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Impaired drinking response in histamine H3 receptor knockout mice following dehydration or angiotensin-II challenge

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Abstract

Histamine H3 receptors (H3Rs) are presynaptic receptors that negatively regulate the release of histamine. The present study examined the physiological role of H3Rs in drinking behavior. In water-replete rats, intracerebroventricular (i.c.v.) administration of *R*-α-methylhistamine (RαMeHA), an H3R agonist, elicited drinking behavior. In contrast, i.c.v. administration of thioperamide, an H3R inverse agonist, significantly attenuated the drinking behavior elicited by either overnight dehydration or i.c.v. administration of angiotensin-II (AT-II). Inhibition of histamine release with α-fluoromethylhistidine, an inhibitor of histidine decarboxylase, did not elicit drinking behavior. Moreover, the inhibitory effects of thioperamide on drinking behavior in water-depleted rats were not mimicked by i.c.v. administration of histamine. These results suggest that the predominant effects of H3Rs on drinking behavior are not mediated by the modulation of histamine release. In H3R-deficient (H3RKO) mice, drinking behavior induced by overnight dehydration or i.c.v. administration of AT-II was significantly impaired compared to wild type mice. Collectively, these observations suggest that brain H3Rs play a pivotal role in drinking behavior in response to dehydration and AT-II, and these effects may be largely independent of the modulation of histaminergic tone.

Keywords: Histamine; H3 receptor; Thirst; Drinking behavior; Angiotensin-II; Dehydration; Thioperamide; Methylhistamine

1. Introduction

Regulation of volume and osmolality of body fluid is fundamental to survival in animals and is achieved by a precise balance between intake and excretion of water and electrolytes. Fluid intake is elicited in response to dehydration, eating and hypovolmia, which involve multiple neuroendocrinal changes in the brain and peripheral tissues. A number of neurotransmitters and hormones such as angiotensin-II (AT-II), neuropeptide Y and serotonin regulate fluid intake in the brain (Antunes-Rodrigues et al., 2004). In addition to these substances, a range of evidence has shown that histamine, a classical mediator of inflammation and vasoconstriction, also contributes to fluid intake by peripheral and central actions (Gerald and Maickel, 1972; Leibowitz, 1973; Kraly et al., 1995a,b, 1996; Lecklin et al., 1999).

A number of previous studies have suggested that H1 and H2 receptors regulate drinking behavior. Systemic administration of histamine elicits drinking behavior, which are antagonized by H1 and H2 antagonist in rats (Goldstein and Halperin, 1977; Kraly, 1983). Since histamine is a hydrophobic substance, the targeted regions are considered to be located in peripheral tissues. In support of this, eating releases histamine from gastric mucosa and H1 and H2 receptor antagonists inhibit drinking behavior associated with eating in rats, indicating the role of histamine in drinking behavior associated with eating (Kahlson et al., 1964; Kraly and Specht, 1984). In addition, histamine also elicits drinking behavior when administered in the brain (Leibowitz, 1973; Gerald and Maickel, 1972). Although the responsible receptors for the dipsogenic effects of i.c.v. histamine are not clear, H1 and H2 receptors in the brain participate in drinking behavior in response to dehydration and angiotensin-II-induced thirst (Magrani et al., 2004, 2005). Furthermore, evidence has also suggested that H3 presynaptic autoreceptors contribute to drinking behavior in the brain and peripheral tissues. I.c.v. H3

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receptor agonist elicits drinking behavior and the administration of H3 receptor antagonist inhibits drinking behavior induced by peripheral administration of histamine or eating (Clapham and Kilpatrick, 1993; Kraly et al., 1995a,b, 1996). However, few studies have investigated the role of H3 receptors in the brain in other physiological stimuli. The present study addressed the involvement of H3 receptor in drinking behaviors induced by dehydration and i.c.v. administration of angiotensin-II using rats and H3 receptor-deficient mice.

2. Materials and methods

2.1. Animals

Male Sprague Dawley rats (Charles River, Japan) and H3RKO mice were housed individually in plastic cages and were kept at 23±2 °C and 55±15% relative humidity under a light–dark cycle from 7:00 to 19:00. Water and regular chow (CE-2, CLEA Japan Inc.) were available ad libitum unless otherwise indicated. H3RKO were generated and littermate mice backcrossed for five generations to the C57BL/6J background were used for all experiments (Takahashi et al., 2002). All experimental procedures followed the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Surgical procedure

8–10-week-old rats (300–390 g) were anesthetized with 3.6% ketamine and 0.5% xylasine. An 11 mm long guide cannula was implanted in the third cerebroventricle. Stereotaxic coordinates for the guide cannula were 2.2 mm posterior to the bregma to the midline and 8.0 mm below the surface of the skull. 10–11-month-old mice were anesthetized with 80 mg/kg pentobarbital and a guide cannula was implanted into the lateral ventricle. Stereotaxic coordinates were 0.4 mm posterior to the bregma, 0.8 mm lateral to the midline and 2.0 mm from the surface of the skull. The guide cannula was fixed to the skull by screws and dental cement. Animals were used for experiments after a 1-week recovery period.

2.3. Rat study

All experiments were conducted between 9:00 and 12:00. Rats were denied access to drinking water before dark onset with ad libitum access to food. On the next day, compounds or vehicle (PBS) was injected in the third cerebroventricle and water was supplied 10 min after the injection. When AT-II (9.6 pmol) was used, it was simultaneously injected with other compounds. Food was withdrawn 1 h before the injection in order to avoid drinking associated with eating. Water consumed over a 30-min period was measured by weighing the water-containing bottles before and after the experiment. Cannulated rats were repeatedly used for 2 months after surgery, with at least 4-day washout period. Rats were subjected to thioperamide, RαMeHA, histamine or angiotensin-II during this period. Rats having received α-FMH were not used for further experiments since it irreversibly inhibits histidine decarboxylase. As far as we conducted water intake study (more than 20 times), the consumed water in response to dehydration varied from 10 ml to 20 ml even though animals of similar ages and body weights are used. Animals were fully acclimatized to handling stress and room temperature and humidity are strictly controlled, excluding the possibility that these factors might lead to variable water consumption among experiments. Although we are not able to fully explain these variants, some other factors might have influenced the amount of consumed water.

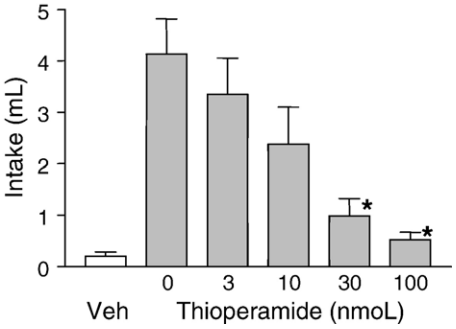

Fig. 1. Effects of thioperamide on drinking behavior elicited by RαMeHA (2.4 nmol, gray bars) in water-replete rats. Veh represents rats that were treated with vehicle alone. *$p<0.05$ vs. vehicle control (0 nmol thioperamide). $N=8–12$.

2.4. Mouse study

Mice (5–6 months old, Wt 31.1±0.6 g, H3RKO 38.8±0.7 g, $n=12$ each) were dehydrated with ad libitum access to food before dark onset and water was presented between 9:00 and 12:00. In another experiment, urine was collected using metabolic cage. Mice were acclimatized to the cage for one week prior to the experiment. Excreted urine volume was measured by weighing and osmolality was measured using an osmometer (Advanced Micro-Osmometer, Advanced Instruments, USA). Angiotensin-II or vehicle was intracerebroventriculary administered in 11 Wt mice and 10 H3RKO mice and water intake was measured for 1 h. After 1 week recovery, they were subjected to either vehicle or angiotensin-II in crossover. Water intake was determined by averaging values obtained in two sets of experiments.

2.5. Compounds

Histamine, thioperamide, *R*-α-methylhistamine (RαMA) and α-fluoromethylhistidine (α-FMH) were purchased from Sigma (Sigma-Aldrich, USA), Angiotensin-II (AT-II) from Peptide Institute (Osaka, Japan) and losartan from Wako Pure Chemical (Osaka, Japan).

2.6. Statistics

Unpaired Student's *t*-test or one-way ANOVA followed by Bonferroni/Dunnett test was used to compare two or more than two groups, respectively.

3. Results

I.c.v. administration of RαMeHA (2.4 nmol), an H3R agonist, elicited robust drinking behavior in water-replete rats, as

previously reported (Clapham and Kilpatrick, 1993). Most rats started drinking within 10 min and finished at 20 min (Fig. 1). Simultaneous administration of thioperamide, an H3R inverse agonist, dose-dependently inhibited the drinking behavior induced by RαMeHA (Fig. 1). No abnormal behavior was observed after administration of thioperamide.

The effects of H3R ligands on drinking behavior were investigated in water-depleted rats. Either RαMeHA or thioperamide was administered to rats that were dehydrated overnight and subsequent drinking behavior was monitored. The results showed that RαMeHA and thioperamide augmented and inhibited drinking behavior, respectively, in a dose-dependent manner (Fig. 2A and B). In overnight-fasted rats, thioperamide did not alter food intake (Fig. 2C).

H3Rs are autoreceptors that provide a negative feedback loop for histamine release and production. Pharmacologically, H3R agonists and H3R inverse agonists decrease and increase histamine release, respectively (Arrang et al., 1983). To address the role of histaminergic tone in the control of drinking behavior, we investigated the effects of α-fluoromethylhistidine (α-FMH) on drinking behavior in rats. α-FMH irreversibly inhibits histidine decarboxylase, the key enzyme for histamine synthesis, and thereby decreases histamine release (Garbarg et al., 1980). In water-replete rats, i.c.v. administration of α-FMH did not elicit, but rather inhibited, drinking behavior for up to 2 h when compared with vehicle (vehicle: 1.0±0.2 ml, α-FMH: 0.4±0.1 ml, $p<0.05$). Subsequent administration of RαMeHA significantly elicited drinking behavior in rats that were treated with α-FMH (Fig. 3). The magnitude, however, was reduced when compared with that in the rats that were treated with vehicle (Fig. 3).

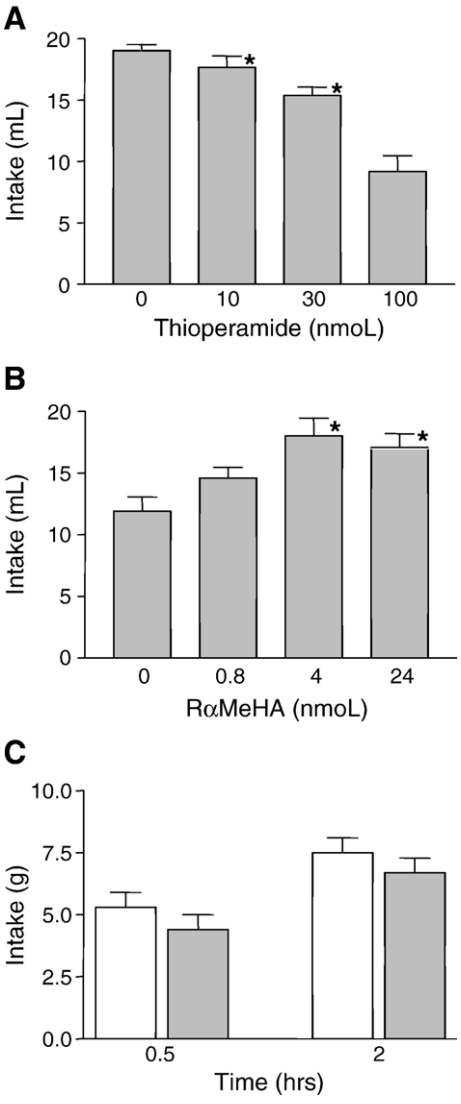

Fig. 2. Effects of thioperamide (A) and RαMeHA (B) on drinking behavior in water-depleted rats. (C) Effects of vehicle (white bars) and thioperamide (100 nmol, gray bars) on food intake in fasted rats. *$p<0.05$ vs. vehicle control. $N=8–11$.

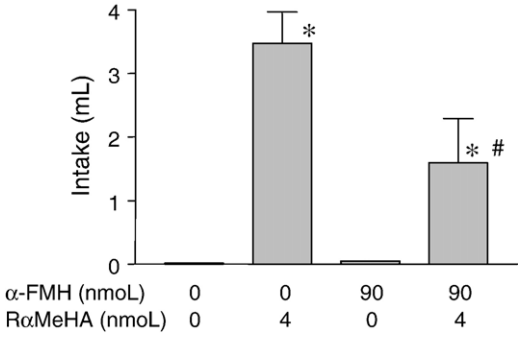

Fig. 3. Effects of pretreatment with vehicle or α-FMH on the drinking behavior elicited by RαMeHA in water-replete rats. Vehicle or α-FMH was administered 2 h before ICV injection of RαMeHA. *, #$p<0.05$ vs. vehicle (0 nmol α-FMH) and vehicle (90 nmol α-FMH), respectively. $N=10–11$.

We next addressed whether the inhibitory effects of thioperamide on drinking behavior in water-depleted rats was attributable to the enhancement of histamine release. Histamine was administered to the brains of dehydrated rats and subsequent drinking behavior was monitored. The results showed that the rats became slightly immobilized in response to histamine and the drinking behavior tended to decrease for the first 30 min after administration (Fig. 4A). However, the drinking behavior was significantly augmented in the next 30 min (Fig. 4B). Overall, the total water intake consumed in 1 h was not significantly altered by histamine (vehicle: 15.9±1.3, 30 nmol; 16.3±1.1, 100 nmol; 15.9±1.7, 300 nmol; 14.8±1.9 ml).

It has been documented that AT-II plays a pivotal role in the regulation of drinking behaviors (Antunes-Rodrigues et al., 2004). I.c.v. administration of AT-II elicits robust drinking behavior preferentially via AT-1 receptors and antagonists for AT-1 receptors inhibit drinking behavior in water-depleted animals (Hogarty et al., 1992; Beresford and Fitzsimons, 1992; Blair-West et al., 1992; Weisinger et al., 1997). To address the relationship between AT-II and H3Rs, we investigated the effects of thioperamide on drinking behavior elicited by ICV administration of AT-II. AT-II elicited dose-dependent drinking behavior at the range of 0.5 to 15 pmol (data not shown) and 9.6 pmol gave reproducible results. The results showed that thioperamide partially inhibited drinking behavior in a dose-dependent manner, while losartan, an AT-1 receptor antagonist, completely inhibited drinking behavior (Fig. 5).

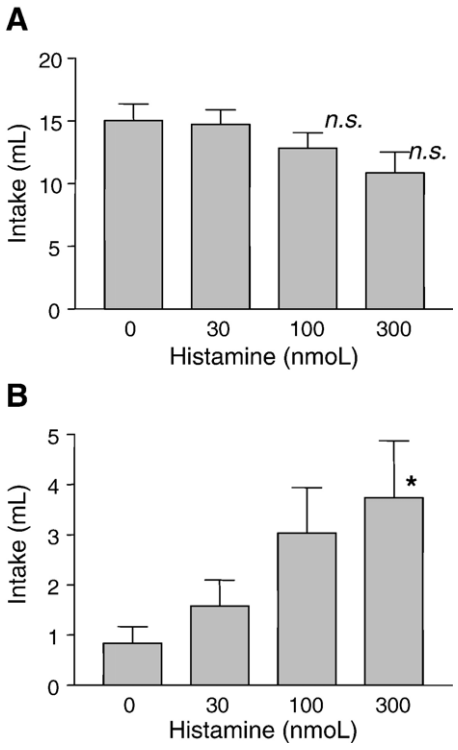

Fig. 4. Effects of histamine on drinking behavior in water-depleted rats for 30 min (A) and from 30 to 60 min (B) after administration. *$p<0.05$ vs. vehicle control. n.s.: not significantly different. $N=8–12$.

Finally, we investigated drinking behavior in H3RKO mice. H3RKO mice consumed as much water as Wt littermate mice in a daily basis when they were freely allowed access to water (Wt: 4.4±0.2 ml, KO: 4.4±0.2 ml, $p>0.05$). Furthermore, H3RKO mice showed similar urine volume and osmolality when compared with Wt mice when water was freely available (Fig. 6B and C). In water-replete mice, i.c.v. administration of AT-II elicited drinking behavior in both mouse genotypes, but the consumed water was significantly smaller in H3RKO mice compared to Wt mice (Fig. 6A, $p<0.05$ vs. Wt mice, unpaired Student's t-test). Furthermore, H3RKO mice consumed less water in response to overnight dehydration when compared with Wt mice (Fig. 6A). The urinary volume comparably decreased and osmolality comparably increased in response to dehydration in both mice (Fig. 6B and C).

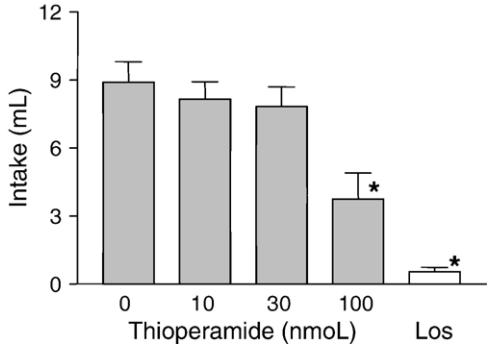

Fig. 5. Effects of thioperamide (gray bars) or losartan (6.5 nmol, white bar) on drinking behavior elicited by AT-II (9.6 pmol) in water-replete rats. *$p<0.05$ vs vehicle control. $n=9–10$.

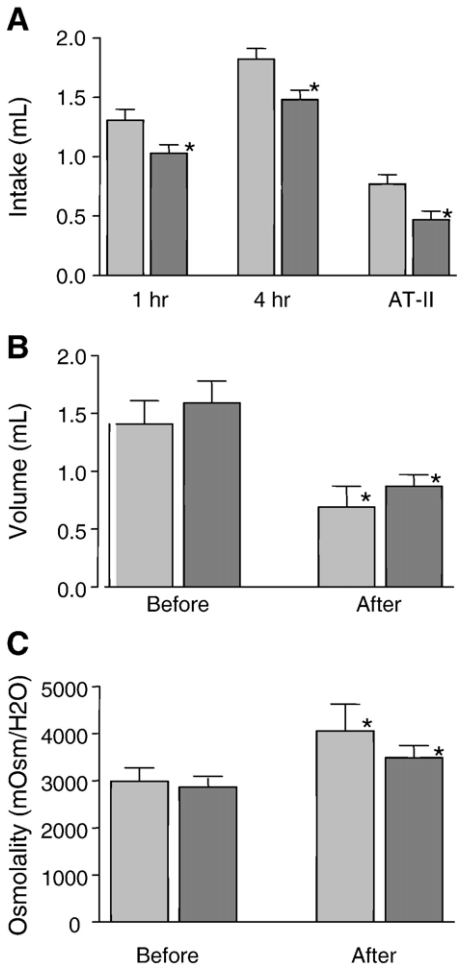

Fig. 6. Drinking behavior over 1 and 4 h after overnight dehydration or ICV administration of AT-II (9.6 pmol) (A). Urine volume (B) and urine osmolality (C) before and after overnight dehydration in Wt (gray bars) and H3RKO mice (dark bars). p value was evaluated using unpaired (A, Wt vs. KO) and paired Student's t-test (B, C, before vs. after). $N=12$.

4. Discussion

The present study demonstrated that ICV administration of thioperamide inhibited drinking behavior, while RαMeHA augmented drinking behavior in water-depleted rats. Consistent with this, genetic disruption of H3R in mice resulted in reduced drinking behavior when challenged to dehydration. Moreover, the drinking behavior induced by AT-II was reduced by administration of thioperamide in rats or in H3RKO mice. These results suggest the important role of H3Rs during dehydration in rodents and the participation of H3Rs in angiotensinergic pathways.

Fluid intake is initiated by a number of hormonal and neuronal stimuli associated with dehydration, hypotension and eating behavior, which activate specific brain areas such as the organum vasculosum of the lamina terminalis, median preoptic nucleus and preoptic periventricular nucleus of the third ventricle (Antunes-Rodrigues et al., 2004). Brain histaminergic neurons project

throughout the brain including the above regions and central administration of histamine elicits drinking behaviors (Gerald and Maickel, 1972; Leibowitz, 1973). Moreover, several observations have demonstrated the involvement of H1Rs and/or H2Rs in the drinking behavior induced by dehydration, eating and systemic administration of histamine (Kraly et al., 1995a,b, 1996; Eidi et al., 2003; Magrani et al., 2004). H3Rs also contribute to drinking behavior as evidenced in several reports and Kraly et al. have extensively studied the role in drinking behavior induced by systemic administration of histamine or high osmolality loading (Clapham and Kilpatrick, 1993; Kraly et al., 1995a,b, 1996). However, the role of H3Rs in drinking behavior in response to other physiological stimuli is less understood.

In the present study, we confirmed previous studies showing that ICV administration of RαMeHA-induced drinking behavior in water-replete rats (Clapham and Kilpatrick, 1993; Kraly et al., 1995a). This effect was completely inhibited by simultaneous administration of thioperamide in a dose-dependent manner. It is unlikely that thioperamide inhibited drinking behavior due to other factors, such as aversive responses, as neither thioperamide elicited abnormal behavioral change nor had any effect on food intake in fasted rats. Furthermore, thioperamide inhibited drinking behavior, while RαMeHA further augmented drinking behavior in water-depleted rats. These results strongly indicate the involvement of H3Rs in drinking behavior particularly in response to dehydration. In support of this, immunohistological analysis has shown that the number of c-fos positive cells in histamine neurons increases after dehydration and turnover of histamine neurons is elevated in response to dehydration (Kjaer et al., 1995; Miklos and Kovacs, 2003). Therefore, the present results together with previous studies suggest that histamine neurons are activated in response to dehydration and subsequent activation of H3Rs as well as H1Rs and H2Rs might contribute to initiation of drinking behavior.

It has been demonstrated that H3R agonists decreases histamine release, while H3R inverse agonists increase histamine release (Arrang et al., 1987, 1988). In terms of negative regulation of H3Rs for histamine release, the dipsogenic effects obtained with RαMeHA are paradoxical. Because blockade of postsynaptic H1Rs and/or H2Rs reduces drinking behavior, the stimulation of presynaptic H3Rs by RαMeHA might lead to the reduced tone of postsynaptic H1Rs and/or H2Rs (Eidi et al., 2003; Magrani et al., 2004, 2005). To address whether RαMeHA reduces the histermingeric tone to elicit drinking behavior, we investigated the effects of α-FMH, an irrevsesible inhibitor of histidine decarboxylase, on drinking behavior (Garbarg et al., 1980). Results showed that administration of α-FMH in water-replete did not elicit but rather inhibited drinking behavior for up to 2 h, suggesting that the inhibition of histamine release does not lead to an initiation of drinking behavior. Furthermore, RαMeHA was able to elicit drinking behavior in rats treated with α-FMH, although the magnitude was less than that in rats treated with vehicle (discussed below). A-FMH rapidly and irreversibly inhibits histidine decarboxylase and almost completely depletes neuronal histamine (Garbarg et al., 1980; Maeyama et al., 1982; Soe-Jensen et al., 1993; Chen et al., 1999). Therefore, it might be concluded that rats with depleted histamine remain responsive to ICV administration of RαMeHA, further indicating that reductions in histamine release are not a prerequisite for initiation of drinking behavior by RαMeHA.

In water-depleted rats, no significant inhibition of drinking behavior was observed during the first 30 min after administration of histamine, indicating that histamine does not mimic the regulatory action of thioperamide. Therefore, it could be suggested that thioperamide inhibits drinking behavior independently of facilitating histamine release. Although a slight but not significant inhibition of drinking behavior was observed with histamine in the first 30 min, we speculate that this was due to slight immobilization in response to histamine, since (1) histamine decreases locomotor activity shortly after injection, (2) histamine elicits drinking behavior in water-replete rats, which is not mimicked by thioperamide (data not shown), and (3) 100 nmol of histamine is sufficient to release coriticosterone, which is considered independent of behavioral abnormalities (Bristow and Bennett, 1988; Chiavegatto et al., 1998; Lecklin et al., 1988; Bugajski and Janusz, 1983; Tsujimoto et al., 1993). Conversely, stimulatory effects were observed in the next 30 min when the behavioral changes were restored, thus supporting a recent study showing that histamine elicits drinking behavior even in water-depleted rats (Eidi et al., 2003). Although we could not exclude the possibility that the stimulatory effects are compensatory for the apparent inhibition during the first 30 min, it might be concluded that histamine does not mimic the effect of thioperamide. These results are in good agreement with the results obtained with RaMeHA, further suggesting that the modulation of drinking behavior by H3Rs is largely independent of histamine release.

The amount of water consumed over 2 h was reduced by treatment with α-FMH and the dipsogenic effects of RαMeHA were reduced in the presence of α-FMH. A recent study has shown that antagonists of H1Rs and H2Rs inhibit drinking behavior in both water-depleted rats and water-replete rats (Magrani et al., 2004). Thus, it is possible that the administration of α-FMH reduced the activity of postsynaptic H1Rs and H2Rs, leading to inhibition of spontaneous drinking behavior. Accordingly, these results suggest that H3Rs are involved at least two discrete pathways regulating drinking behavior; activation of H3Rs augments drinking behavior independently of histamine modulation and inhibits drinking behavior in a histamine-dependent manner. H3Rs regulate the release of other biogenic amine such as noradrenaline, dopamine and serotonin, all of which have been implicated in the regulation of drinking behavior (Antunes-Rodrigues et al., 2004; Brown et al., 2001). Thus, it is possible that H3 ligands modulate drinking behavior by regulating the release of such biogenic amines. However, we cannot rule out the possibility that the reduced response to RaMeHA in the presence of α-FMH might be caused by other factors, because other evidence have suggested that inhibition of histidine decarboxylase reduces behavioral responsiveness to external stimuli (Onodera et al., 1992; Sakai et al., 1992; Parmentier et al., 2002).

AT-II is one of the strongest and well-characterized neuropeptides that elicit drinking behavior in the brain and it has been documented that the angiotensinergic pathway in the brain is

activated in response to dehydration (Antunes-Rodrigues et al., 2004). In the present study, thioperamide inhibited AT-II-induced drinking behavior in water-replete rats, thus suggesting that H3Rs are involved in the dipsogenic actions of AT-II. Although the detailed expression patterns of H3Rs in the brain are unclear, slight to moderate expression of H3Rs has been observed in brain regions such as the median preoptic nucleus and vascular organ of lamina terminalis. These regions are involved in the dipsogenic actions of AT-II and easily accessible to compounds when administered in the ventricle, suggesting that H3Rs might regulate drinking behavior in these regions (Antunes-Rodrigues et al., 2004; Pillot et al., 2002). In addition, we observed that losartan (21 nmol) partially but significantly inhibited RaMeHA (2.4 nmol)-induced drinking behavior in rats, suggesting that histamine (H3) and angiotensin might have reciprocal regulatory interaction in drinking behavior (RαMeHA alone: 4.8±0.6 ml, RαMeHA+losartan: 2.4±0.5 ml, $p<0.05$ Student's t-test, $n=16–17$). Moreover, a recent study indicated the involvement of H1Rs and H2Rs in the dipsogenic actions of AT-II (Magrani et al., 2005). These observations indicate complex interactions between the angiotensinergic and histaminergic pathways in drinking behavior.

The present study using H3RKO mice further confirmed that H3Rs physiologically regulate drinking behavior in response to dehydration. The drinking behavior in H3RKO mice was comparable to Wt mice when they were allowed free access to water but it was significantly impaired in response to dehydration, suggesting a pivotal role for H3Rsin dehydrated conditions. Dehydration elicits not only drinking behavior but also urinary condensation and brain histamine has been implicated in the regulation of arginine vasopressin, a potent anti-diuretic hormone (Kjaer et al., 1994, 1995). To address whether the impaired drinking behavior in H3RKO mice is due to differences in systemic fluid balance or motivation for thirst, urinary volume and osmolality after dehydration were measured. The results showed that urinary volume and osmolality were comparable in H3RKO and Wt mice. Therefore, it is likely that the impaired drinking behavior in H3RKO mice in response to dehydration was primarily due to the impairment of brain signals to initiate and/or sustain drinking behavior. This may involve the angiotensinergic pathway, as the response to ICV administration of AT-II was reduced in H3RKO mice, which is in good agreement with the pharmacological studies in rats.

In summary, the present study demonstrated the novel regulation of drinking behavior by H3Rs in response to dehydration and AT-II. It is likely that the predominant effects involve H3Rs independent of histamine modulation.

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