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Research article

Effects of human opiorphin on food intake and water intake in mice following central administration

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HIGHLIGHTS

- Human opiorphin inhibited food intake in fasted and freely feeding mice during the dark period.
- Human opiorphin increased water intake in fasted and freely feeding mice during the dark period or the light period.
- The anorexic effect of opiorphin was mainly related to the opioid system and the renin–angiotensin system.
- The effects of opiorphin on water intake are mediated mainly through renin–angiotensin system via potential protection of endogenous angiotensin from degradation by NEP and APN.

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ABSTRACT

Human opiorphin plays an important pharmacological functions in rats or mice. The present study was performed to investigate effects and underlying mechanism of central injected opiorphin on food intake and water intake in mice. Intracerebroventricularly (i.c.v.) administered opiorphin (5–20 μg/kg) dose-dependently suppressed food intake in fasted mice, but had no influence on food intake in freely feeding mice. The cumulative food intake was significantly decreased at 60 min after injection of 10 and 20 μg/kg opiorphin and the food intake was significantly reduced during the 20–60 min period after treatment. Non-selected opiate receptor antagonist naloxone could fully block the inhibitory effect induced by opiorphin on cumulative food intake at 60 min in fasted mice, suggesting that the anorexic effect of opiorphin was related to the opioid system. Moreover, the anorexic effect induced by opiorphin in fasted mice was also significantly inhibited by pretreatment with captopril or valsartan, which suggested that endogenous angiotensin may be involved in the response to opiorphin. Interestingly, the effect of opiorphin on water intake was increased in both fasted and freely feeding mice, which was completely blocked by captopril and valsartan. Furthermore, naloxone did not modify the effect of opiorphin on water intake. All together, the food and water intake effects of opiorphin may be due to the protection of the endogenous angiotensin and opioid peptides from degradation by NEP or APN.

1. Introduction

Human opiorphin, isolated from human saliva, is an identified endogenous pentapeptide, which is encoded by ProL1 multigenes family [31]. Opiorphin homologs are encoded by three genes: ProL1, HSMR3A and HSMR3B [27], and opiorphin corresponds to the secreted mature pentapeptide product of the ProL1 precursor protein [31]. It has been reported that opiorphin acts as a natural dual peptidase inhibitors by inhibiting two zinc metal ectopeptidases, human neutral ecto-endopeptidase NEP (EC 3.4.24.11) and human ecto-aminopeptidase APN (EC 3.4.11.2). Previous studies have also proved that opiorphin increases the levels of endogenous opioid peptides through an inhibition of enkephalin-inactivating ectopeptidases, and displays potent analgesic activity by potentiating endogenous μ- and δ-opioid receptor-dependent enkephalinergic pathways [24,31].

NEP and APN are membrane-bound metallopeptidases that play important roles in turning off neural and hormonal peptide signaling at the cell surface by hydrolyzing a variety of neuropeptides and regulatory peptides [19,28], among them enkephalins, endorphins, endothelin, substance P, bradykinin and angiotensin. NEPs are widely distributed in systemic and nervous tissues particularly profusely expressed in the renal epithelial cells and gastrointesti-

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nal mucosa where they have important functions as ectoenzymes, catalysing the postsecretory processing or metabolism of several signaling peptides, which decrease food intake, such as enkephalins, endothelin, substance P, and bradykinin [14,22]. APNs, which are located in the brain, intestinal, lung and kidney epithelial cells [9,11,23], cleave the N-terminals amino-acid of biologically active peptides such as enkephalin, angiotensin, neurokinin and cytokines, and exert profound activity on vital processes such as immune response, cellular growth, food intake and water intake [13,17,20]. Therefore, both NEPs and APNs are expressed in the central nervous system (CNS) and peripheral nervous nerves (PNS), where neuropeptides, regulatory peptides and their receptors are widely distributed. Studies have addressed that central administration of Ang II and III suppress food intake and increase water intake [13]. Peripheral and central administration of neurotensin suppress food intake in rodents [8]. Besides, endogenous opioid peptides regulate drinking and feeding in CNS [20]. Given the food and water intake effects of these peptides, peptidase inhibitors opiorphin could play important roles in regulating the reaction of food and water intake at central level, which are not yet to be studied.

Opiorphin, acting as an inhibitor of both NEP and APN, has been implicated in important biological functions including nociception, colonic contraction, modulating penile erection and cardiovascular system [24,25,27,29]. Rougeot et al. also characterized sialorphin, the rat functional homolog of human opiorphin, and suggested that rat sialorphin is an endocrine peptide signal whose secretion is stimulated under adrenergic-mediated response to environmental stress in male rat [21]. In addition, opiorphin and sialorphin are released into blood stream in the regulation of epinephrine [21,26], which causes anorexic response in rats [4]. It is well known that epinephrine is related to the renin–angiotensin system (RAS). There are tissue-specific RAS, including adipose RAS and brain RAS. In the adipose RAS, circulating angiotensin II produced by adipocytes increases leptin release from adipocytes [3]. To our knowledge, leptin decreases in food intake and body weight in CNS in the region of the hypothalamus [10]. Moreover, all the components of RAS, including angiotensinogen, enzymes responsible for releasing angiotensins and angiotensin receptors, are present in CNS, which is known to play important roles in regulating food intake and water intake [18,30]. Therefore, to further evaluate the pharmacological characterization of opiorphin, we evaluated the effects and underlying mechanisms of i.c.v. opiorphin on food and water intake in mice.

2. Materials and methods

All experiments were carried out according to a protocol approved by the guidelines of the Ethics Committee of Animal Experiments at Lanzhou University and in accordance with guidelines from the China Council on Animal Care and International

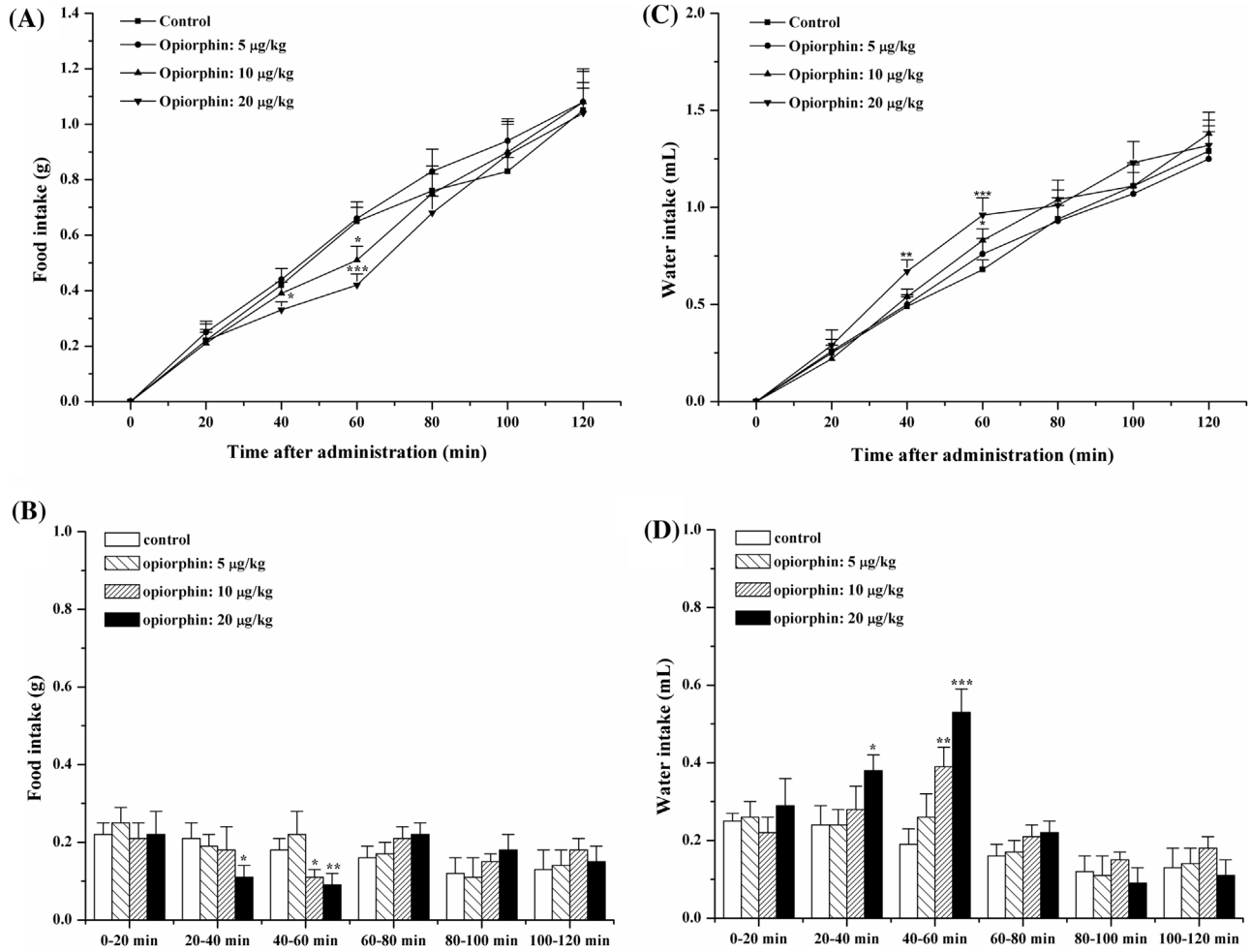

Fig. 1. The effect of opiorphin on cumulative food intake (A), food intake by period of time (B),cumulative water intake (C) and water intake by period of time (D) in fasted mice during the dark period. Opiorphin (5, 10 and 20 μg/kg, i.c.v.) or normal saline (control) was administrated at the onset of the dark cycle. All data are presented as mean ± S.E.M. from experiments conducted on n = 10 mice/group. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with control group according to ANOVA followed by Dunnett's post-hoc test.