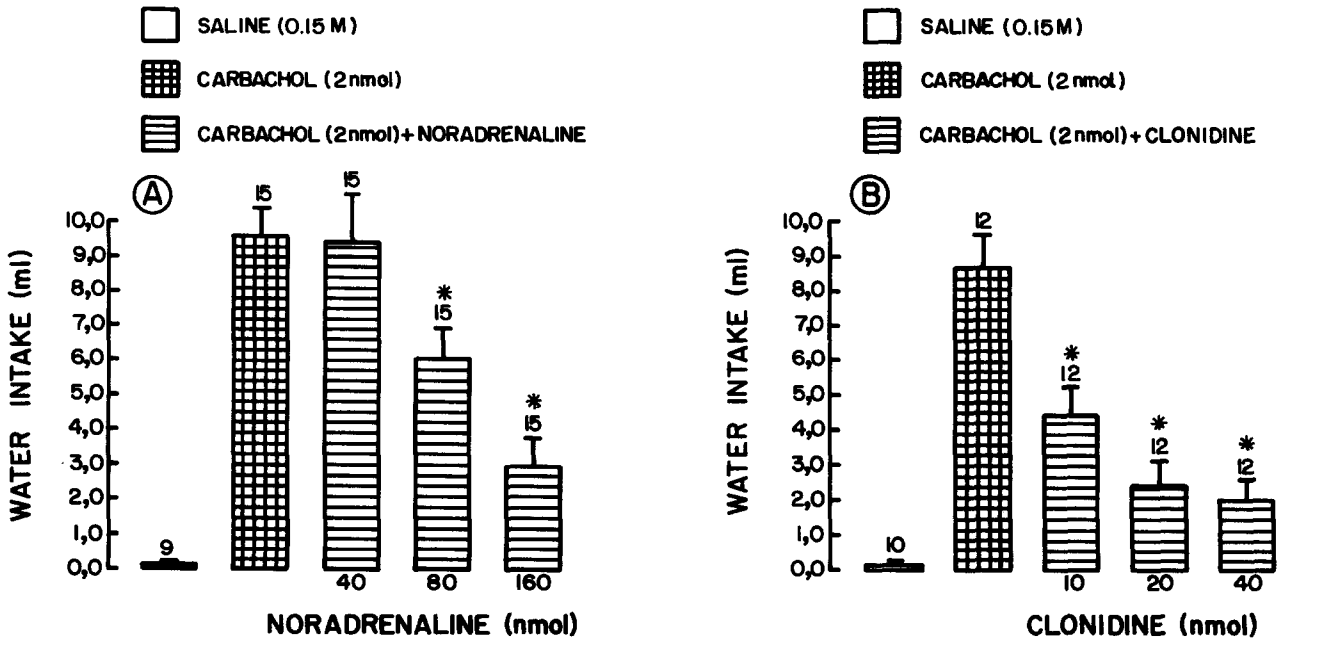

FIG. 2. Water intake after injection of saline (control), carbachol (2 nmol), (A) noradrenaline (40, 80, and 160 nmol) + carbachol and (B) clonidine (10, 20, and 40 nmol) + carbachol into the MSA. Results are reported as means ± SEM. The number of animals is indicated at the top of each column. *Significant difference ($p < 0.05$) compared with carbachol alone.

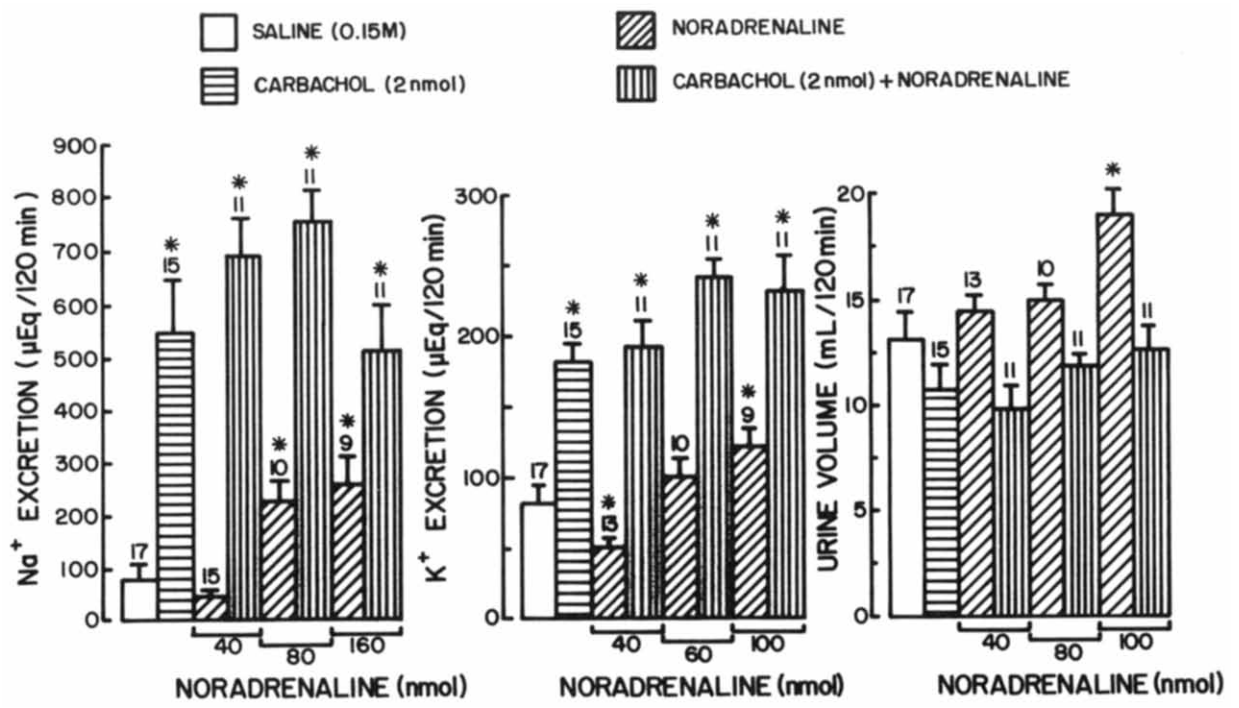

FIG. 3. Urinary Na^+ and K^+ excretion and urinary volume after injection of saline (control), carbachol (2 nmol), noradrenaline (40, 80, and 160 nmol) and noradrenaline + carbachol into the MSA. Results are reported as mean ± SEM. The number of animals is indicated at the top of each column. *Significant difference ($p < 0.05$) compared with control.

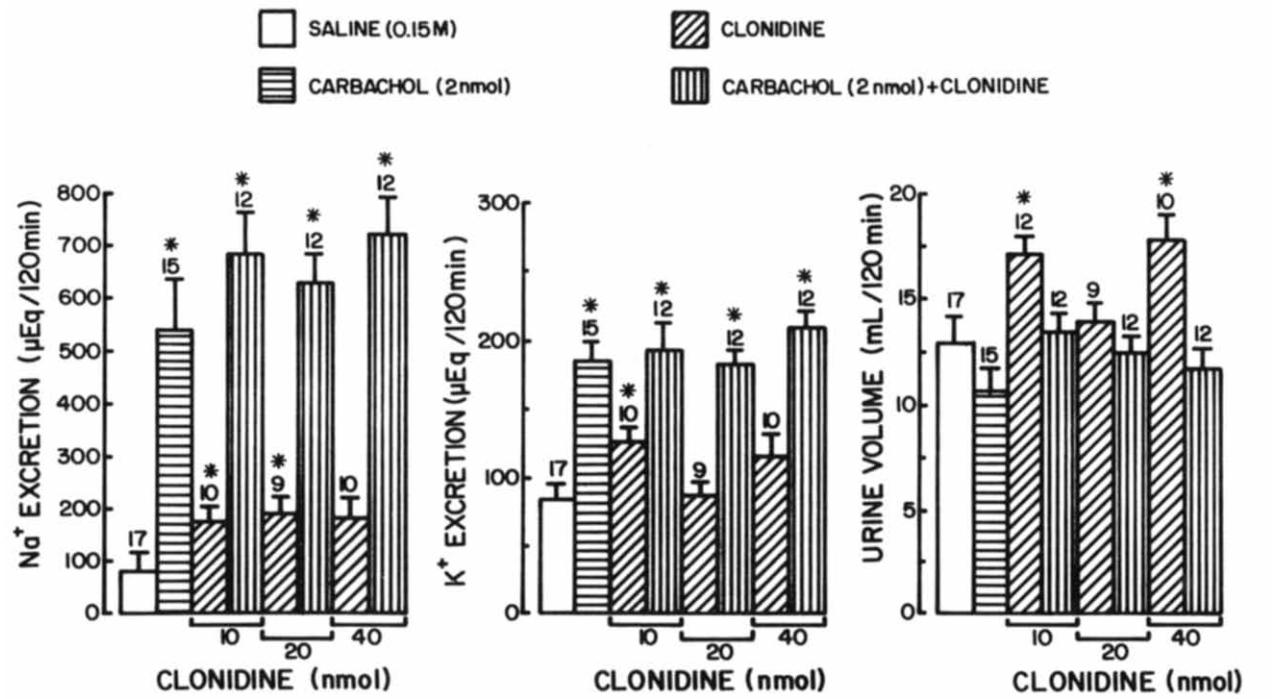

FIG. 4. Urinary Na^+ and K^+ excretion and urinary volume after injection of saline (control), carbachol (2 nmol), clonidine (10, 20, and 40 nmol) and clonidine + carbachol into the MSA. Results are reported as mean ± SEM. The number of animals is indicated at the top of each column. *Significant difference ($p < 0.05$) compared with control.

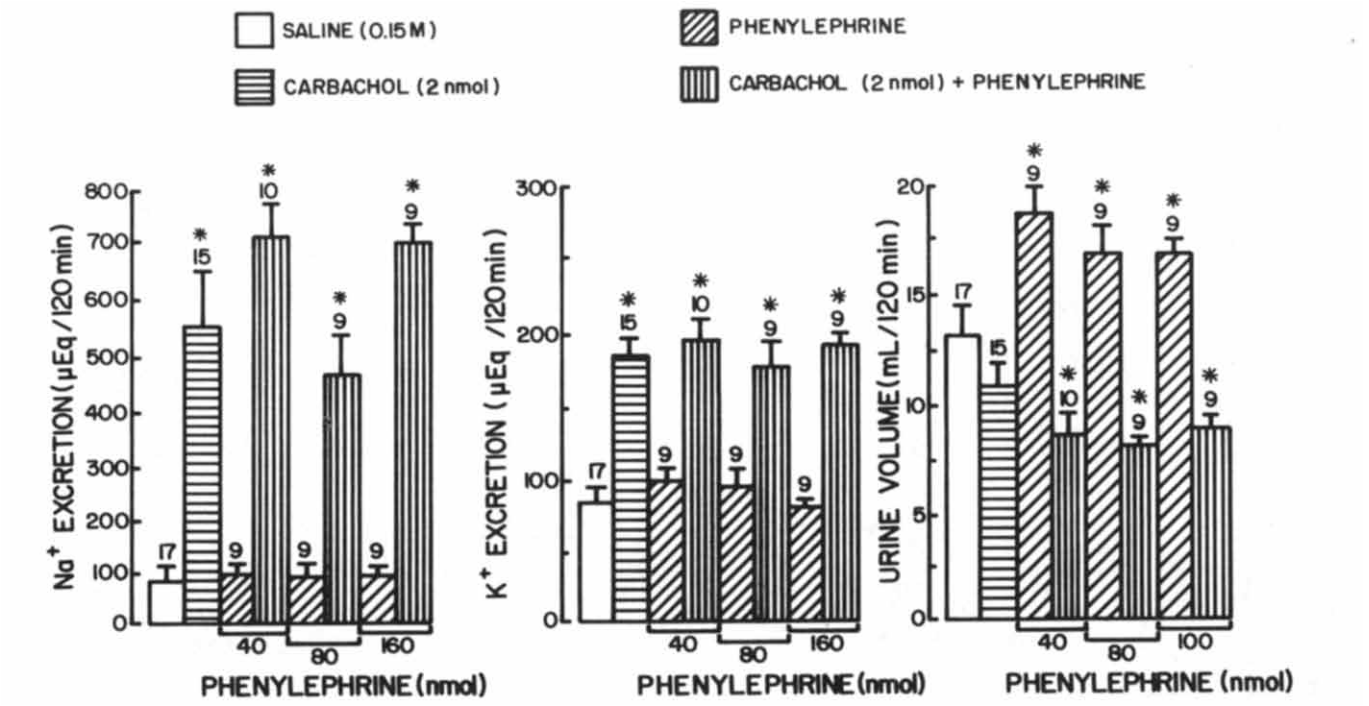

FIG. 5. Urinary Na^+ and K^+ excretion and urinary volume after injection of saline (control), carbachol (2 nmol), phenylephrine (40, 80, and 160 nmol), and phenylephrine + carbachol into the MSA. Results are reported as mean ± SEM. The number of animals is indicated at the top of each column. *Significant difference ($p < 0.05$) compared with control.

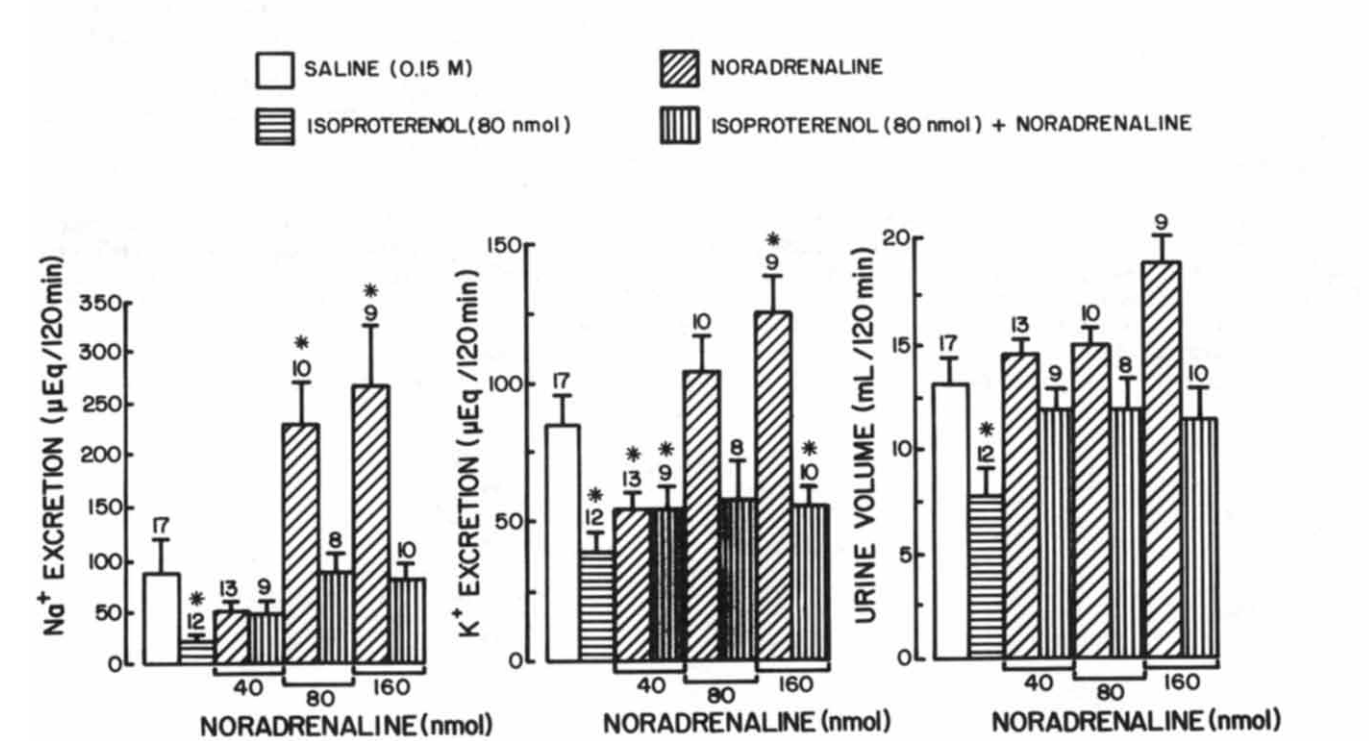

FIG. 6. Urinary Na^+ and K^+ excretion and urinary volume after injection of saline (control), isoproterenol (80 nmol), noradrenaline (40, 80, and 160 nmol), and noradrenaline + isoproterenol into the MSA. Results are reported as mean ± SEM. The number of animals is indicated at the top of each column. *Significant difference ($p < 0.05$) compared with control.

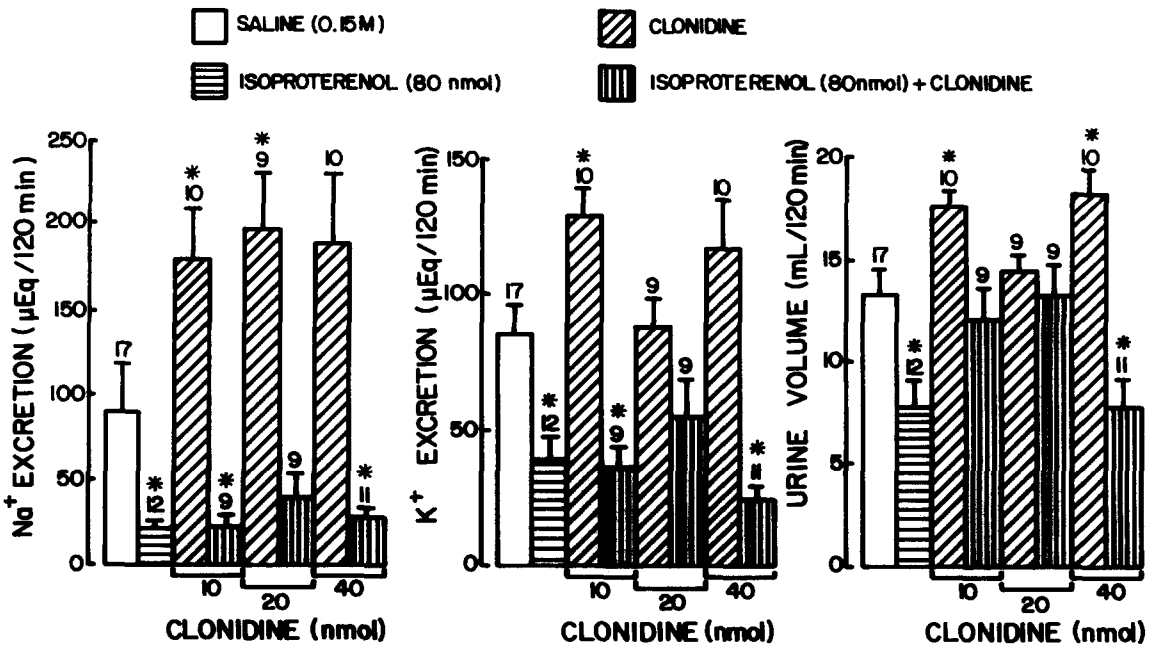

FIG. 7. Urinary Na^+ and K^+ excretion and urinary volume after injection of saline (control), isoproterenol (80 nmol), clonidine (10, 20, and 40 nmol) and clonidine + isoproterenol into the MSA. Results are reported as mean ± SEM. The number of animals is indicated at the top of each column. *Significant difference ($p < 0.05$) compared with control.

(160 nmol) partially reduced the antinatriuretic and antikaliuretic effect and fully blocked the antidiuretic effect of isoproterenol (Table 1).

DISCUSSION

There are several evidences for an interaction between brain catecholamines and acetylcholine (19,24,28). The present study adds new information about the effects of adrenergic agonists on sodium excretion and their interaction with cholinergic receptors in the MSA.

First, the natriuresis induced by noradrenaline is likely a result of an α_2-adrenergic receptor activation since clonidine, but not phenylephrine, increased sodium excretion. Clonidine induced natriuresis in doses smaller than those of noradrenaline. This is partially explained by noradrenaline acting also on β-adrenergic receptors, the activation of which reduces sodium excretion. A higher intrinsic activity of clonidine that could induce stronger effects on sodium excretion is less likely to occur because clonidine 40 nmol failed to inhibit the reduction in sodium excretion induced by isoproterenol, whereas a similar dose of noradrenaline inhibited that reduction. Noradrenaline and phenylephrine could also reduce the tonic inhibition of sodium excretion maintained by β-adrenergic activation. The idea of a tonic inhibition of sodium excretion is reinforced by the slight, but significant, natriuresis induced by injection of a β-adrenergic antagonist in the SA (3). The opposite actions of α- and β-adrenergic receptors suggest a dual role for noradrenergic pathways in the control of sodium excretion. Similar conclusions apply for potassium excretion.

Second, the natriuresis induced by carbachol injection into the MSA was not altered by previous injection of either specific α-adrenergic agonists or noradrenaline. This differs from the antagonism shown by α_2-adrenergic and cholinergic receptors activation for water intake. Indeed, clonidine activated sodium excretion, like noradrenaline. Therefore, according to

TABLE 1

URINARY Na^+ AND K^+ EXCRETION AND URINARY VOLUME AFTER INJECTION OF SALINE (CONTROL), ISOPROTERENOL (80 nmol), PHENYLEPHRINE (160 nmol), AND PHENYLEPHRINE + ISOPROTERENOL INTO THE MSA

Group	n	Na^+ (μEq/120 min)	K^+ (μEq/120 min)	Volume (ml/120 min)
Control	17	89 ± 30	85 ± 11	13.2 ± 1.2
Isoproterenol	12	22 ± 4*	39 ± 8*	7.7 ± 1.3*
Phenylephrine	9	94 ± 18	81 ± 5	16.9 ± 0.6*
Phenylephrine + Isoproterenol	9	39 ± 6*†	44 ± 9*	10.7 ± 1.5

*Significant differences ($p < 0.05$) compared with control.
†Significant differences compared with isoproterenol.

this result, one would expect a potentiation of the natriuretic effect of carbachol, which did not happen. This absence of a potentiation results, probably, from the utilization of a dose of carbachol that has a maximum effect.

There is a more complex relationship between α-adrenergic receptors on the one hand and β-adrenergic or cholinergic receptors on the other hand concerning the control of urine volume. Phenylephrine combined with carbachol induced antidiuresis, but phenylephrine inhibited the antidiuresis induced by isoproterenol. Clonidine and noradrenaline also inhibited the antidiuresis induced by isoproterenol, a result that is consistent with their activation of diuresis, but this diuretic effect was absent when they were combined with carbachol. Note that there was an asymmetry between the effects of α-adrenergic activation on electrolyte (Na^+, K^+) and volume excretion when they were combined with carbachol. This suggests that α-adrenergic receptors participate in separate systems for the control of electrolyte and volume excretion. The differences in the interaction of α-adrenergic receptors with β-adrenergic receptors or with cholinergic receptors suggests that β-adrenergic and cholinergic receptors are also components of separate systems for the control of urine volume excretion.

The mechanism by which carbachol and the two α-adrenoceptor agonists injected in the MSA change renal electrolyte excretion is not yet completely understood. Carbachol or noradrenaline injected into the MSA increases arterial pressure, a finding that may account for the changes in electrolyte excretion. Although others have also shown that centrally injected carbachol produces an increase in arterial blood pressure, it has been found that the natriuresis and kaliuresis induced by carbachol are not dependent on renal innervation or hemodynamics (23). Since central injection of cholinergic agonists increases antidiuretic hormone (ADH) secretion and this hormone induces natriuresis and kaliuresis (5), it is possible that ADH secretion plays a role in the natriuresis and kaliuresis obtained with carbachol injection into the MSA. Another possibility is the increased level of atrial natriuretic peptide (ANP). Baldissera et al. (1) showed that ICV injection of carbachol increases plasma and central ANP in rats.

And, third, there are α_2-adrenergic receptors, not α_1, that inhibit the water intake induced by carbachol since this effect was obtained with clonidine and noradrenaline but not with phenylephrine. The inhibitory effect of noradrenaline and the absence of an effect of phenylephrine on water intake is in agreement with the results obtained by Schmidt et al. (22), who also combined these drugs with carbachol in the SA. They do not report results with clonidine or another α_2-adrenergic agonist, but they showed that the dipsogenic effect of carbachol is also inhibited by activation of β-adrenergic receptors in the SA. The failure of phenylephrine to inhibit the water intake induced by carbachol in the MSA contrasts with the antidipsogenic effect of phenylephrine injected into other areas when water intake is elicited by central angiotensin II or water deprivation (6,7,22). There is a possibility for clonidine exerting its effect by acting on autoreceptors (4,16,26), but they must have opposite roles concerning water intake and renal excretion. These results disclose an asymmetry in the interaction between α-adrenergic and cholinergic receptors concerning water intake and sodium or potassium excretion.

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