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Review Article

Uncovering the neural circuitry involved in the stress-attenuation effects of chewing

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Abstract Previous animal studies have indicated that coupling restraint stress load with activation of the masticatory organs (chewing) causes a reduction in the systemic and central nervous system stress response. However, the brain mechanism underlying this effect is unknown. Therefore, in this review, we summarize the literature regarding brain regions involved in the attenuating effects of chewing and the systemic stress response attenuation effects induced by those brain regions. In addition, we also focusing on the amygdala, as the emotional control center, and the hypothalamic–pituitary–adrenal axis, as one of the outputs of the systemic response. In particular, we will report on one of the chewing-related stress attenuation mechanisms within the brain brought about by the activation of the inhibition pathway accompanying the activation of the amygdala's GABAergic function.

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1. Introduction

In this article, we will review the literature on how chewing can alleviate stress responses. As one of the first studies to investigate this, in 1983, Vincent et al. reported that, in animals subjected to restraint and water inundation stress, those that could chew on a nylon brush developed fewer and smaller gastric lesions, and were better able to maintain body temperature when compared to animals exposed only to stress [1]. This suggests that increased afferent information input, mainly from the trigeminal nerve, via chewing under conditions of stress, induces a stress attenuation mechanism. However, the pathways by which this occurs has yet to be fully elucidated.

Similar animal experiments have since been conducted, including gene analysis studies and studies investigating the expression of specific proteins in regions of the brain that exhibit chewing-related stress responses (Table 1). To study systemic responses, serum levels of stress hormones and immune system parameters accompanying hypothalamic—pituitary—adrenal (HPA) axis activation have also been investigated [2]. In addition, researchers have investigated heart rate increases and the incidence of arrhythmia accompanying activation of the autonomic nervous system [3]. These studies indicate that chewing under stress has an inhibitory effect on stress responses, which involve the HPA axis, the sympathoadrenal system, and hyperactivation of the immune system (Table 1).

Restraint stress is commonly used in such experiments, and involves stress-related behavioral, biochemical, and physiological changes in laboratory animals. Restraint stress has been used in the context of a mental and physical stress experiment system in our previous studies [4—6], the basis of which is the expression of affective reactions resulting from the activated output accompanying the integration and evaluation of external stimulation as sensory information input. This sensory information follows a direct pathway from the thalamus to the cerebral neocortex and an indirect pathway from the thalamus through the archicortex, which includes the hippocampus, to the amygdala [2,7—9]. The amygdala integrates this information and interconnects with the neocortex, hippocampus, hypothalamus, and brainstem. This reduces physical and emotional reactions and allows the animal to adapt to the external environment [10].

In this review, we will report the results of stress response behavior tests, focusing on their influence on brain regions previously found to be involved in the attenuation of stress via chewing, in particular, the amygdala and the HPA axis. In addition, we will discuss the importance of the activation of gamma-aminobutyric acid (GABA)ergic function within the amygdala in the context of a chewing-induced stress inhibition mechanism.

2. Ex vivo and in vivo analysis of the effects of chewing-induced stress attenuation in the hypothalamus

In 2005, Miyake et al. [11] measured the effects of stress on the amount of free radicals and active oxygen within the entire brain in mice. They performed their experiments in a control group, a 30-min stress-only group, and a 30-min stress-with-chewing group. To obtain ex vivo measurements of the effects of chewing on stress, the authors injected a blood-brain barrier-permeable nitroxyl spin probe, 3-methoxycarbonyl-2,2,5,5-tetramethyl-pyrrolidine-1-oxyl (MC-PROXYL), into the tail vein. They then used the L-band electron spin resonance technique to measure the decay rate of MC-PROXYL within the brain. While the stress-only group showed a significant increase in the levels of active oxygen and free radicals within the hypothalamic region when compared to the control group, the stress-with-chewing group exhibited significantly lower levels of active oxygen and free radicals than the stress-only group. While free radicals and active oxygen are necessary for life, the balance between their formation and the elimination by antioxidants is crucial, as excessive oxidative stress has harmful systemic effects and is considered to be involved in brain ischemia, acceleration of aging, and neurodegenerative disease [12—15].

In a similar experimental series using small-animal positron-emission tomography with F-fluorodeoxyglucose injected via the tail vein, Ono et al. [16] carried out a whole-brain analysis. They found that glucose uptake in the hypothalamic region was significantly increased under stress conditions, and that chewing during stress counteracted this effect, reducing glucose uptake to control levels. Simultaneous measurements of plasma corticosterone changes have confirmed previous research findings [17] that chewing significantly counteracts stress-induced corticosterone elevation. Detailed analysis of region-of-interest-based glucose uptake has revealed that there is a significant reduction of uptake in the paraventricular hypothalamic nucleus (PVN) [16].

These results indicate that stress rapidly and significantly increases the levels of local active oxygen and free radicals, and glycometabolism within the hypothalamus, which is the stress response center. These changes caused by stress suggest that stress increases neural activity within the hypothalamic region. Getting together, both ex vivo and in vivo experiments have shown that chewing inhibits this neural activity. Given that glucose metabolism within the PVN, the control center of the HPA axis, was reduced and neural activity was inhibited, it is thought that secretion of the stress hormone, namely, plasma corticosterone was significantly inhibited as a consequence. The aforementioned results suggest that chewing may act as some kind

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