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## Anxiolytic efficacy of repeated oral capsaicin in rats with partial aberration of oral sensory relay to brain

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### ABSTRACT

**Objective:** This study was conducted to examine if taste over load with oral capsaicin improves the adverse behavioural effects induced by partial aberration of oral sensory relays to brain with bilateral transections of the lingual and chorda tympani nerves.

**Design:** Male Sprague-Dawley rats received daily 1 ml of 0.02% capsaicin or water drop by drop into the oral cavity following the bilateral transections of the lingual and chorda tympani nerves. Rats were subjected to ambulatory activity, elevated plus maze and forced swim tests after 11th, 14th and 17th daily administration of capsaicin or water, respectively. The basal and stress-induced plasma corticosterone levels were examined after the end of behavioural tests.

**Results:** Ambulatory counts, distance travelled, centre zone activities and rearing were increased, and rostral grooming decreased, during the activity test in capsaicin treated rats. Behavioural scores of capsaicin rats during elevated plus maze test did not differ from control rats. Immobility during the swim test was decreased in capsaicin rats with near significance ( $P = 0.0547$ ). Repeated oral capsaicin increased both the basal level and stress-induced elevation of plasma corticosterone in rats with bilateral transections of the lingual and chorda tympani nerves.

**Discussion:** It is concluded that repeated oral administration of capsaicin reduces anxiety-like behaviours in rats that received bilateral transections of the lingual and chorda tympani nerves, and that the increased corticosterone response, possibly modulating the hippocampal neural plasticity, may be implicated in the anxiolytic efficacy of oral capsaicin.

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Abbreviations: ANOVA, analysis of variance; HPA, hypothalamic-pituitary-adrenal; AA, ambulatory activity; EPM, elevated plus maze; FST, forced swim test.

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## 1. Introduction

Taste sensory information that reached the nucleus tractus of solitarius is principally relayed to the gustatory cortex, 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.<sup>1–3</sup> Functions of the cerebral cortex, hippocampus, amygdala and nucleus accumbens are well known to be involved in the psycho-emotional behaviours including depression- and anxiety-like behaviours.<sup>4–10</sup> 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.<sup>6,7</sup> Sweet solutions have been shown to rapidly calm stress responses in human newborns,<sup>11</sup> and in adults, experimentally induced negative mood is improved immediately and selectively after eating palatable food,<sup>12</sup> suggesting that immediate positive affective reactions elicited by palatable foods diminish the impact of stress. Indeed, eating has been viewed as a strategy to improve negative mood<sup>13</sup> and to mask stress,<sup>14</sup> and studies indicate that healthy, normal-weight persons regulate negative emotions by eating palatable food.<sup>15,16</sup> Collectively, it is hypothesized that alterations in oral sensory information can modulate the psycho-emotional status of individuals. Indeed, altered taste sensation has been reported in depression and anxiety, especially reduced sweet sensation in depression,<sup>17,18</sup> and the general anxiety level was related to taste perception.<sup>19</sup>

Lingual nerve can be damaged by dental surgery or trauma such as physical irritation, radiation, chemotherapy, or viral infection. Some patients report not only altered taste perception but also negative emotion after lingual nerve damages, suggesting that the deprivation or disruption of oral sensory relays to brain may affect the emotional status of individuals. In fact, we have found that bilateral transections of the lingual and chorda tympani nerves led to the development of depression- and anxiety-related disorders in rats.<sup>20</sup> The chorda tympani nerve joins the lingual division of the trigeminal nerve, the lingual nerve, and distributes together to the fungiform papillae on the anterior two thirds of the tongue and may reach also the anterior portion of the foliate papillae. Axons of glossopharyngeal nerve supply both tastes buds and general sensory innervations to the vallate and foliate papillae, and also tastes buds in the pharynx.<sup>21</sup> Thus, it is suggested that partial aberration of oral sensory relays to brain; i.e. lose of the sensory information from the anterior two thirds of tongue with bilateral transections of the lingual and chorda tympani nerves, may affect the psycho-emotional behaviours of rats.

Rats with bilateral transections of the lingual and chorda tympani nerves showed anhedonia, a core symptom of depression, with reduced preferences to sweet solution.<sup>20</sup> It is generally believed that hot spicy food improves negative mood, and study showed that individuals who enjoy spicy, capsaicin-containing, foods exhibit higher sensitivity to reward traits,<sup>22</sup> suggesting a functional effect of capsaicin on the reward circuit. Dysfunctions in the reward circuit have been implicated in the development of anhedonia.<sup>4</sup> Capsaicin

has been reported to modulate sensory responses to sweet and bitter stimuli in human.<sup>23–26</sup> Capsaicin receptors, transient receptor potential vanilloid type 1, are co-localized with sweet or bitter receptors in taste sensing cells of the circumvallate papillae of rat<sup>27</sup> and human.<sup>28</sup> In rats, repeated oral administration with edible doses of capsaicin increased consumption of sweet solution,<sup>29</sup> and altered psycho-emotional behaviours with increased activity of the hypothalamic-pituitary-adrenal (HPA) axis responding to stress.<sup>30</sup> This study investigated if the adverse behavioural effects induced by partial aberration of oral sensory relays to brain could be improved by oral administration with capsaicin. Rats with bilateral transection of the lingual and chorda tympani nerves were subjected to the behavioural sessions scoring the psycho-emotional behaviours after repeated oral administration of capsaicin in an edible dose, and their HPA axis activities responding to stress were examined.

## 2. Materials and methods

### 2.1. Animals

Male Sprague-Dawley rats (200–250 g) were purchased (Orient, Co., Korea), and acclimated to the laboratory condition in a specific-pathogen-free barrier area where the temperature ( $22 \pm 1^\circ\text{C}$ ) and humidity (55%) were controlled constantly with a 12/12 h light/dark cycle (lights-on at 07:00 AM). Rats had ad libitum access to standard laboratory food (Purina Rodent Chow, Purina Co., Seoul, Korea) and tap water. All rats were habituated in the animal colonies at least for a week and were cared according to the Guideline for Animal Experiments, 2000, edited by the Korean Academy of Medical Sciences, which is consistent with the NIH Guidelines for the Care and Use of Laboratory Animals, revised 1996. All animal protocols were approved by the Committee for the Care and Use of Laboratory Animals at Seoul National University.

### 2.2. Surgery

Rats were anaesthetized with an intraperitoneal injection of a 4:1 mixture of ketamine hydrochloride (100 mg/kg, Ketara<sup>®</sup>, Yuhan, Korea) and xylazine hydrochloride (25 mg/kg, Rumpun<sup>®</sup>, 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 lingual nerve and chorda tympani nerve as it bifurcated from the lingual branch of the trigeminal nerve. Transection of the lingual and chorda tympani nerves 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<sup>®</sup>, UK). Body weight gain and food intake were monitored during the post-operational recovery period.

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