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EFFECT OF ALPHA1 ADRENOCEPTOR ANTAGONIST NAFTOPIDIL ON THE ARGININE-VASOPRESSIN SECRETION AND URINE VOLUME IN CENTRALLY NORADRENALINE-ADMINISTERED RATS

Hypothesis / aims of study

Naftopidil (Naf), an alpha1 adrenoceptor antagonist, has been shown to improve micturition frequency and urine production in the light-cycle of a rat model of hypertension-related bladder dysfunction, and nocturnal polyuria in male patients with lower urinary tract symptom (LUTS) [1, 2]. Arginine-vasopressin (AVP) has powerful antidiuretic action and is also known as antidiuretic hormone. These reports suggested that the secretion of AVP might have an influence on the nocturnal polyuria, and a possibility that adrenoceptors in the brain are involved in the regulation of AVP secretion. We investigated the effect of Naf on plasma level of AVP and urine volume in centrally noradrenaline (NA) administered rats.

Study design, materials and methods

Male Wistar rats were anesthetized under urethane (1.0 g/kg, ip). Blood samples were collected from the inferior vena cava 1 h after NA administration (3 or 30 µg/kg, icv) into the left ventricle (0.8 mm posterior, 1.5 mm left from the bregma), or 4 h after Naf administration (10 or 30 mg/kg, ip). In another study, NA (30 µg/kg, icv) was administered 3 h after Naf administration (10 or 30 mg/kg, ip). All blood samples were collected at 4:00 pm. Plasma levels of AVP in these samples were measured by ELISA (ab133028, Abcam).

Additionally, the catheterized bladder in the rat was emptied and then the urethra was clamped for preventing urine leakage. Vehicle or NA (30 µg/kg, icv) was centrally administered 3 h after pre-treatment with vehicle or Naf (30 mg/kg, ip). Subsequently urine was collected 1 and 3 h after the central administration.

Voiding functions by metabolic cages (dark- and light-cycle, separately) were measured in conscious male Wistar rats that were administered Naf (30 mg/kg, ip) once a day at 10:00 am, for 2 days. The data were measured for 24 h from 12:00 pm on the second day.

Results

Centrally administered NA at the high dose significantly reduced plasma levels of AVP (Table 1). Alternatively, the high dose of NA-induced decrease in plasma levels of AVP was significantly inhibited by systemic pre-treatment with Naf at the high dose (Table 2). Centrally administered NA at a high dose significantly increased the urine volume. However, systemic pre-treatment with Naf at the high dose significantly inhibited the NA-induced increase in the urine volume (Table 3). Treatment with Naf by itself had no significant effect on the AVP levels neither on urodynamic parameters (micturition frequency and urine output) in whole day, or dark- and light-cycle (data not shown).

Interpretation of results

The presented data show that centrally administered NA dose-dependently reduced plasma AVP concentration, indicating that AVP secretion can be modulated by brain adrenoceptors. Systemic pre-treatment with Naf improved the NA-induced decrease in the plasma levels of AVP and increase in the urine volume in the rat. Considering a previous report showing that Naf has been detected in the rat spinal cord and cerebrum after oral administration, it seems that it can cross the blood brain barrier to enter the central nervous system [3]. These findings suggest that systemic administration of Naf may modulate secretion of AVP in the brain in centrally NA administered rats, thereby reducing nocturnal urine production.

Concluding message

Systemic treatment with Naf could centrally inhibit the brain noradrenergic nervous system-mediated decrease of AVP secretion and increase of urine production in animal or human with LUTS.

Table 1. Effect of centrally administered NA on plasma level of AVP

Group	V	NA (3)	NA (30)
N	7	7	8
AVP (pg/mL)	19.2 ± 4.0	15.6 ± 3.0	7.5 ± 0.9*

NA (3 or 30 µg/kg, icv) was administered 1 h before collecting blood sample from inferior vena cava for AVP measurements. Data are shown as mean ± SEM. *: $P < 0.05$, when compared with the analysis of variance and Fisher's multiple comparison tests to the V group. AVP: arginine-vasopressin; N: number; NA: noradrenaline; V: vehicle.

Table 2. Effect of systemically administered Naf on the centrally NA-induced decrease of plasma level of AVP

Group	V (ip) + V (icv)	V (ip) + NA (30)	Naf (10) + NA (30)	Naf (30) + NA (30)
N	6	7	8	6
AVP (pg/mL)	20.9 ± 4.4	8.1 ± 0.8*	10.4 ± 1.7*	28.9 ± 3.6#

NA (30 µg/kg, icv) was administered 3 h after the treatment with V (ip) or Naf (10 or 30 mg/kg, ip), subsequently blood sample was collecting from inferior vena cava for AVP measurement 1 h after the NA administration. Data are shown as mean ± SEM. *: $P < 0.05$, #: $P < 0.05$ when compared with analysis of variance and Fisher's multiple comparison tests to the V (ip) + V (icv) group or to the V (ip) + NA (30) group, respectively. Naf: naftopidil.

Table 3. Effect of systemically administered Naf on the centrally NA-induced increase in urine volume

Group	V (ip) + V (icv)	V (ip) + NA (30)	Naf (30) + NA (30)
N	4	5	5
0~1 h after NA icv: urine volume (mL)	0.56 ± 0.09	0.92 ± 0.11*	0.73 ± 0.12
1~3 h after NA icv: urine volume (mL)	0.80 ± 0.09	1.58 ± 0.25*	0.75 ± 0.07#
Total urine volume (mL)	1.36 ± 0.16	2.50 ± 0.26*	1.48 ± 0.10#

The catheterized bladder in the rat was emptied and then the urethra was clamped for preventing urine leakage. NA (30 µg/kg, icv) was administered 3 h after treatment with V or Naf, subsequently urine was collected 1 h or 3 h after the NA administration. Urine volume means total collected volume. Data are shown as mean ± SEM. *: $P < 0.05$, # $P < 0.05$ when compared with analysis of variance and Fisher's multiple comparison tests to the V (ip) + V(icv) group or the V (ip) +NA (30) group, respectively.

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Disclosures

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