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The interaction between the oxytocin and pain modulation in headache patients

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ABSTRACT

Oxytocin (OXT), a nonapeptide hormone of posterior pituitary, reaches the central nervous system from systemic blood circulation with a difficulty because of the blood–brain barrier (BBB). The interest has been expressed in the use of the nasal route for delivery of OXT to the brain directly, exploiting the olfactory pathway. Our previous study has demonstrated that OXT in the central nervous system rather than the blood circulation plays an important role in rat pain modulation. The communication tried to investigate the interaction between the OXT and pain modulation in Chinese patients with headache to understand the OXT effect on human pain modulation. The results showed that (1) intranasal OXT could relieve the human headache in a dose-dependent manner; (2) OXT concentration in both plasma and cerebrospinal fluid (CSF) increased significantly in headache patients in relation with the pain level; and (3) there was a positive relationship between plasma and CSF OXT concentration in headache patients. The data suggested that intranasal OXT, which was delivered to the central nervous system through olfactory region, could treat human headache and OXT might be a potential drug of headache relief by intranasal administration.

1. Introduction

Oxytocin (OXT), a nonapeptide hormone of posterior pituitary, is mainly synthesized and secreted in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON). This hormone, combined with an apparent carrier protein (neurophysin), is transported along the hypothalamo-hypophyseal pathway to the neurohypophysis, where it is stored for subsequent release (Antunes and Zimmerman, 1978). The remarkable functions of OXT include uterine contraction during parturition, milk-ejection reflex during lactation, cardiovascular regulation, sex activity, learning and memory (McEwen, 2004).

Many studies demonstrated that OXT in central nervous system was related with the pain modulation (Yang et al., 2007a,b). Intraventricular injection (*icv*) of OXT has an analgesic effect in a patient

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with intractable cancer pain (Brown and Perkowski, 1998). OXT in the spinal cord relates to antinociception in the dog (Madrazo et al., 1987) and OXT takes part in the chronic and acute low back pain in human (Yang, 1994). Our previous study has discovered that the pain threshold is elevated by OXT following *icv* or intrathecal injection (*ith*), and reduced by anti-OXT serum (*icv* or *ith*), but the pain threshold is not altered by intravenous injection (*iv*) of OXT or anti-OXT serum (Yang et al., 2007b). Pain stimulation induces the SON release of OXT, which can be transferred to the locus coeruleus (LC), nucleus raphe magnus (NRM), caudate nucleus (CdN) and spinal cord (Yang et al., 2007a). Although some reports showed that OXT (intraperitoneal injection, *ip*) increased the pain threshold, which was prevented by OXT antagonist (icv) (Uvnas-Moberg et al., 1998), this OXT pharmacological analgesic effect in the peripheral system needed a very high dose OXT (10–200 mg OXT/rat) and a very long period (60 days) to treat the animal.

OXT reaches the central nervous system from systemic blood circulation with a difficulty because of the blood–brain barrier (BBB) (Antunes and Zimmerman, 1978). For developing OXT-related drugs in the field of pain relief, it is very important to find one way that rapidly delivers OXT from systemically administration to central nervous system. The interest has been expressed in the use of the nasal route for delivery of peptides to the brain directly, exploiting the olfactory pathway (Dhuria et al., 2010; Illum, 2004; Pietrowsky et al., 1996; Veronesi et al., 2011). However, few studies reported that intranasal OXT influenced on headache in Chinese patients. The communication tried to investigate the effect of intranasal OXT on the human headache, so as to understand the interaction between the OXT and pain modulation in Chinese patients with headache.

2. Materials and methods

2.1. Materials

OXT was obtained from Peninsula Laboratories, San Carlos, CA, USA. ^{125}Iodine was from Amersham Pharmacia, Buckinghamshire, UK. The other chemicals were from Sigma Co., St. Louis, MO, USA.

Rabbit anti-human OXT serum was made by Department of Neurobiology, Second Military Medical University, Shanghai, China (Song et al., 1987). The specificity of the antiserum was 99.99% cross-reactivity with OXT and less than 0.01% cross-reactivity with arginine vasopressin, lysine-vasopressin, vasotocin, vasoactive intestinal peptide, neurotensin, leucine-enkephalin, methionine-enkephalin, β-endorphin and dynorphin A_{1-13}. The dilution of the antiserum was more than 1:40,000 for radioimmunoassay.

2.2. Participants

2.2.1. Headache patients

One hundred and twelve outpatients including 49 male and 63 female, 20–62 years old, average 44.5 ± 8.2 years old, whose suffered with headaches, were asked to participate in the study between May 2010 and November 2011. The patients were only diagnosed as tension-type headache and migraine. The patients were classified as 1–4 pain level depending on the International Headache Society's International Classification of Headache Disorders (ICHD). The patients, which headache history was 4–12 months (average 5.4 ± 2.1 months), did not receive any treatments before the experiment.

2.2.2. Health volunteers

One hundred and three health volunteers including 42 male and 61 female, 19–64 years old, average 45.6 ± 8.1 years old were asked to participate in the study between May 2010 and November 2011. They have not been suffering from any headaches.

2.2.3. Inclusion criteria

Inclusion criteria in those were as follows: (a) agreement to sign the informed consent form; (b) eligibility was checked before the experiments (exclusion criteria: pregnancy, menstrual period, tumor, cardiovascular, gastrointestinal, respiratory, brain, endocrine, psychiatric or other diseases, smoking, intake of drugs); (c) participants were asked not to drink any alcohol, caffeine containing beverages and analgesic medication during the experiment; (d) participants were asked not to eat anything before collecting the blood and cerebrospinal fluid during the day of sample collection; (e) all experimental sessions were carried out between 08:00 am and 09:00 am; and (f) over 18 years old.

All experiments were approved by the relative hospital Ethics Committees and carried out according to the Declaration of Helsinki.

2.3. Procedure

The experiments were only carried out during the patients filling ill of headache. Participants were instructed to abstain from smoking, caffeine and analgesic medication. Subsequently, participants completed a set of questionnaires and were checked with the physical examination. The experimental sessions were conducted in a double-blind and placebo controlled within-subject cross-over design. OXT or the placebo was administered intranasal. Following a standardized protocol, the participants self-administered three puffs of OXT per nostril, which were controlled in the volume with a different OXT concentration (100 ng, 200 ng or 400 ng OXT) or placebo (containing all ingredients except for the peptide) under the supervision of the study coordinator. The total time of an experimental session was 3 h. The health volunteers were done as the patients except the headache. All participants received monetary compensation after completion of the study.

2.4. Sample collection

2.4.1. Blood sample

Blood was taken by vein-puncture between 08:00 am and 09:00 am. The blood was collected using the EDTA·Na_2-treated vacutainer and immediately placed on ice.

2.4.2. Cerebrospinal fluid (CSF) sample

CSF was taken by lumbar puncture between 08:00 am and 09:00 am. The CSF was collected using the silicone oil-treated tube and immediately placed on ice.

2.4.3. Sample treatment

After the centrifugation at 10,000*g* for 20 min at 4 °C, the supernatants were withdrawn and stored at −80 °C until OXT determination.

2.5. OXT assay

OXT concentration was measured by radioimmunoassay with specific rabbit antiserum against human OXT. OXT was labeled ^{125}Iodine using the chloramines-T method and iodinated peptide was purified by Sephadex G-50. The assay sensitivity of OXT was 0.8 pg/tube and the normal range for plasma OXT was 1–64 pg/ml. The intra- and inter-assay coefficients of variation were less than 3.8% and 6.5%, respectively.