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Oral Sensory Alteration Affects Psycho-emotional Behaviors in Rats

: The effects of oral capsaicin or lingual nerve transection

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ABSTRACT

Oral sensory alteration affects psycho-emotional behaviors in rats

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PURPOSE

Sensory information plays an important role in determining psycho-emotional behaviors of individuals. This study was conducted to examine the psycho-emotional effects of oral sensory alteration by repeated oral exposure to capsaicin or bilateral transection of the lingual and chorda tympani nerves.

MATERIALS AND METHODS

In order to examine the effects of repeated oral capsaicin rats received 1

ml of 0.02% capsaicin into the oral cavity daily, and were subjected to behavioral tests and plasma corticosterone assay following 10 daily administration of capsaicin. And c-Fos immunohistochemistry in the hypothalamic paraventricular nucleus and the brainstem nucleus tractus solitarius was performed one hour after a single exposure to either capsaicin or water.

In order to examine the effects of lingual nerve transection, rats were tested for anxiety and depression-related behaviors after either bilateral transection of the lingual and chorda tympani nerves or sham operation. Tissue contents of serotonin and its metabolite in the hippocampus, hypothalamus, and nucleus accumbens were analyzed by high-performance liquid chromatography.

RESULTS

The result from the capsaicin-treated rats is as follows. In ambulatory activity test, stereotypy counts and rostral grooming significantly increased, whereas caudal grooming decreased. In elevated plus maze test, not only time spent in open arms but also the rate of entry into open arms were reduced in capsaicin-treated rats. In forced swim test, struggling increased in the experimental group, with the swimming duration decreased. But immobility duration did not differ from the control group. Repeated oral capsaicin did not affect the basal level of plasma corticosterone. However, the stress-induced elevation of plasma corticosterone was prolonged in capsaicin-treated rats. Oral capsaicin exposure significantly increased c-Fos expression not only in the nucleus tractus solitarius but also in the paraventricular nucleus.

After bilateral transection of the lingual and chorda tympani nerves, the rats showed the result as follows. Sucrose preference was reduced in

comparison with sham rats, suggesting the development of anhedonia, which means decreased pleasure-seeking behavior. Ambulatory activity decreased and anxiety-related behaviors during the activity test increased. Time spent in the open arms during elevated plus maze test decreased, and immobility duration during forced swim test increased. Serotonin level in the hippocampus decreased significantly compared with sham rats.

CONCLUSION

Repeated oral exposure to capsaicin increased anxiety-like behaviors in rats, and dysfunction of the hypothalamic-pituitary-adrenal axis may play a role in its pathophysiology. And aberration of oral sensory relay to brain, by bilateral transection of the lingual and chorda tympani nerves, may lead to the development of depression- and anxiety-related disorders, and decreased serotonergic neurotransmission in the hippocampus may play a role in its underlying mechanism.

Collectively this study suggests that oral sensory alteration could result in psycho-emotional changes through neural mechanism.

Keywords : oral capsaicin, lingual nerve, anxiety, depression, anhedonia, behavior

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CONTENTS

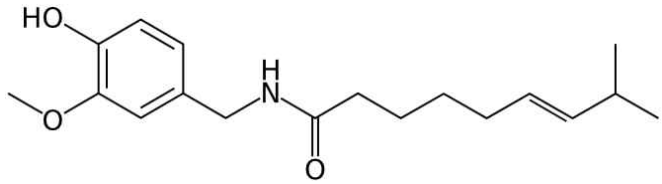
Ⅰ. INTRODUCTION

1.1 Capsaicin

Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) is the pungent ingredient in hot chili peppers of the *Capsium* family, and pharmacologic dose of capsaicin evoke burning and painful sensation when capsaicin interacts with its receptors located at sensory nerve endings.[1] Pure capsaicin is a volatile, lipophilic, colorless, odorless and crystalline to waxy compound.

The compound was first extracted in 1816 by Christian Friedrich Bucholz(1770–1818).[2] He called it "capsicin", after the genus *Capsicum* from which it was extracted. John Clough Thresh, who had isolated capsaicin in almost pure form,[3] gave it the name "capsaicin" in 1876. But it was Karl Micko who first isolated capsaicin in pure form in 1898.[4] Capsaicin's empirical formula (chemical composition) was first determined by E. K. Nelson in 1919; he also partially elucidated capsaicin's chemical structure.[5] Capsaicin was first synthesized in 1930 by E. Spath and S. F. Darling.[6]

The application of capsaicin has two contradictory effects: 1) it can excite subsets of sensory neurons associated with pain and thermo-reception, and cause release of neuropeptides, e.g. substance P and calcium gene-related peptide, thus inducing hyperalgesia and inflammation[7-9]; 2) it can also act as an anti-inflammatory and antinociceptive agent, depending on the duration and amount of application. The effect of nociceptor desensitization is the reason for using capsaicin as an analgesic agent in the treatment of painful disorders, e.g. bladder hyperreflexia, rheumatoid arthritis and postherpetic neuralgia.[10-11]



Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide)

1.2 TRPV1 at peripheral nervous system

The capsaicin receptor TRPV1 (transient receptor potential, vanilloid subfamily, member 1), a nonselective cation channel, predominantly expressed in a subset of primary sensory neurons with A-δ and C fibers,[12] which plays a key role in the detection of noxious heat (> 43℃) and acid (pH < 6).[13-15] And TRPV1, formerly called as VR1(vanillod receptor 1), belongs to a large family of calcium-permeable cation channel. The cloned TRPV1 encodes a protein of 838 amino acids with a predicted molecular weight of 92,000.

Although the effects of capsaicin on sensory nerve endings are well known, direct effects of capsaicin on taste receptor cells have been poorly understood. Intensely labeled VR1-immunoreactive (VR1-IR) fibers were concentrated in the circumvallate, foliate, and fungiform papillae, while sparse VR1-IR fibers were scattered throughout the tongue. VR1-positive taste-bud cells were not observed. Although VR1-immunoreactivity was not observed in taste-bud cells, evidence of a large number of VR1-IR fibers concentrated in the taste papillae suggests that capsaicin easily reaches the VR1 nerve terminals because of its lipophilic nature.[16] TRPV1 mRNA expression and its immuno-positive nerve fibers have been demonstrated in the taste buds.[17-18] *In vitro* study has suggested that capsaicin may enhance or modify taste perception directly in taste receptor cells, possibly, in

mediation of its receptor TRPV1.[19]

In human studies, capsaicin suppressed responses to sweet, bitter and umami, but not sour and salty stimuli.[20-23] Recently, TRPV1 receptors are co-localized with sweet or bitter receptors in taste sensing cells of the circumvallate papillae of rats[24] and human.[25] Oral exposure to capsaicin in rats results in increased consumption of sweet solutions with decreased expression of sweet receptors in the circumvallate papillae.[26]

1.3 TRPV1 at central nervous system

The role of TRPV1 in brain, previously thought to only function in sensory neurons, is also emerging.[27-29] TRPV1 mRNA and immunoreactivity were found throughout the whole neuroaxis, including the cortex, hypothalamus, cerebellum and basal ganglia.[30-31] Mezey et al. used an antibody and a complimentary RNA probe to explore the distribution of neurons that express VR1 in rat and in certain areas of human brain. In the rat, they observed VR1-expressing neurons throughout the whole neuroaxis, including all cortical areas (in layers 3 and 5), several members of the limbic system (e.g., hippocampus, central amygdala, and both medial and lateral habenula), striatum, hypothalamus, centromedian and paraventricular thalamic nuclei, substantia nigra, reticular formation, locus coeruleus, cerebellum, and inferior olive. VR1-immunopositive cells also were found in the third and fifth layers of human parietal cortex. Reverse transcription–PCR performed with rat VR1-specific primers verified the expression of VR1 mRNA in cortex, hippocampus, and hypothalamus. In the central nervous system, neonatal capsaicin treatment depleted VR1 mRNA from the spinal nucleus of the trigeminal nerve, but not from other areas such as the inferior olive. The finding that VR1 is expressed not only in primary sensory neurons but also in several brain nuclei is of great

importance in that it places VRs in a much broader perspective than pain perception. VRs in the brain (and putative endogenous vanilloids) may be involved in the control of emotions, learning, and satiety, just to name a few exciting possibilities. Immunohistochemical localization of TRPV1 receptors was also observed in the prefrontal cortex, nucleus accumbens, amygdala and hippocampus.[32]

Localization of TRPV1 in those brain regions suggests its implication in the control of psycho-motor activities. Indeed, systemic injections of the prototypical TRPV1 agonists and various analogs inhibited ambulation, stereotypic behavior and activity in the open field test in rats.[33] Also, it has been suggested that the brain TRPV1 participates in anxiety- and depression-like behaviors.[32-35] Anxiety-like behaviors decreased in TRPV1 receptor-deficient mice with reduced long-term potentiation in the hippocampus,[35] and systemic capsaicin caused anxiogenic effects in rats.[36] Intraperitoneal injection of TRPV1 agonists including capsaicin increased depression-like behaviors in rats.[33-34]

TRPV1 represents a novel target for analgesic drugs. With potent small-molecule TRPV1 antagonists undergoing clinical trials, the effect of brain TRPV1 blockade might determine the future of analgesics. TRPV1 inhibitors aim to prevent pain by blocking a receptor where the pain is generated.[27]

1.4 Sensory system

Sensory systems are responsible for generating an internal representation of the outside world, including its chemical (taste and olfaction) and physical (mechanical, sound, vision and temperature) features. Neuronal circuits in sensory system are closely connected with other nerve systems for efficient handling of sensory information.[37] For example, taste sensory

information that reached the nucleus tractus solitarius is principally relayed to the gustatory cortex via the parabrachial nucleus, but also targets to the other brain area such as the cerebral cortex, hippocampus, amygdala, hypothalamus and nucleus accumbens for the better storage or recall of taste memory or the innate and instinctive response such as preference and aversion.[38-40] Thus, it is suggested that the deprivation or disruption of taste sensory relay may affect the function of those brain regions.

1.5 Taste sensory system and anhedonia

Taste sensory system is in charge of evaluating the nutritious content of food and preventing the ingestion of toxic substances, and importantly has the additional value of contributing to the overall pleasure and enjoyment of a meal. Eating has been viewed as a strategy to improve negative mood[41] and to mask stress,[42] and studies indicate that healthy, normal-weight persons regulate negative emotion by eating.[43,44] It has been reported that decreased responses in the reward network including the nucleus accumbens to palatable food may be a trait marker of vulnerability to depression.[45,46] In rodents, anhedonia, a reduced sensitivity to reward, which is a core symptom of major depression, can be measured by decreased intake of and preference for sweet solutions. Indeed, sweet solutions have been shown to rapidly calm stress responses in human newborns,[47] and in adults, experimentally induced negative mood is improved immediately and selectively after eating palatable food,[48] suggesting that immediate positive affective reactions elicited by palatable food diminish the impact of stress. Collectively, it is hypothesized that alteration in oral sensory information can modulate the psycho-emotional status of individuals.

1.6 Innervation of the tongue

The chorda tympani nerve joins the lingual nerve of trigeminal nerve, and distributes to the fungiform papillae on the anterior two thirds of the tongue and may reach the anterior portion of the foliate papillae. Axons of glossopharyngeal nerve supply both tastes buds and general sensory innervation to the vallate and foliate papillae, and also tastes buds in the pharynx.[49] Thus, it is expected that with bilateral transection of the lingual and chorda tympani nerves, rats may lose the sensory information from the anterior two thirds of the tongue.

1.7 Purpose of the present study

This study was conducted to examine the psycho-emotional effects of oral sensory alteration by repeated oral exposure to capsaicin, or by bilateral transection of the lingual and chorda tympani nerves.

Many Koreans generally believe that hot spicy food improves negative mood. In this study, we have examined how oral administration of capsaicin, the principal active component of chili pepper, influences the psycho-emotional behaviors of rats, compared to capsaicin injection which is more invasive and stressful. Rats received oral capsaicin daily at an edible dose, and then were subjected to the ambulatory activity test and the elevated plus maze test to assess anxiety-like behaviors, and also the forced swim test to assess depression-like behaviors. The dose of capsaicin used in this study was determined by other studies.[50-52]

Lingual nerve can be damaged by oral & maxillofacial surgery or trauma. This study was conducted to define the psycho-emotional effects of the lingual nerve damage in which oral sensory relay to the brain is disrupted, and the rats were tested for anxiety- and depression-like behaviors

after bilateral transection of the lingual and chorda tympani nerves.

Ⅱ. MATERIALS AND METHODS

2.1 Animals

Male Sprague–Dawley rats (200–250 g, Samtako Bio, Osan, Korea) were individually housed and maintained in a specific pathogen-free (SPF) barrier zone with the constantly controlled temperature (22 ± 1°C) and humidity (55%) on a 12 hour light–dark cycle (lights on at 07:00 a.m.) in the Seoul National University Animal Facility Breeding Colony. Rats had *ad libitum* access to standard rodent chow (Purina Rodent Chow, Purina Co., Seoul, South Korea) and tap water, and were habituated in the animal colony at least for a week before experiments began. Animals were cared for according to 'The Guide for Animal Experiments 2000', edited by the Korean Academy of Medical Sciences, which is consistent with the NIH Guideline Guide for the Care and Use of Laboratory Animals 1996 revised. All animal protocols were approved by the Committee for the Care and Use of Laboratory Animals at Seoul National University.

CAP rats indicate the rats treated with capsaicin, and **NTx rats** mean the rats with bilateral transection of the lingual and chorda tympani nerves.

Rats were placed in the test room at least 2 hour prior to each test to minimize unwanted stress effects, and all behavioral assessments were performed between 09:00 AM and 12:00 PM of the day to avoid the influences of circadian variances.

2.2 Capsaicin treatment

Rats (n = 8 in each group, total 16 rats) were gently handled by the experimenter daily for several days prior to the experiment to minimize undesirable effects. Each rat received 1 ml of capsaicin (0.02% suspension

in water, Sigma Co., St Louis, MO, USA) or water drop by drop into its oral cavity daily by the same experimenter. Capsaicin dose, 0.02% (approximately 655 μM), used in this study was decided according to previous report.[39] It has been reported that oral capsaicin at 320 μM concentration effectively interacts with other taste stimuli[23] and 1% of capsaicin application to skin induces a burning pain in human.[53] Rats showed aversive responses, such as chin rubs, paw wipes and head shakes after each capsaicin treatment, which disappeared within 5 min. Oral administration of capsaicin or water continued until the end of the whole experiment. The behavioral sessions were followed after the 10th daily administration of capsaicin, and each behavioral session was performed 30 min after the oral exposure to capsaicin (n = 8 in each group).

2.3 Bilateral transection of the lingual and chorda tympani nerves

Rats were anesthetized with an intraperitoneal injection of a 4:1 mixture of ketamine hydrochloride (100 mg/kg, Ketara®, Yuhan, Korea) and xylazine hydrochloride (25 mg/kg, Rumpun®, Bayer, Korea), and placed on the surgical plate equipped with a non-traumatic head holder. The surgical field was prepared by hair trimming and applying 10% povidone iodine, and then, a ventral–medial incision was made in the neck. Digastric and masseter muscles were bluntly dissected to allow the visualization of the chorda tympani nerve and lingual nerve as it bifurcated from the lingual branch of the trigeminal nerve (**Figure 1**). Transection of the lingual and chorda tympani nerve was made using sharp microfine forceps; the proximal and distal stumps of the nerve cuts were visualized to verify complete transection. The wound was closed in a single layer by the use of 4-0

Nylon sutures (Ethicon®, UK). Sham surgeries were processed in same manner, but the nerves were not touched. Body weight gain and food intake were monitored during the post-operational recovery period.

2.4 Sucrose drinking test

Sucrose drinking test was performed only for NTx rats after 10 days of post-operational recovery. Rats were divided into 4 groups (n = 6 - 8 in each group, total 28 rats); i.e., NTx rats that received either 1% or 5% sucrose and sham operated groups that received either 1% or 5% sucrose. Rats in each group were deprived from water, but not chow, for 20 hour prior to the drinking test, and received free choices of sucrose solution and water for 30 min. The test sessions were repeated for 3 consecutive days, and the positions of sucrose and water bottles were exchanged daily.

2.5 Ambulatory activity test

CAP rats (n = 8 in each group, total 16 rats) were subjected to the ambulatory test on day 11. On each trial, the rat was placed in the center of the activity chamber (43.2 cm in length, 42.2 cm in width, and 30.5 cm in height, MED Associates, VT, USA), a transparent acryl chamber equipped with two horizontal planes of 16 infrared photocell-detector pairs placed in x, y dimension, spaced 2.5 cm apart, and its ambulatory activity was monitored by the computerized system for 30 min. Light condition of the test room was maintained in the same intensity with animal rooms under day-light condition. Ambulatory activity was measured as the total counts of beam interruptions in the horizontal sensors during each consecutive 5 min session. Stereotypic activities, such as body sway, head weaving, grooming and rearing were measured as the total counts of beam interruptions in the

vertical sensors. Defecation activity, number of fecal boli, during the ambulation test of each rat was scored as well. Grooming activity was further analysed; i.e. forepaw and head grooming was considered as rostral grooming, and body, legs, and tail/genital grooming as caudal grooming (Kalueff et al. 2007).[54] The activity chamber was cleaned with 70% ethanol after each use to eliminate any olfactory cues of the previously tested rat.

NTx rats and sham operated rats (n = 6 in each group, total 12 rats) were subjected to the ambulatory test at 20 days after the surgery using the same manner and facility as CAP rats. Centre zone activity and rearing activity, repetitive standing with the forepaws up, during the ambulation test of each rat were scored as well.

2.6 Elevated plus maze test

Rats were subjected to the behavioral assessment in an elevated plus maze on day 14 for CAP rats and on day 23 for NTx rats, a plus shaped acryl maze with two opposite open arms (50 cm in length and 10 cm in width) and two opposite closed arms (50 cm in length, 10 cm in width, and 31 cm in height), extending out from a central platform (10 cm × 10 cm). The whole apparatus was elevated 50 cm above the floor. The test procedure was followed as previously described (Daniels et al. 2004).[55] Each rat was placed in the centre of the maze facing one of the open arms, and then allowed to explore the open or closed arms of the maze for 5 min. The time spent in the different arms was recorded, respectively. Four paws had to be inside the entrance line to each arm, which signaled the start of the time spent in the specific arm, and then the end time was recorded when all four paws were outside the line again. The maze was cleaned with 70% ethanol after each test to prevent influences of the previously tested rat.

2.7 Forced swim test

Rats were subjected to the forced swim test on day 16 for CAP rats and on day 26 for NTx rats according to the method previously described (Porsolt et al. 1977).[56] Each rat was allowed to swim in a glass cylinder (54 cm in height and 24 cm in diameter) filled with water in 40 cm of depth (23 – 25°C) for 5 min. All test sessions were recorded by a video camera from the side of the cylinder. Duration of rat's immobility in the water was scored from videotapes by a trained observer who was blinded to the experimental conditions. Immobility was defined as the state in which rats were judged to be making only the movements necessary to keep their head above the surface. Swimming was defined as the state in which rats were judged to be making active swimming motions more than necessary to merely maintain its head above water, and struggling to be climbing, usually directed against the walls.

After the end session of the swim test, rats were allowed to rest in their home cages for a week to minimize any effects of previous stress.

2.8 Plasma corticosterone assay

On day 24, CAP rats were placed in a restraint box for 2 hour, in which rats were able to move their four limbs but not to change their body orientation. Tail blood was collected at 0, 20, 60 and 120 min time points during the restraint period, and centrifuged at 2,000 rpm for 20 min. The plasma samples were frozen in liquid nitrogen, and stored at −80°C until used for the assay. Plasma levels of corticosterone were determined by radioimmunoassay using ^{125}I-labelled Coat-A-Count kit (Siemens, CA, USA). The sensitivity of the assay was 5.7 ng/ml. The intra-assay coefficient of

variation was 4 – 12.2%.

2.9 c-Fos immunohistochemistry

One hour after a single oral exposure to capsaicin or water (n = 4 in each group), only CAP rats were anesthetized with over-doses of sodium pentobarbital (Hallym Pharmaceutical Co., Seoul, Korea) and transcardially perfused first with heparinized isotonic saline and then with 4% paraformaldehyde (Merck Co., Damstadt, Germany) in 0.1M sodium phosphate buffer. Brains were rapidly dissected out, blocked, post-fixed for 2 hour, and then transferred into 30% sucrose (Sigma Co., MO, USA) overnight for cryoprotection. Forty-micron coronal sections were cut on a freezing, sliding microtome (HM440E, Microm Co., Germany). Alternate sections were collected throughout the rostro-caudal extent of the nucleus tractus solitarius (NTS; between bregma −3.2mm and −14.3mm) and the hypothalamic paraventricular nucleus (PVN; between bregma −1.3mm and −2.1mm). The coordinates were based on Paxinos and Watson (2005).[57] Immunohistochemistry was performed with standard DAB reaction using commercial ABC kit (Vectastain Elite Kit, Vector Laboratories, CA, USA) as previously described (Jahng et al. 2004). Polyclonal rabbit anti-c-Fos antibodies (1:20,000 dilution, Calbiochem, Darmstadt, Germany) were used as primary antibodies, and biotinylated anti-rabbit IgG (1:200 dilution, Vector Laboratories, CA, USA) as secondary. Immunostained sections were mounted in an anatomical order onto gelatin-coated slides from 0.05 M phosphate buffer, air-dried, dehydrated through a graded ethanol to xylene, and cover-slipped with Permount.

The number of c-Fos immune-positive nuclei in each section was blind-counted by hand after digitizing the immune-stained sections in 720 × 540 micron images using an Olympus BX-50 microscope (Olympus Co.,

Tokyo, Japan) and Leica image analysis system (Leica Microsystems, Wetzlar, Germany). Cells containing a distinct brown dot were counted as c-Fos-positive cells. The number of cells in two sections from the PVN region (closest sections to bregma－1.88 mm) from each brain was averaged. The NTS was divided into two subregions: caudal (ventral and caudal to the area postrema) and intermediate (abutting the forth ventricle). Each of these two subregions was represented by four sections of the NTS sections collected from each rat. Cell counts for all sections within each region of each rat were averaged per section, and the individual mean counts for each region averaged across rats by region within experimental groups.

2.10 High-performance liquid chromatography

On day 33, NTx rats were rapidly decapitated after brief anaesthesia in a carbon dioxide chamber. Tissue samples of the dorsal hippocampus, hypothalamus and the nucleus accumbens were rapidly dissected on ice immediately after decapitation, frozen in liquid nitrogen and stored at －80℃ until used. Tissue contents of serotonin (5-hydroxytryptamine; 5-HT) and its metabolite (5-hydroxyindoleacetic acid; 5-HIAA) were measured by high-performance liquid chromatography (Waters Instrument, Model 700, Milford, MA, USA), which is consisted of a 600E solvent delivery system equipped with a 2487 UV Detector set at 254 nm and a 717 Auto-sampler. The mobile phase, comprising of 88% distilled water, 2% acetonitrile and 10% ammonium acetate buffer (0.1M, pH 5.0) was pumped at a rate of 1 ml/min. The column used is a Atlantis dC18 (150 mm × 4.6 mm, 5 μm particle size, Waters, Milford, MA, USA).

2.11 Statistical analysis

All data was analysed by one- or two-way (corticosterone data; treatment×time) analysis of variance (ANOVA), and preplanned comparisons with the controls were performed by post hoc Fisher's PLSD(Protected Least Significant Difference) test when necessary, using StatView software (Abacus, Berkeley, CA, USA). Values are presented by mean ± S.E.. For all comparisons, the level of significance was set at $P \leq 0.05$.

Ⅲ. RESULTS

3.1 The effects of repeated oral capsaicin treatment

3.1.1 Food intake and body weight change

Repeated oral exposure to capsaicin (1 ml of 0.02% capsacin suspended in water daily) did not affect daily food or water intake (**Figure 2**). Body weight gain of capsaicin-treated rats (CAP rats) did not differ from water-treated rats (control rats).

3.1.2 Ambulatory activity

Each rat was placed in the activity chamber 30 min after toral exposure to capsaicin on day 11 (after the 11th oral capsaicin exposure) and their ambulatory activities were recorded for 30 min (**Figure 3**). Ambulatory counts, the total counts of beam interruptions in the horizontal sensors, and the travelled distance were gradually decreased during the test session both in CAP rats and control rats, with no differences between the groups (**Figure 3**). Centre zone activity, the time spent in the centre zone and defecation activity during the activity test were not significantly reduced in CAP rats, compared to control rats (**Figure 4. A and B**). However, stereotypy counts, the total counts of beam interruptions in the vertical sensors, were significantly increased in CAP rats [$F(1,14)=5.516$, $P=0.034$] compared with control rats (**Figure 4. C**). The number of rostral grooming was markedly increased [$F(1,14)=14.952$, $P=0.0017$], and caudal grooming decreased [$F(1,14)=15.250$, $P=0.0016$], in CAP rats compared with control rats (**Figure 4. D**).

3.1.3 Elevated plus maze test

In order to further assess the anxiety-like behaviors, rats were subjected to an elevated plus maze test 30 min after the oral exposure to capsaicin on day 14 (after the 14th oral capsaicin exposure). Not only the time spent in open arms [$F(1,14)=21.502$, $P=0.0004$] but also the percent arm entry into open arms [$F(1,14)=5.341$, $P=0.0366$] was reduced in CAP rats compared with control rats (**Figure 5. A and B**).

3.1.4 Forced swim test

To assess depression-like behaviors, rats were subjected to the forced swim test 30 min after the oral exposure to capsaicin on day 17 (after the 17th oral capsaicin exposure). Swimming duration during the 5 min of test session was decreased [$F(1,14)=9.837$, $P=0.0073$], and struggling increased [$F(1,14)=10.921$, $P=0.0052$], in CAP rats compared with control rats, but immobility duration did not differ between the groups (**Figure 5. C**).

3.1.5 Plasma corticosterone assay

A week after the swim test, rats received 2 hour of restraint stress, and the tail blood was collected at 0, 20, 60 and 120 min time points during the restraint session, used for plasma corticosterone assay (**Figure 6**). Analysis of the plasma corticosterone levels by two-way ANOVA showed main effect of restraint time [$F(3, 24)=12.708$, $P < 0.0001$], and significant interaction between treatment and time [$F(3,24)=3.811$, $P=0.023$]. The plasma corticosterone levels of control rats were significantly increased at 20 min after the onset of restraint stress ($P<0.05$ vs 0 time point) and restored to the basal levels at 60 min after the restraint onset. However, in CAP rats, the stress-induced corticosterone increase was persisted until 60min after the onset of restraint (**Figure 6**). Basal levels of corticosterone (0 time point)

did not differ between the groups.

3.1.6 c-Fos immunohistochemistry

Rats were sacrificed for c-Fos immunohistochemistry 1 hour after a single exposure to oral capsaicin or water. c-Fos immuno-positive nuclei was significantly increased in the PVN [F(1,6)=7.947, P=0.0304] and the intermediate NTS [F(1,6)=21.497, P=0.0435] of CAP rats compared with control rats (**Figure 7**). c-Fos immunoreactivity in the caudal NTS of CAP rats did not differ from control rats.

3.2 The effects of bilateral transection of the lingual and chorda tympani nerves

3.2.1 Food intake and body weight change

NTx rats, with bilateral transection of the lingual and chorda tympani nerves, became significantly lighter than sham rats on the post-operational day 10 ($P < 0.05$); i.e., body weights of NTx rats were 284.137 ± 8.533 g and sham rats 284.943 ± 5.132 g on the operation day, and 251.146 ± 13.548 g in NTx rats, 310.377 ± 14.609 g in sham rats on the post-operational day 10. Although the weight loss in NTx rats persisted, total weight gain during the experimental period did not differ between the groups (118.592 ± 19.351 g in NTx, 128.305 ± 14.916 g in sham). Daily food intake of NTx rats did not significantly differ from sham rats; i.e. averaged daily intake during the experimental period was 34.438 ± 3.113 g in NTx rats and 33.420 ± 1.605 in sham rats.

3.2.2 Sucrose drinking test

Sucrose drinking test was performed during 3 consecutive days starting on the post-operational day 10. During each test session, NTx and sham rats had free choices of sucrose (1% or 5%) and water for 30 min. Sham rats drank sucrose solutions (either 1% or 5%) more than water on the test days 2 and 3, whilst the amount of sucrose solutions consumed by NTx rats on those days did not differ from water consumption (**Figure 8. A and B**). Moreover, NTx rats consumed significantly reduced amount of 1% sucrose compared with water on the test day 1 (**Figure 8. A**).

3.2.3 Ambulatory activity test

Ambulatory activities of NTx and sham rats were measured in a computerized activity chamber for 30 min on the post-operational day 20. Ambulatory counts, the total counts of beam interruptions in the horizontal sensor, and the travelled distance were gradually decreased during the test session both in NTx and sham rats, with decreased scores in NTx rats at each time point (**Figure 9. A and B**). Centre zone activities, such as entry into, stay and travel in the centre zone, and rearing activity during the activity test were significantly reduced in NTx rats, compared to sham rats (**Figure 9. C – F**), and the number of rostral grooming was markedly increased in NTx rats compared with sham rats (**Figure 9. G**).

3.2.4 Elevated plus maze test

In order to further assess the anxiety-like behaviors, NTx and sham rats were subjected to an elevated plus maze test 3 days after the ambulatory activity test. NTx rats spent less time in open arms compared with sham rats ($P < 0.05$), and the time spent in closed arms tended to be increased in NTx rats without statistical significance (**Figure 10. A**).

3.2.5 Forced swim test

To assess depression-like behaviors, NTx and sham rats were subjected to forced swim test 3 days after the elevated plus maze test. Swimming duration during the 5 min of test session tended to be decreased and immobility duration was significantly increased ($P < 0.05$) in NTx rats compared with sham rats (**Figure 10. B**).

3.2.6 Serotonin level

Tissue levels of serotonin (5-HT) and its metabolite 5-HIAA were examined in each brain regions a week after the end of behavioral sessions. 5-HT levels in the hippocampus of NTx rats were decreased significantly compared with sham rats (**Figure 11. A**). The hypothalamic 5-HT and 5-HIAA levels did not appear to be affected by bilateral transection of the lingual and chorda tympani nerves (**Figure 11. B**). Tissue levels of 5- HT and 5-HIAA in the nucleus accumbens tended to be decreased in NTx rats compared to sham rats, but statistical significances were not found ($P = 0.110$ and $P = 0.184$ for 5-HT and 5-HIAA, respectively) (**Figure 11. C**).

Ⅳ. DISCUSSION

Human studies have demonstrated that consumption of red pepper decreases appetite, and increases satiety[58,59] and energy expenditure,[60,61] which is thought to be mediated by increased activity of sympathetic nervous system by capsaicin, the principal active component of red pepper.[62] In this study, oral pre-treatment with capsaicin at 0.02% concentration did not affect daily consumption of standard chow or water. Furthermore, body weight gain of capsaicin-treated rats did not differ from control rats. This result is in accordance with the previous study,[26] revealing that oral capsaicin at the dose used in this study may not affect ingestive behavior and/or energy expenditure in rats.

It has been reported that systemic capsaicin decreases dopamine release in the striatum,[63] diminishing motor activity in rodents,[64,65] possibly due to the mediation of the brain TRPV1 receptors. Intraperitoneal capsaicin at 1 mg/kg dose caused a significant reduction in locomotion,[66] and the effective systemic dose of capsaicin on locomotion was as low as 0.1 mg/kg.[33] However, in this study, repeated oral exposure to capsaicin at a daily dose of 0.2 mg/rat did not affect the locomotor activity; i.e. the ambulatory counts, the total counts of beam interruptions in the horizontal sensors, and travelled distance did not decrease in capsaicin-treated rats. This discrepancy may be due to the differences in administration route and/or treatment duration. In the previous study[33] a single intraperitoneal injection of capsaicin was employed, while repeated oral administration was used in this study.

Anxiogenic effects induced by systemic injection with TRPV1 agonists have been reported.[27-29] In this study, repeated oral administration of

capsaicin increased stereotypy counts of rats during the activity test, suggesting increased anxiety-like behaviors. Indeed, rostral grooming increased noticeably, but caudal grooming decreased in capsaicin-treated rats. Grooming is often considered in animal models to show stress and anxiety,[67,68] leading to a long-standing view of grooming as an anxiogenic response.[69,70] It has been reported that highly stressed mice spend even more time grooming rostral areas than caudal.[68,71] Thus, the current result reveals that repeated oral administration of capsaicin increases stress-induced anxiety-like behaviors in rats. Increased anxiety-like behaviors by repeated oral capsaicin were further confirmed by decreased scores in open arm stay and entry, and increased scores in closed arm stay and entry, during the elevated plus maze test.

It has been shown that alteration in the depression-like state in rodents by chronic stress affects grooming behaviors,[72-74] and that intraperitoneal injection of TRPV1 agonists including capsaicin increases depression-like behaviors in rats.[33,34] Oral capsaicin affected grooming behaviors of rats as mentioned above, and also reduced swimming duration in forced swim test in this study. It has been reported that reduced swimming and increased immobility during forced swim test represent increased depression-like behaviors in rodents.[75,76] However, immobility duration of capsaicin-treated rats during the swim test did not differ from control rats and the decreased swimming appeared to be mainly due to increased struggling in this study. Thus, it is concluded that repeated oral administration of capsaicin may increase the depression-like state in rats, as indicated by the affected grooming behaviors and reduced swimming, but its depressive effect appears to be subtle; i.e. it did not affect immobility duration in the swim test. Kasckow et al.[34] reported that systemic injections of TRPV1 agonist olvanil increased immobility of rats during forced swim test, but they did not

analyse swimming duration in their study. Recently, Hayase[77] has reported that intraperitoneal injection of TRPV1 agonists capsaicin and olvanil did not affect either immobility or swimming of naïve mice during forced swim test; however, these produced antidepressant-like effects in nicotine-treated mice, showing increased immobility. Swimming behaviors of nicotine-treated mice were not affected by intraperitoneal injection of TRPV1 agonists. Collectively, behavioral effect of capsaicin in forced swim test is controversial.

In this study, the stress-induced elevation of plasma corticosterone was prolonged in capsaicin-treated rats compared with control rats, suggesting dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis by repeated oral capsaicin. Dysfunction of the HPA axis has been implicated in anxiety[78] and depression,[79] and in animal models, stress-induced anxiety- and depression-like behaviors were associated with the HPA axis dysfunction.[80] Thus, it is likely that the HPA axis dysfunction may be implicated in the pathophysiology of anxiety-like behaviors by repeated oral administration of capsaicin. Plasma level of glucocorticoids is elevated in consequence of the HPA axis activation responding to stress, and the hypothalamic paraventricular nucleus (PVN) is located at the center of the HPA axis. Many studies have reported that meal ingestion activates neurons in the PVN and the nucleus tractus of solitarius (NTS), and oralpharyngeal-esophageal and gastric cues may contribute to meal-induced c-Fos expression, a conventional marker for neuronal activation in brain regions.[81-83] The taste information relay is delivered to the PVN neurons via the rostral and intermediate NTS,[84,85] and the visceral information via the caudal NTS.[85-87]

This study has demonstrated that oral exposure to capsaicin increases c-Fos expression in the PVN and the intermediate NTS, but not in the

caudal NTS. This suggests that the capsaicin-induced oral information relay to the PVN via the intermediate NTS may activate the HPA axis. Further studies should attempt to define the underlying mechanism by which repeated oral capsaicin affects the HPA axis function, such as c-Fos expression in the PVN and NTS following repeated capsaicin administration and the PVN expression of corticotropin-releasing hormone after a single and repeated oral capsaicin.

The capsaicin dose used in this study (0.02%) was based on the prior study, indicating that this dose, when presented in the form of capsaicin-containing food, is voluntarily ingested by rats.[39] However, the current study utilized experimenter-controlled administration of 0.02% capsaicin suspended in water, which produced acute aversive response and an anxiogenic profile following repeated administration. It is possible that a different pattern of 'psycho-emotional' effects may have been observed with voluntary ingestion of the same dose mixed with other palatable substances, which is relevant to the typical human form of capsaicin consumption, as mentioned above (it is generally believed that hot spicy food improves negative mood). Human study has reported that, in general, there were no correlations between depressive symptoms and either intensity or pleasantness of the sweet, bitter, sour and salty tastants,[88] suggesting that depressive symptoms may not influence taste reactivity. However, anxiety level was positively correlated with bitter and salty taste thresholds.[89] Thus, it is plausible that aversive property of oral capsaicin dose could have contributed to its anxiogenic potential, and this could be confirmed in future studies by the inclusion of additional aversive tastants.

Collectively, repeated oral exposure to capsaicin increased anxiety-like behaviors in rats, which was accompanied by a prolonged elevation of the plasma corticosterone responding to restraint stress. The result suggests that

the HPA axis dysfunction may be implicated in the pathophysiology of anxiety-like behaviors caused by repeated oral capsaicin.

When an animal ingests a harmless new substance or liquid, it shows neophobia, i.e., cautious intake towards the first experience of new edibles, and it increases the consumption at subsequent exposures after learning that the substance is safe to consume.[90] In this study, the amount of sucrose solution consumed by sham rats did not differ from water consumption on the first test day, but significantly increased during the following test days at both concentrations of sucrose solution. This reveals that sham rats showed first neophobia to the unfamiliar sucrose taste and then increased preferences to the sweet solution after repeated exposures. Interestingly, NTx rats, with bilateral transection of the lingual and chorda tympani nerves, showed even clearer neophobia to sucrose taste as revealed with decreased consumption of 1% sucrose solution compared to water during the first drinking test, and they did not show any preference for the sweet solution over water during the following test days. This result suggests that the development of sweet preference without recognition of new taste may be affected by bilateral transection of the lingual and chorda tympani nerves. In rodents, anhedonia a reduced sensitivity to reward, which is a core symptom of major depression, can be measured by decrease in intake of and preference for sweet solution. In comparison to sham rats, In this study, NTx rats showed decline in sweet consumption, not in water consumption which supports the development of anhedonia by the transection of the lingual and chorda tympani nerves. Sensory information from the anterior two thirds of tongue might have been disrupted by the bilateral transection of the lingual and chorda tympani nerves in NTx rats, although taste information from the vallate, foliate papillae and the pharynx may still be

relayed via intact glossopharylgeal nerves.[52] Thus, it is concluded that sensory information from the anterior two thirds of tongue may not be required for new taste recognition, but necessary for the development of sweet preference, and its disruption result in the development of anhedonia.

Development of anhedonia has been ascribed to dysfunction of the reward pathway, in which nucleus accumbens plays a pivotal role.[91,92] The nucleus accumbens core and shell receive dense serotonergic innervation from the raphe nucleus,[93] and chronically stressed rats, a model of depression, showed reduced serotonin response in the nucleus accumbens shell to cocaine.[94] Also, it was suggested that mal-regulation of dopaminergic activity in the nucleus accumbens by serotonin may be involved in depressive phenotype.[95] These reports suggest possible implication of serotonergic dysfunction in the nucleus accumbens, perhaps mal-regulating dopaminergic activity in the pathophysiology of anhedonia. However, in this study, serotonin level in the nucleus accumbens did not drop significantly even a month after the bilateral transection of the lingual and chorda tympani nerves. Thus, it is concluded that the pathophysiology of anhedonia induced by the bilateral transection of the lingual and chorda tympani nerves may not comprise a serotonergic dysfunction in the nucleus accumbens.

In this study, NTx rats showed behavioral depression with increased anxiety-like behaviors; i.e., ambulatory activities, centre zone activities and number of rearing decreased, and rostral grooming increased during the activity test; open arm stay was decreased during elevated plus maze test; immobility increased during forced swim test. Dysfunction in the brain serotonin system is implicated in a variety of psychiatric disorder, including major depression[96] and anxiety.[97] Many studies have suggested that disrupted hippocampal function is implicated in depression-[98] and anxiety-like

behaviors,[99] and that serotonin modulates the hippocampal function.[100] In this study, the hippocampal serotonin level decreased considerably in NTx rats compared to sham rats although its metabolite 5-HIAA level did not differ between NTx and sham rats, suggesting that serotonergic neurotransmission in the hippocampus decreased following the bilateral transection of the lingual and chorda tympani nerves. We have previously reported that in an animal model of early life stress experience, depression- and anxiety-like behaviors were accompanied by decreased serotonin neurotransmission in the raphe–hippocampus axis,[101] and improved depression-like behaviors were associated with increased serotonergic activity in the raphe–hippocampus axis.[102] Taken together, it is concluded that decrease in serotonin neurotransmission in the hippocampus may be implicated in the pathophysiology of depression- and/or anxiety-like behaviors induced by bilateral transection of the lingual and chorda tympani nerves.

Currently, it is not clear how the sensory loss from the anterior two third of tongue alters serotonergic neurotransmission in the hippocampus. The peripheral gustatory system consists of neural-epithelial machinery, linking the sensory epithelial cells in the oral cavity to the first gustatory relay centre in the brain. Branches of the facial and glossopharyngeal nerves, which synapse with receptor cells in the taste buds, convey taste messages to the first relay nucleus, the rostral part of the nucleus tractus solitarius in the medulla.[103] Taste information delivered to taste neurons in the nucleus tractus solitarius is relayed to other brain regions such as the hypothalamus, the ventral tegmental area and the nucleus accumbens via the parabrachial nucleus.[41,90] In humans, striatal dopamine release reflects perceived pleasantness of meal.[42] Intra-oral infusion of sweet and bitter stimuli differentially modulate dopaminergic activity in the nucleus accumbens.[104] Taste of aversive flavour increased serotonin release in the

hypothalamus.[105] These reports together suggest that long-term disruption in taste sensation may reduce dopaminergic and/or serotonergic activities in the brain regions.

Sensory deprivation with bilateral olfactory bulbectomy, a well-known animal model of depression, results in a complex constellation of behavioral, neurochemical, neuroendocrine and neuroimmune alteration.[106] Especially, serotonin neuro-transmission decreased in the hippocampus of olfactory bulbectomized rats.[107] Morales-Medina et al.[108] have suggested that the lack of input from the olfactory bulbs may result in serial neuronal rearrangement in the piriform cortex, entorhinal cortex and hippocampus leading, at least partially, to behavioral deficit in emotion process. In the same study, dendritic structures in the nucleus accumbens were not affected by olfactory bulbectomy.[108] Together with the present study, we propose that the hippocampal dysfunction such as decreased serotonin neurotransmission is a common mechanism involved in the pathophysiology of depression by sensory deprivation in taste or olfaction, and serotonergic activity or dendritic structure in the nucleus accumbens may not play a key role in it.

Ⅴ. CONCLUSION

Repeated oral administration of capsaicin increased anxiety-like behaviors in rats, which was accompanied by a prolonged elevation of the plasma corticosterone level responding to restraint stress. This result suggests that the hypothalamic-pituitary-adrenal (HPA) axis dysfunction may be implicated in the pathophysiology of anxiety-like behaviors. In addition, oral exposure to capsaicin increased c-Fos expression in the paraventricular nucleus (PVN) and the intermediate nucleus tractus solitarius (NTS). This means that the capsaicin-induced oral information relay to the PVN via the intermediate NTS may activate the HPA axis. Contrary to expectations, the depressive effect of oral capsaicin was not significant during the forced swim test.

Sweet consumption decreased in NTx rats, with bilateral transection of the lingual and chorda tympani nerves. This means the development of anhedonia, which is a core symptom of major depression. And the hippocampal serotonin level decreased considerably in NTx rats compared to sham rats. It suggests that serotonergic neurotransmission in the hippocampus decreased following bilateral transection of the lingual and chorda tympani nerves. Additionally anxiety-like behaviors increased in NTx rats during the activity test and the elevated plus maze test, and also depression-like behaviors increased during the forced swim test. It is concluded that decrease in serotonin neurotransmission in the hippocampus may be implicated in the pathophysiology of depression- and/or anxiety-like behaviors induced by bilateral transection of the lingual and chorda tympani nerves.

Collectively this study suggests that oral sensory alteration by oral

capsaicin or lingual nerve transection could result in psycho-emotional changes based on neural mechanism.

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Ⅶ. FIGURES

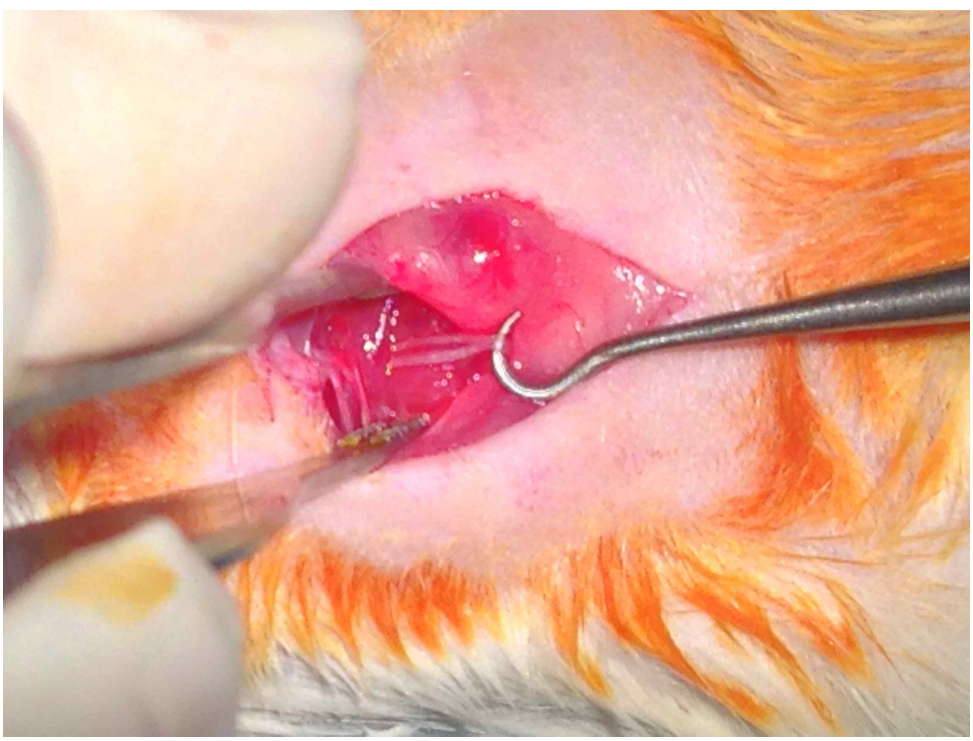

Figure 1. The chorda tympani nerve joins the lingual nerve.

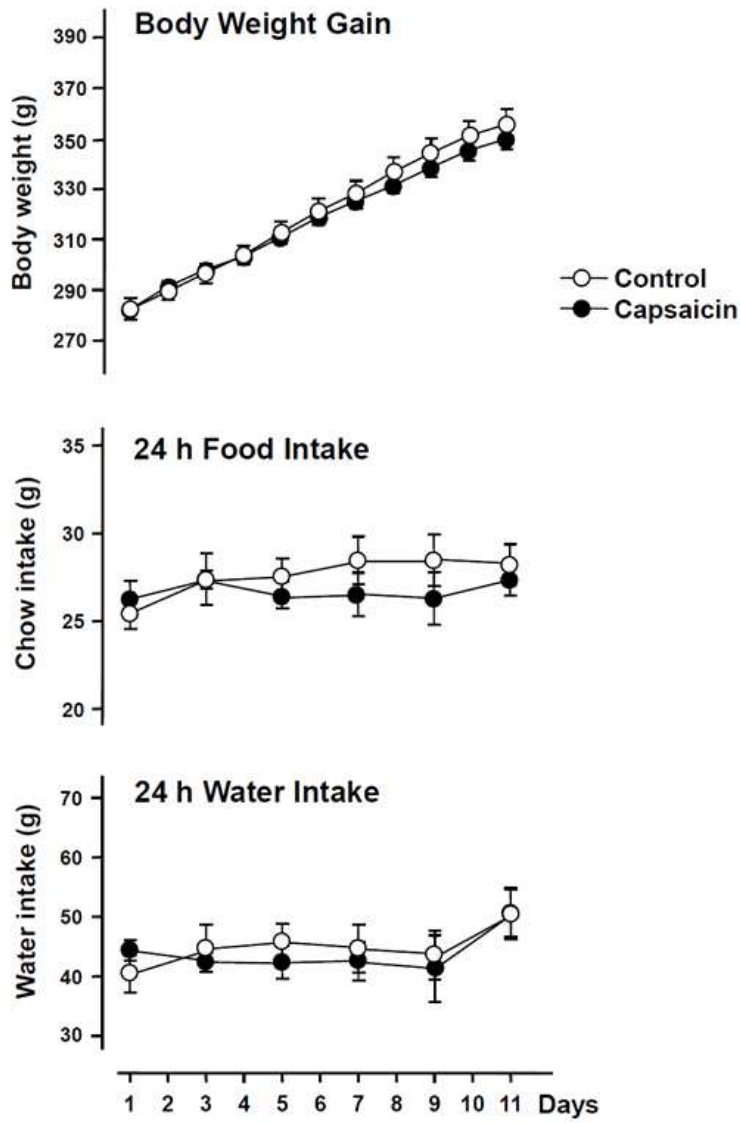

Figure 2. Body weight gain and daily consumption of chow and water. Rats received an oral administration of 1 ml of 0.02% capsaicin or water daily. Data are presented by mean ± S.E.

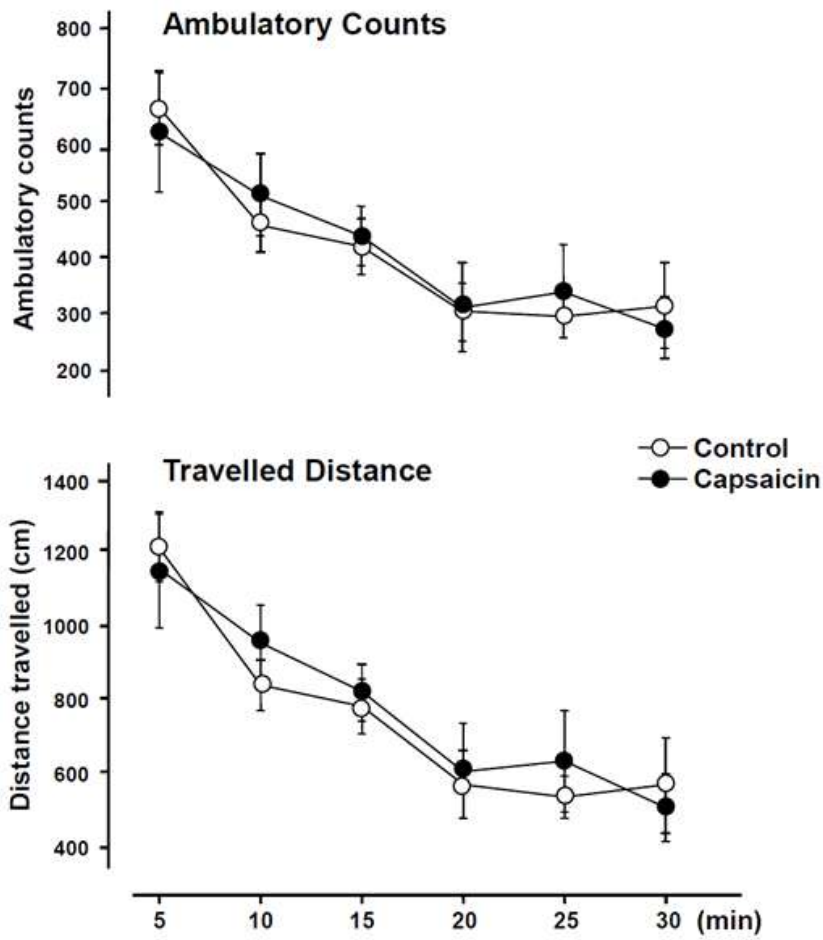

Figure 3. Ambulatory counts and the distance travelled during 30 min of ambulatory activity test, which were scored consecutively at every 5 min session. Rats were placed in the activity chamber 30 min after the 11th oral exposure to capsaicin. Data are presented by mean ± S.E.

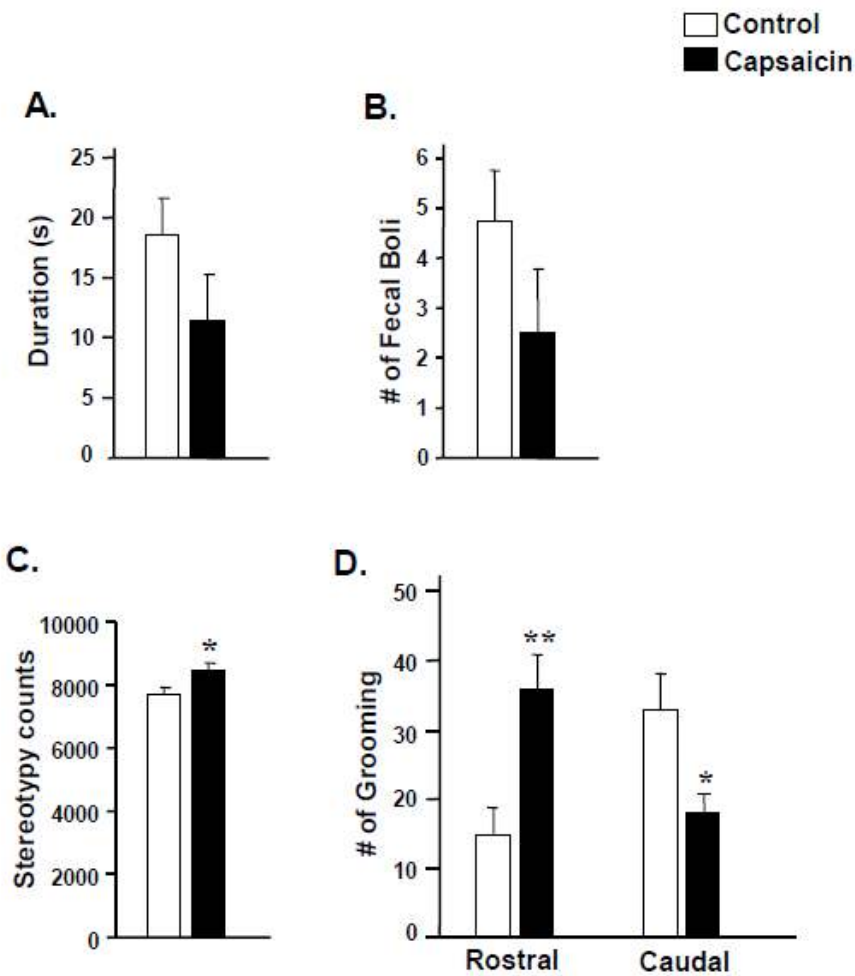

Figure 4. Time spent in the center zone (A), defecation activity (B), stereotypy counts (C) and grooming behaviors (D), which were scored during 30 min of activity test. *P<0.05, **P<0.01 vs controls. Data are presented by mean ± S.E.

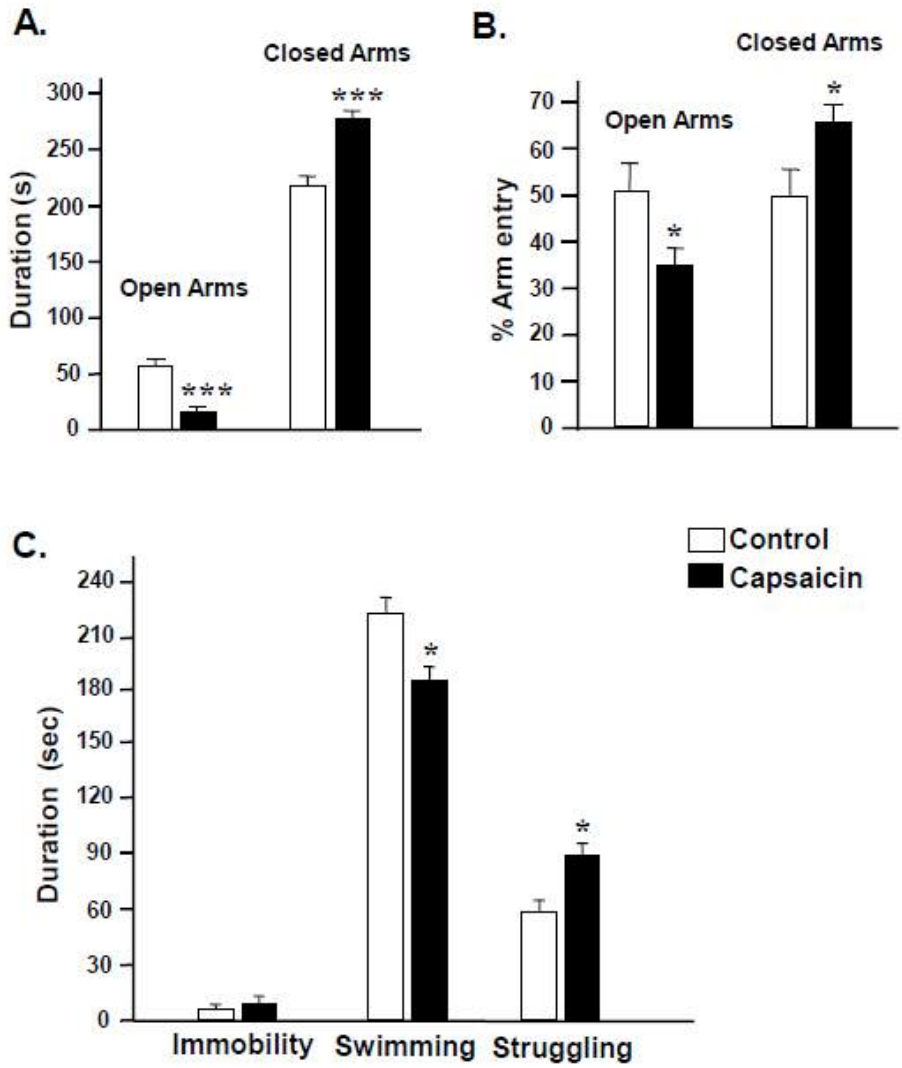

Figure 5. Time spent in each arms (A) and percent arm entry (B) during elevated plus maze test, and the scores during forced swim test (C). Rats were subjected to elevated plus maze test 30 min after the 14th oral exposure to capsaicin, and to forced swim test 30 min after the 17th oral exposure to capsaicin with a 15 min of pre-swim test on the prior day. *P<0.05, ***P<0.001 vs controls. Data are presented by mean ± S.E.

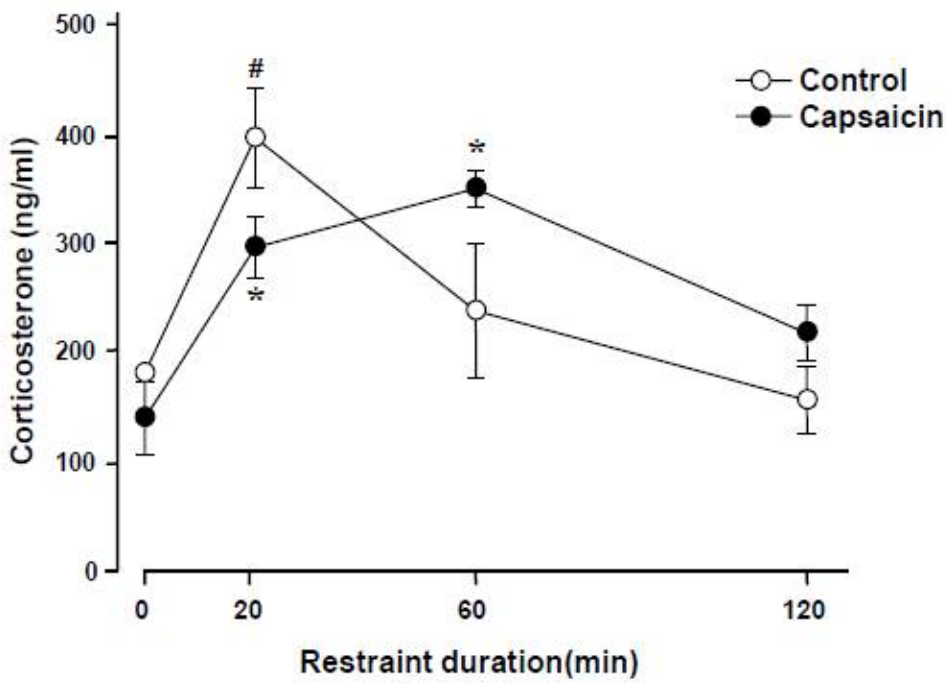

Figure 6. Plasma corticosterone levels during 2 h of restraint session. Rats were subjected to restraint stress following a week of recovery from the forced swim test. Oral treatment of capsaicin or water continued during the recovery period. Rats were placed in the restraint box 30 min after the oral exposure to capsaicin, and tail blood was collected at each time point. *P<0.05 vs 0 time point of capsaicin rats, #P<0.05 vs 0 time point of control rats. Data are presented by mean ± S.E.

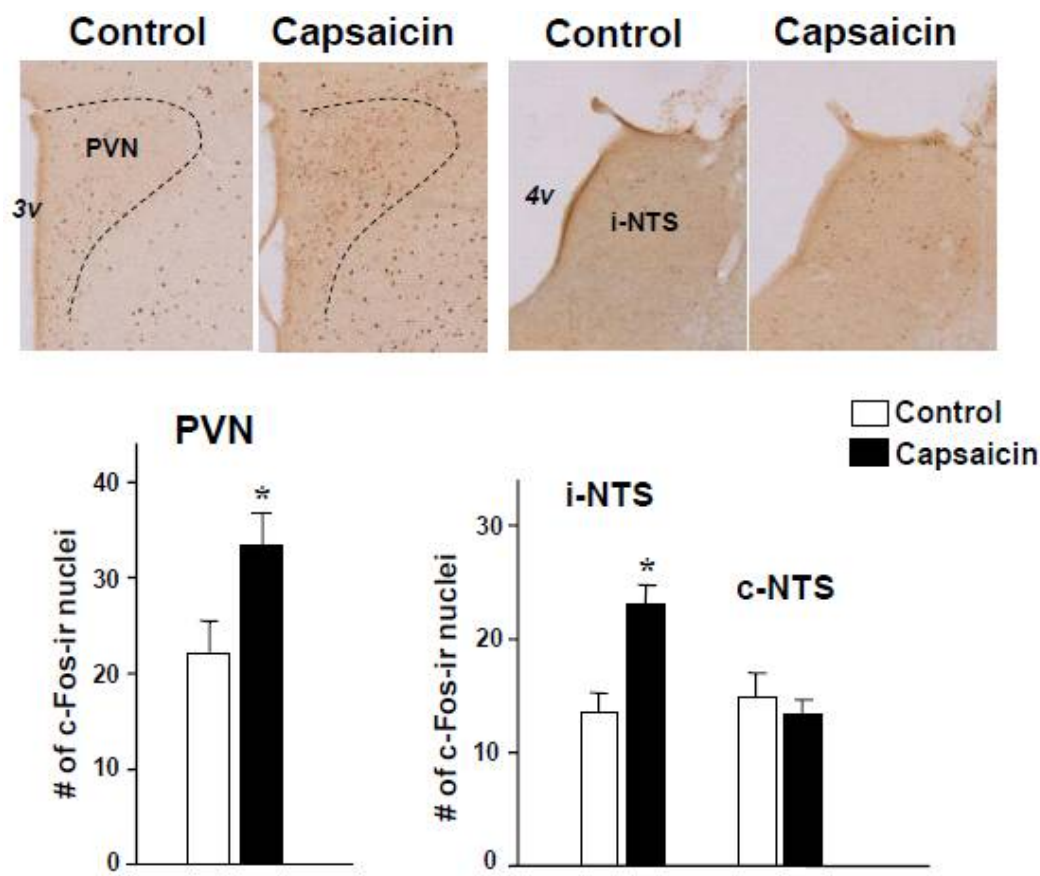

Figure 7. c-Fos immunohistochemistry in the hypothalamic paraventricular nucleus and the brainstem nucleus tractus solitarius. Rats were transcardially perfused with 4% paraformaldehyde 1 hour after a single administration of oral capsaicin. *P<0.05 vs controls, PVN; paraventricular nucleus, 3v; third ventricle, 4v; fourth ventricle, i-NTS; intermediate nucleus tractus of solitaries, c-NTS; caudal nucleus tractus of solitaries. Data are presented by mean ± S.E.

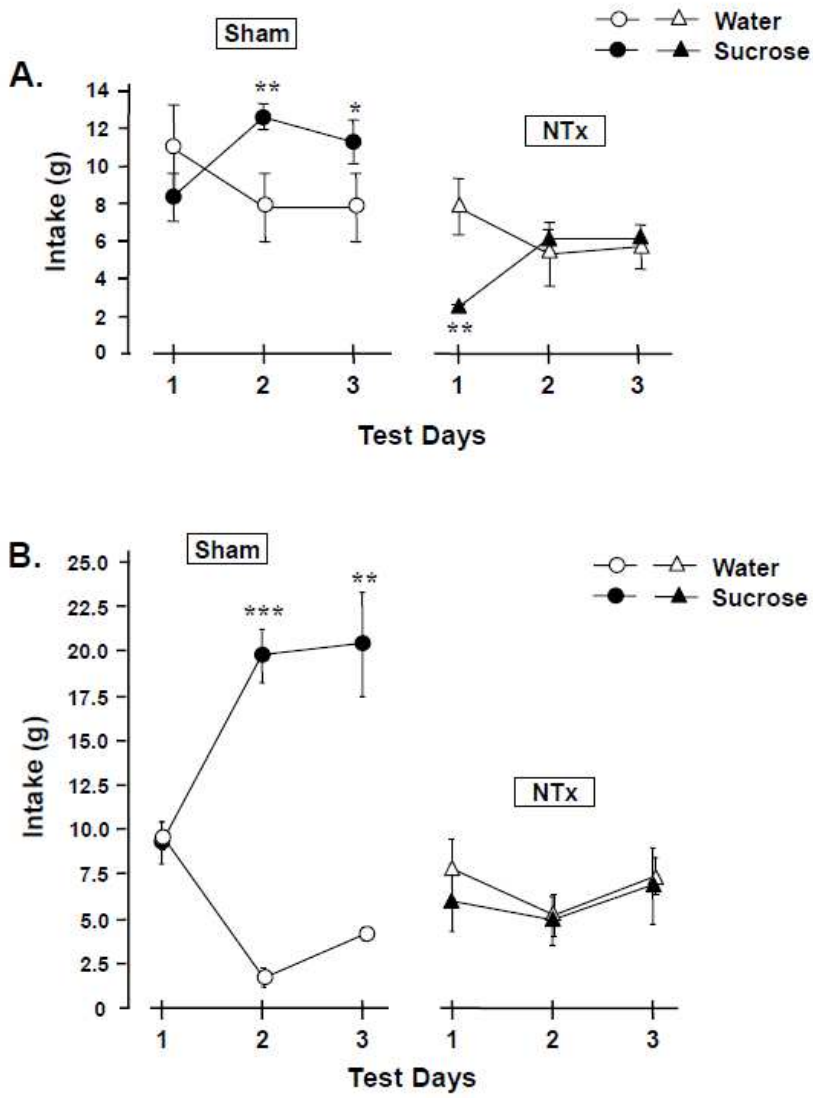

Figure 8. Sucrose preference test. Nx and sham rats had free choices of 1% sucrose and water (A), or 5% sucrose and water (B) for 30 min following 20 h of water deprivation. NTx; rats with bilateral transection of the lingual and chorda tympani nerves, sham; rats with sham operation, *P < 0.05, **P < 0.01, ***P < 0.001 vs. water on each day, data are presented by mean ± S.E.

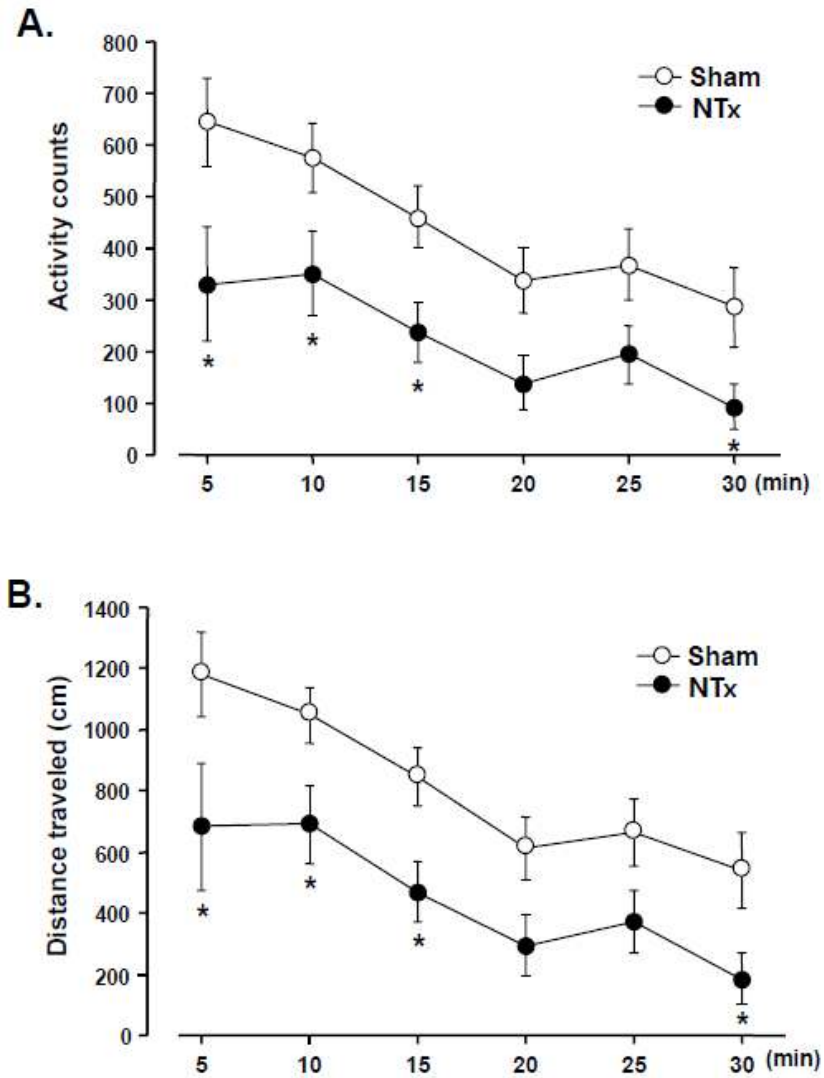

Figure 9. Ambulatory activity test. Ambulatory counts (A) and the travelled distance (B) during 30 min of ambulatory activity test, which were scored consecutively at every 5 min session. (continued to next page)

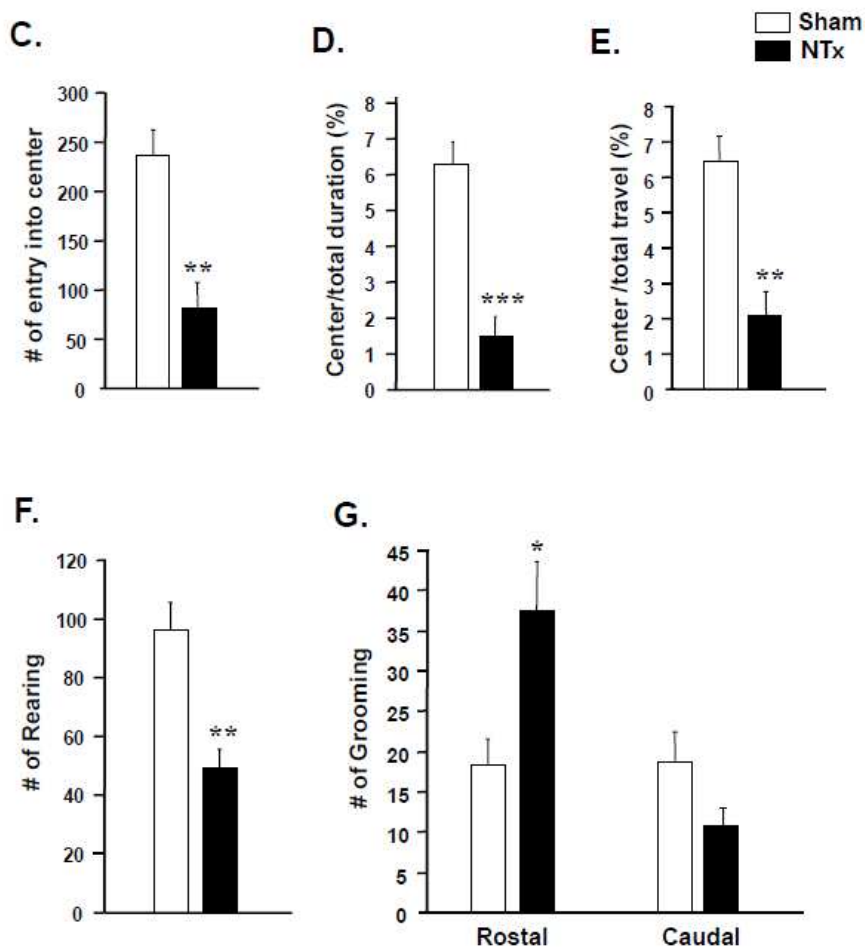

Figure 9.(continued) Ambulatory activity test. Centre zone activities; i.e., number of entry into the centre (C), percent stay in the centre (D) and percent travel in the centre (E), and stereotyped behaviors; i.e., number of rearing (F) and number of grooming (G) were scored during 30 min of the activity test. NTx; rats with bilateral transection of the lingual and chorda tympani nerves, sham; rats with sham operation, *P < 0.05 vs. sham at each time point scored (A and B), *P < 0.05, **P < 0.01, ***P < 0.001 vs. sham (C – G), data are presented by mean ± S.E.

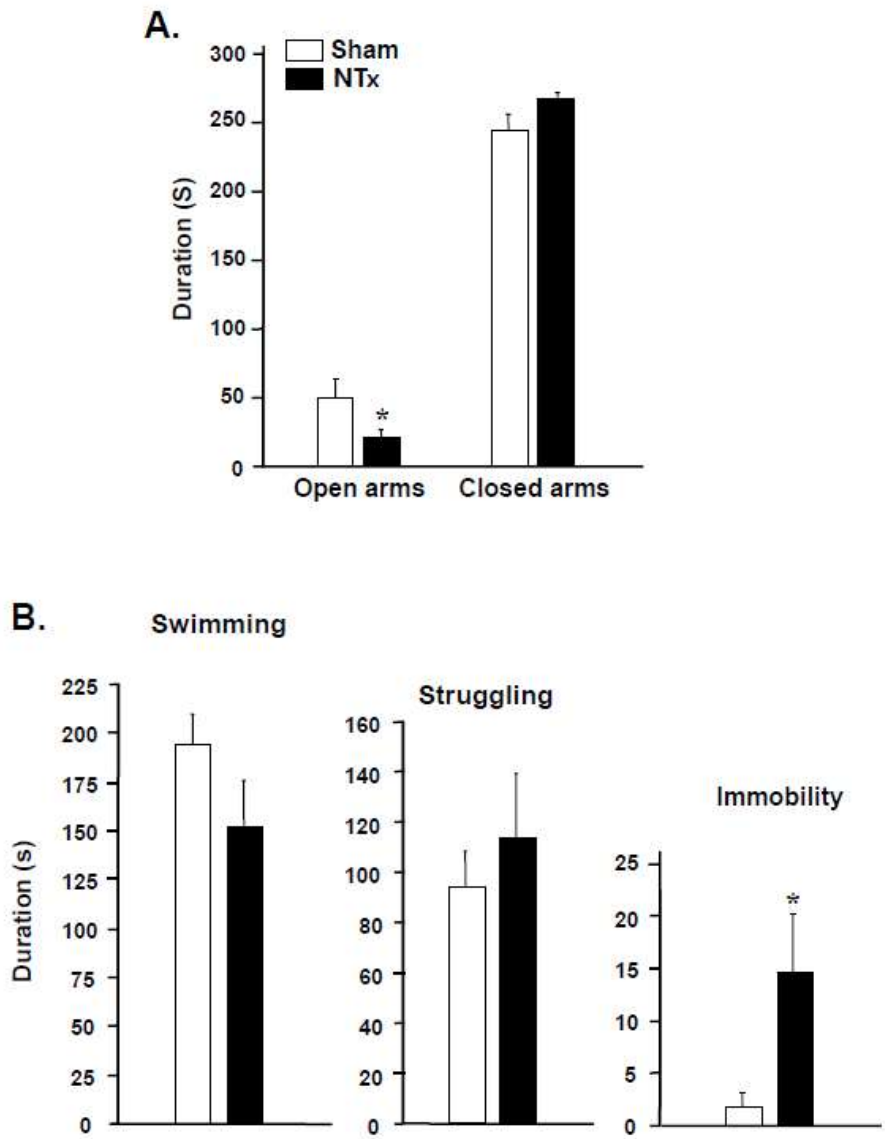

Figure 10. Time spent in each arms during elevated plus maze test (A), and the scores during forced swim test (B). NTx; rats with bilateral transection of the lingual and chorda tympani nerves, sham; rats with sham operation, *P < 0.05 vs. sham, data are presented by mean ± S.E.

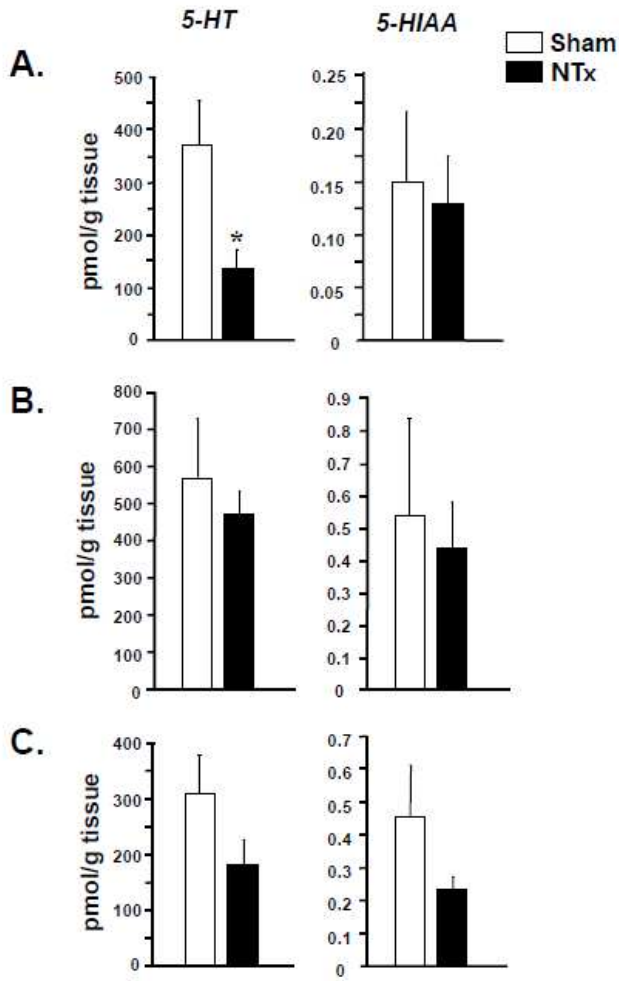

Figure 11. Tissue contents of serotonin (5-HT) and its metabolite 5-HIAA in the hippocampus (A), the hypothalamus (B), and the nucleus accumbens (C). Brain tissues were collected a week after the end session of behavioral tests, and the tissue contents of 5-HT and 5- HIAA in each brain region were analyzed by high performance liquid chromatography. NTx; rats with bilateral transection of the lingual and chorda tympani nerves, sham; rats with sham operation, *P < 0.05 vs. sham, data are presented by mean ± S.E.

Ⅷ. ABSTRACT in KOREAN (국문초록)

구강감각변조에 의한 정신심리행동 변화

: 캡사이신 구강투여 및 설신경 절단의 효과

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연구목적

감각정보는 개체의 정신감정 행동을 결정하는데 중요한 역할을 한다. 본 연구에서는 반복적인 캡사이신 구강투여와 신경절단(양측 설신경 및 고삭신경)에 의한 구강감각 변조가 어떠한 신경행동 변화(불안장애와 우울증 관련 행동)를 나타내는지 관찰하고자 하였으며 그 조절기전을 연구하고자 진행되었다.

연구재료 및 연구방법

캡사이신 구강투여로 인한 백서의 신경행동 변화를 연구하기 위해 매

일 10일 동안 0.02% 캡사이신 1 ml를 구강투여 하였고 이어 운동 활성도검사와 혈장 코티코스테론 검사를 시행하였다. 또한 0.02% 캡사이신 1 ml를 일회성으로 구강투여 한 후 측뇌실핵(paraventricular nucleus)과 고속핵(nucleus tractus solitarius) 부위에서의 활성도 변화를 c-Fos 면역조직화학법으로 검색하여 캡사이신 대신 물을 투여한 대조군과 비교하였다.

또한 백서의 양측 설신경과 고삭신경 절단 후 불안 관련 및 우울 관련 행동변화를 조사하였으며 대조군(sham operation)과 비교하였다. 그리고 해마, 시상하부 및 중격핵 부위에서의 세로토닌과 그 대사물의 수준을 HPLC로 검사하였다.

* HPLC: high-performance liquid chromatography (고성능 액체 크로마토그래피)

연구결과

캡사이신의 구강투여 효과를 관찰하고자 한 연구에서는 다음과 같은 결과를 얻었다. 운동 활성도검사에서는 대조군(물을 투여한 그룹) 보다 실험군(캡사이신을 구강 투여한 그룹)에서 stereotypy count와 rostral grooming은 유의하게 증가되었으나 caudal grooming은 감소하였다. Elevated plus maze test에서는 실험군이 대조군에 비해 open arm에서 보낸 시간도 적었고 open arm으로의 출입빈도 또한 적었다. Forced swim test에서는 실험군에서 struggling이 증가하면서 swimming duration은 감소하였고 immobility duration에서는 대조군과 유의한 차이를 보이지 않았다. 혈장 코티코스테론 검사결과, 부가적인 스트레스를 주지 않은 상태에서의 혈장 코티코스테론 수준은 실험군과 물을 투여한 대조군 사이에서 차이를 보이지 않았다. 하지만 부가적인 스트레스(구속틀에 2시간 감금)를 준 상황에서는 대조군에 비해 실험군에서 혈장 코티코스테론 수준이 연장되어 높게 나타났다. 마지막으로 캡사이신을 일회성으로 구강투여한 군이 물을 투여한 군에 비해 측뇌실핵 및 고속핵 부위에서의 c-Fos 발현이 유의하게 증가되었음을 관찰할 수 있었다.

양측 설신경 및 고삭신경을 절단한 후 신경행동 변화를 관찰한 연구에서는 다음과 같은 결과를 얻었다. 대조군(sham operation)에 비해 실험군(양측 설신경 및 고삭신경을 절단한 그룹)에서 자당 선호도의 감소를 보였으며 이는 쾌감결여(anhedonia)로 해석할 수 있다. 대조군에 비해 실험군에서 운동 활성도가 감소했고 불안장애 관련 행동이 증가했다. Elevated plus maze test에서는 대조군에 비해 실험군에서 open arm에서 보낸 시간이 적었고 forced swim test에서는 대조군에 비해 실험군 백서의 immobility duration가 증가했음을 관찰하였다. 실험군 해마(hippocampus)에서의 세로토닌 수준은 대조군에 비해 유의하게 감소되어 있었다.

결론

반복적인 캡사이신 구강투여로 인한 구강감각 변조는 불안장애 행동을 증가시켰으며 이는 스트레스 대응축(hypothalamic-pituitary-adrenal axis)의 기능이상이 병인에 중요한 역할을 담당한다고 볼 수 있다. 그리고 양측 설신경 및 고삭신경 절단에 의한 구강감각의 변조는 우울증 및 불안장애 관련 행동변화를 초래하는 것으로 나타났는데 이러한 현상의 원인은 해마에서 세로토닌 신경전달의 감소가 조절기전에 중요한 역할을 하는 것으로 나타났다.

본 연구를 통해 구강감각의 변조가 신경과적 기전에 의해 정신감정적 행동변화를 초래할 수 있음을 알 수 있었다.

주요어 : 캡사이신 구강투여, 설신경, 불안장애, 우울증, 무쾌감증, 행동

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