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Prolonged effects of intracerebroventricular angiotensin II on drinking, eating and locomotor behavior in mice

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ABSTRACT

The effects of centrally administered Angiotensin II (Ang II) on water and food intake in rodent models are well known. However, most studies have focused on the acute effects of intracranial Ang II. In the current study, we evaluated the effects of intracerebroventricular Ang II on food and water intake as well as locomotor activity over the entire dark phase of the murine diurnal cycle. Consistent with the previous reports, centrally administered Ang II rapidly stimulated water intake over the initial 1-hour period following treatment. However, this acute increase was immediately followed by a marked reduction in water intake resulting in decreased cumulative water intake approximately 7 h after Ang II treatment. Pretreating animals with an Ang II type 1 receptor blocker, Losartan, completely antagonized the acute effect of Ang II and abolished initial water intake. In contrast, application of an Ang II type 2 receptor blocker, PD123319, abrogated the prolonged inhibitory effect of Ang II on drinking behavior and partially suppressed the initial increases in water intake. The suppressive effects of Ang II on cumulative food intake and spontaneous physical activity were also evident throughout the entire dark phase of diurnal cycle. These experiments are the first to suggest that the stimulatory effect of central Ang II treatment on water consumption is very temporary and that it causes a sustained suppressive effect on voluntary locomotion and food intake behavior in mice.

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1. Introduction

Angiotensin II (Ang II) is a crucial component of the renin–angiotensin system, which plays a major role in maintaining sodium and water balance through a variety of effects on the central nervous system (CNS), adrenal gland, vasculature and kidney [1]. The actions of Ang II in the brain, mediated by angiotensin II type 1 (AT1) or type 2 (AT2) receptors, involve modulating neuronal activity by changing the activity of membrane ion channels and currents [2]. Centrally administered Ang II increases blood pressure, stimulates water and salt intake and promotes hormone release from the pituitary in a process mediated by the AT1 receptor [3]. The AT1 receptor often interacts functionally with the AT2 receptor in the CNS. For instance, the pressor response to centrally injected Ang II was inhibited by intracerebroventricular (ICV) injection of a selective AT1 receptor antagonist, but exaggerated by a selective AT2 receptor antagonist [4].

The rapid and potent dipsogenic effects of centrally administered Ang II are well documented [4–7]. In mice, it has been shown that the increase in water intake due to Ang II are substantially inhibited in the presence of an AT1 receptor blocker and partly inhibited by AT2 receptor blockade [4]. In addition, AT2-deficient mice have an impaired drinking response to water deprivation and altered exploratory behavior and locomotor activity [8,9]. Central administration of Ang II also suppresses food intake [10–13]. In mice, the effect is mainly mediated via the AT2 receptor with a partial involvement of the AT1 receptor [13]. Thus, it is generally agreed that the major central actions of Ang II includes enhanced water intake, suppressed food intake and impaired locomotor activity. However, such conclusions regarding changes in eating and drinking behavior induced by Ang II have largely been based on data obtained from models where the data were only collected for short periods of time, and in which experiments were performed during daylight hours. Hence, it remains unclear whether Ang II exerts similar actions over extended periods of time during the dark phase of the murine diurnal cycle. Accurate evaluation of eating and drinking behavior, as well as locomotor activity, has recently been made possible by a device that allows one to monitor such activities during the entire dark phase.

In this report, we investigated whether the well-documented central effects of Ang II on physical activity and food and water intake are also observed over an extended period of time, and whether such effects could result in altered metabolic or water homeostasis.

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2. Methods

2.1. Animals

The present studies were conducted in accordance to Tokyo Medical and Dental University Guidelines for the Care and Use of Experimental Animals. Male C57BL/6 J mice (CLEA Japan, Tokyo, Japan) weighing 20–25 g were acclimatized to a colony room maintained under controlled temperatures (23 ± 2 °C) and a 12-h light–dark cycle (lights on 07:00 to 19:00). The animals had unlimited access to food (standard laboratory powder chow; MF, Oriental Yeast, Tokyo, Japan) and water.

2.2. Lateral ventricle cannulation

Mice were anesthetized with an intraperitoneal injection of sodium pentobarbital (75 mg/kg) and standard aseptic procedures were used to implant the indwelling guide cannula (0.5 mm o.d., 0.3 mm i.d, 5 mm length; Laboratory & Medical Supplies, Tokyo, Japan). By means of a free hand technique, the cannula were inserted into the lateral cerebral ventricles (0.5, 1.0, and 2.0 mm posterior, lateral, and ventral to the bregma), according to stereotaxic coordinates obtained via Paxinos and Franklin [14] as described [15,16]. Finally the cannula was secured to the skull with stainless steel screws and dental acrylic cement. A wire stylet was then placed in the guide cannula to prevent occlusion. The mice were allowed to recover from the operation for a minimum of seven days before any experimental procedures were introduced. After the completion of the experiments, a dye (5% glycerin, 0.05% bromphenol blue, 0.05% xylenecyanol) was injected through cannula. The brains were then removed and sectioned at injection site. A correct cannula placement was verified by a flow of dye from lateral ventricle to ventral third ventricle.

2.3. Intracerebral microinjection and drugs

At the point of experimentation the mice were divided into the different treatment groups, which consisted of the following: Ang II only, Ang II + AT1 antagonist, Ang II + AT2 antagonist or saline only (n = 7–11 mice/group). To administer the intraventricular injections, the mice were restrained manually while the stylets were removed, and injection needles (6.55 mm, Laboratory & Medical Supplies, Tokyo, Japan) were lowered through the guide cannula [17, 18]. The needles were then connected to a Hamilton syringe and the drugs were administered slowly at a volume of 1.0 μl over 20 s. The mice were injected with a 0.9% saline solution containing the AT1 receptor blocker, Losartan (20 μg; LKT Laboratories, MN, USA) or the AT2 receptor blocker, PD123319 (10 μg; Sigma-Aldrich, St. Louis, MO, USA). Ten minutes later, the mice were also injected with an Ang II solution (200 ng; Peptide Institute, Inc. Osaka, Japan). Experiments commenced between 18:00 and 19:00 h and activity and food/water intake were recorded over the entire dark phase.

2.4. Measurement of spontaneous activity and water/food intake

Spontaneous activity, in addition to water and food intake, were recorded automatically using a feeding, drinking and activity monitoring system (ACTIMO-100 combined with MFD-100; Shinfactory, Fukuoka, Japan). This system consists of a clear acrylic rectangular enclosure with the following external dimensions: 32 × 20.5 × 26.5 cm. To measure movement, sensors are located every 2 cm along the floor of the enclosure (5 cm above the wire floor), and movement is detected by an infrared beam every 0.5 s. To eliminate any artifacts elicited by respiration or nose/tail movements, the simultaneous interruption of more than two neighboring beams are recorded as "an activity output" by ACTIMO-DATA software (Shinfactory, Fukuoka, Japan). Movement signal counts were imported using the Spike2 analysis program (Cambridge Electronic Design, Cambridge, UK). The experiments were performed during the dark phase (19:00 to 07:00) in a dark room that was completely isolated from external noises. A water bottle attached to a drip infusion kit was hung at one end of the chamber and at the opposite end of the chamber there was a food intake monitor filled with standard powder chow. Water and food intake were recorded simultaneously every 3 min using a water droplet detector and high accuracy scale that weighed the chow. The minimum quantities measurable were one drop of water (17 μl) and 0.01 g of chow. The mice were housed in the individual chambers for at least 3 days to be familiarized with the recording environment.

For qualitative analysis of animal behavior during the experimental period, the cages were continuously monitored by a high sensitivity digital video camera (WAT-232, Watec Co. Ltd, Yamagata, Japan) and recorded onto the digital high vision recorder (DV-AC82, Sharp Corporation, Osaka, Japan). The minimum illumination of the video camera is 0.006 lux, F1.2, the effective pixels are 38×10^4, and the resolution is 540 TV lines.

2.5. Statistical analysis

Values are expressed as the mean ± S.E.M. Analysis of variance (ANOVA) followed by Tukey–Kramer test was used to assess differences among groups. A value of $P<0.05$ was considered to be statistically significant.

3. Results

3.1. The effect of centrally administered Ang II on cumulative water intake

Central administration of Ang II had a rapid and potent effect on water intake within the first hour compared with control animals (Fig. 1). However, the Ang II-induced increase in cumulative water intake disappeared by the end of second hour. Moreover, the cumulative water intake in mice receiving Ang II was significantly lower than control animals 7–9 h post treatment (7 h: 43% reduction; 8 h: 34% reduction; 9 h: 31% reduction; $P<0.05$ at each time point) despite the marked increase observed initially. The initial increase in water intake induced by central Ang II was inhibited by pretreatment with the AT1 receptor-selective antagonist Losartan observed by a 96% reduction in water intake ($P<0.05$). On the other hand, subsequent decrease in cumulative water intake was completely blocked by pretreatment with PD123319.

3.2. The effect of centrally administered Ang II on hourly water intake

We next analyzed changes of hourly water intake induced by central Ang II with and without pretreatment with Losartan or PD123319 (Fig. 2). Ang II induced a more than threefold increase in water intake during the initial 1 h period compared with control animals, but caused a marked reduction in the control group during the second hour (97% reduction). Significantly decreased water intake lasted up until 4 h (88% reduction), and disappeared thereafter. The marked suppression of water intake after central Ang II was significantly antagonized by pretreatment with PD123319; the effect was evident from as early as 2 h after treatment and lasted for 4 h.

3.3. The effect of centrally administered Ang II on cumulative food intake

Centrally administered Ang II significantly inhibited cumulative food intake (Fig. 3). The reduced food intake was observed from 2 h post treatment (40% reduction) and lasted until the end of the entire dark phase of the diurnal cycle (at 12 h: 31% reduction). The hypophagic effect was completely abolished by PD123319 for the entire

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