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Effect of naftopidil on brain noradrenaline-induced decrease in arginine-vasopressin secretion in rats

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ABSTRACT

Naftopidil, an α1-adrenoceptor antagonist, has been shown to inhibit nocturnal polyuria in patients with lower urinary tract symptom. However, it remains unclear how naftopidil decreases nocturnal urine production. Here, we investigated the effects of naftopidil on arginine-vasopressin (AVP) plasma level and urine production and osmolality in rats centrally administered with noradrenaline (NA). NA (3 or 30 μg/kg) was administered into the left ventricle (i.c.v.) of male Wistar rats 3 h after naftopidil pretreatment (10 or 30 mg/kg, i.p.). Blood samples were collected from the inferior vena cava 1 h after NA administration or 4 h after peritoneal administration of naftopidil; plasma levels of AVP were assessed by ELISA. Voiding behaviors of naftopidil (30 mg/kg, i.p.)-administered male Wistar rats were observed during separate light- and dark cycles. Administration of NA decreased plasma AVP levels and elevated urine volume, which were suppressed by systemic pretreatment with naftopidil (30 mg/kg, i.p.). Urine osmolality decreased 1 h after NA administration. However, naftopidil by itself had no effect on plasma AVP levels or urodynamic parameters during light- and dark cycles. Our findings suggest that systemic administration of naftopidil could prevent central noradrenergic nervous system-mediated decline in AVP secretion and increase in urine production in rats.

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1. Introduction

Naftopidil is an α_1-adrenoceptor antagonist that used in the treatment of benign prostatic hyperplasia (BPH)-associated lower urinary tract symptoms (LUTS) owing to its effects in reducing resistance in the prostatic urethra (1). In male patients with LUTS, naftopidil has also been shown to be effective against nocturia (2). Furthermore, Yokoyama et al. (3) reported that nocturnal polyuria in male patients with LUTS significantly decreased upon naftopidil administration, indicating that it can directly reduce nocturnal urine production. Recently, another study found that naftopidil can cross the blood–brain barrier to easily enter the central nervous system (4). However, the mechanism by which naftopidil decreases nocturnal urine production has still not been well understood.

Arginine vasopressin (AVP), an antidiuretic hormone, is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and plays an important role in the maintenance of serum osmolality and volume through free water excretion. The release of AVP into the plasma, induced by both osmotic and non-osmotic stimuli, is modulated by brain adrenoceptors (5). In healthy adults, diurnal secretion of AVP into peripheral blood peaks during nighttime (6), and is regulated by the circadian rhythm. However, patients with nocturnal polyuria do not show significantly elevated plasma AVP levels at nighttime, suggesting that abnormal diurnal variation in AVP secretion is highly prevalent in these patients (7,8).

Spontaneously hypertensive rats (SHRs) are a valuable tool for exploring the pathogenesis of hypertension-related bladder dysfunction. These rats exhibit increased voiding frequency and decreased bladder blood flow compared to the non-hypertensive Wistar rats (9,10). Saito et al. (11) revealed that naftopidil decreases micturition frequency and urine production in SHRs during the light-cycle. It has been reported that basal and K^+-stimulated release of endogenous noradrenaline (NA) from the paraventricular hypothalamic nucleus was increased in SHRs compared with

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normotensive control rats, suggesting that noradrenergic neuronal activity is enhanced in the central nervous system of SHRs (12). Furthermore, inhibition of NA synthesis in the posterior hypothalamus by 6-hydroxydopamine was demonstrated to lower blood pressure in SHRs (13).

Based on these reports, we postulated that naftopidil either directly or indirectly regulates AVP secretion via brain adrenoceptors, leading to reduction in urine frequency and production at night. In the present study, we examined whether naftopidil modulates plasma AVP levels and urine production in rats centrally administered with NA.

2. Materials and methods

2.1. Animals

All animal care and experimental procedures complied with the guiding principles for care and use of laboratory animals approved by Kochi University (No. I-00046), in accordance with the "Guidelines for proper conduct of animal experiments" proposed by the Science Council of Japan; these guidelines conform to the standards of the National Institutes of Health. All efforts were made to minimize the suffering of the animals and the number of animals needed to obtain reliable results. In all, 93 eight-week-old male Wistar rats (Japan SLC Inc., Hamamatsu, Japan) weighing 200–250 g were used in the experiments. The rats were housed in pairs in cages, in an air-conditioned room at 22–24 °C under a constant day–night rhythm (14/10 h light–dark cycle, lights on at 05:00) for more than 2 weeks. They had *ad libitum* access to food (laboratory chow, CE-2; Clea Japan, Hamamatsu, Japan) and water. Upon reaching a body weight of 310–360 g, the rats were subjected to the following experiments.

2.2. Intracerebroventricular administration of NA

In the morning (10:30–11:30), rats were placed in a stereotaxic apparatus (Narishige, Tokyo, Japan) under urethane anesthesia (1.0 g/kg, i.p.), as described previously in a published work of this laboratory (14). The skull was drilled for intracerebroventricular administration of NA using a stainless-steel cannula (outer diameter of 0.3 mm). The stereotaxic coordinates of the tip of the cannula were as follows (in mm): AP −0.8, L 1.5, V 4.0 (AP, anterior from the bregma; L, lateral from the midline; V, below the surface of the brain), according to the rat brain atlas (15). The steel cannula was injected into the left lateral ventricle 3 h before NA administration as described below, and was retained until the end of the experiment.

2.3. Drug administration

NA and naftopidil were dissolved in 10 mM phosphate-buffered saline (PBS) containing 0.1% ascorbic acid (pH 7.4) and 10% *N*,*N*-dimethylformamide (DMF), respectively. NA (3 or 30 μg/kg) was slowly administered into the left lateral ventricle in a volume of 10 μL/animal using a cannula connected to a 10-μL Hamilton syringe (Hamilton, Reno, NV, USA) at a rate of 10 μL/min. Naftopidil (10 or 30 mg/kg) was administered intraperitoneally in a volume of 1.0 mL/animal. Subsequently, NA was slowly administered as described above, 3 h following the application of naftopidil. The doses of naftopidil were determined according to previous reports from our and other laboratories that had used similar doses of naftopidil in rats (4,11,16). Furthermore, we have checked the dose-dependent efficacy of naftopidil in our preliminary study. The exact location of the cannula injected in the brain was confirmed at the end of each experiment by verifying that cresyl violet, injected through the cannula, had spread throughout the ventricular system, as described previously (17). For voiding behavior studies, rats were administered naftopidil intraperitoneally at 10:00 am once a day, for two days.

2.4. Measurement of plasma AVP levels

A total of 70 rats placed in a stereotaxic apparatus were randomly divided into ten groups in order to measure their plasma AVP levels: NA administered groups at 3 and 30 μg/kg per animal, i.c.v. (n = 7 and 8, respectively); vehicle-1 (10 μL PBS-containing 0.1% ascorbic acid per animal, i.c.v.) administered group (n = 7); naftopidil administered groups at 10 and 30 mg/kg, i.p. (n = 8 and 7, respectively); vehicle-2 (1.0 mL10% DMF, i.p.) administered group (n = 6); 10 mg/kg naftopidil (i.p.) and NA (30 μg/kg, i.c.v.) administered group (n = 8); 30 mg/kg naftopidil (i.p.) and NA (30 μg/kg, i.c.v.) administered group (n = 6); vehicle-2 and NA (30 μg/kg, i.c.v.) administered group (n = 7); and vehicle-2 and vehicle-1 administered group (n = 6).

Blood samples (5 mL) were collected from the inferior vena cava 1 h after NA or vehicle administration into the left ventricle. All blood samples were collected at 4:00 pm as described previously (18), and were mixed with 1 mg/mL EDTA before centrifuged at 1600 × g for 15 min at 4 °C to obtain the plasma. The obtained plasma samples were mixed with a protease inhibitor cocktail (0.5 μL/mL plasma), and were kept at −80 °C. These samples were concentrated to 400 μL using a centrifugal concentrator, before AVP levels were measured in duplicate using an ELISA kit (#ab133028; Abcam, Cambridge, UK). The sensitivity of this assay (lower limit of detection) was less than 3.39 pg/mL, and the intra-assay precision was less than 5.9%.

2.5. Voiding behavior studies

Rats were randomly divided into two groups for examination of voiding behaviors: naftopidil (30 mg/kg, i.p.) administered group (n = 5) and vehicle-2 administered group (n = 5). Voiding behavior studies were performed according to methods described in our previous reports (11). The rats received food and water *ad libitum* from the time they were initially placed in metabolic cages. The rats were kept for 24 h for adaptation, and recorded for the next 24 h. Micturition frequency and total urine output were evaluated from these recordings.

2.6. Urine production and osmolality

Fourteen rats were divided into the following groups: NA (30 μg/kg, i.c.v.) administered group (n = 5); NA (30 μg/kg, i.c.v.) and naftopidil (30 mg/kg, i.p.) administered group (n = 5); and vehicle-1 and vehicle-2 administered group (n = 4). Before the experiment, rats were catheterized at the bladder dome with a 22G needle for urine collection, and a stainless cannula was inserted into the left lateral ventricle for administration of NA as described above. The catheterized bladder in the rat was emptied and the urethra was clamped to prevent urine leakage. Vehicle-1 or NA (30 μg/kg, i.c.v.) was centrally administered 3 h after intraperitoneal pretreatment with vehicle-2 or naftopidil (30 mg/kg). Urine was collected 1 and 3 h after NA administration (at 4:00 pm and 6:00 pm, respectively).

We also determined urine osmolality for the following groups: NA (30 μg/kg, i.c.v.) administered group (n = 5); NA (30 μg/kg, i.c.v.) and naftopidil (30 mg/kg, i.p.) administered group (n = 5); and vehicle-1 and vehicle-2 administered group (n = 5). Urine was collected 1 and 3 h after NA administration (at 4:00 pm and 6:00 pm, respectively), and was centrifuged at 1600 × *g* for 15 min at 4 °C to remove impurities. The urine osmolality (mOsmolality/kg H_2O) of

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