Masticatory function and cognitive function

By

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Summary: Recent studies have suggest that masticatory (chewing) function is useful for maintaining neurocognitive function in the elderly. For example, a reduced ability to masticate, such as that resulting from toothlessness or soft-diet feeding, causes learning and memory deficits in aged animals and pathologic changes in the hippocampus. In addition, occlusal disharmony impairs hippocampal memory processes via chronic stress, and induces similar hippocampal pathology. Chewing, however, rescues stress-induced suppression of long-term potentiation in the hippocampus and the stress-induced impairment of hippocampal-dependent learning. These findings strongly suggest a link between mastication and neurocognitive function.

Introduction

Mastication is highly important, not only for food intake but also for systemic, psychologic, physical, and cognitive functions¹⁸⁻⁵. Positron emission tomography and functional magnetic resonance imaging (fMRI) show increased blood flow in the bilateral lower frontal and parietal lobes during gum-chewing⁶ and widespread activation in various areas of the somatosensory, supplementary motor, and insular cortices, as well as the striatum, thalamus, and cerebellum⁷,⁸. Impaired mastication is considered to be an epidemiologic risk factor for Alzheimer’s dementia and systemic health, such as physical disability, mental impairment, and mortality⁹. Further, changing from tube feeding to oral feeding leads to an increase in motivation and to higher levels daily living skill levels in elderly patients; in contrast, decreased oral ingestion of food orally reduces motivation and daily living skill levels¹⁰. These findings suggest that masticatory function has an important role in preventing senile dementia and stress-related disorders, which are often associated with cognitive dysfunction such as impaired spatial memory and amnesia. Here, we provide an overview of the interaction between masticatory function and cognitive function, focusing on the hippocampus, which has a critical role in learning and memory.

Effect of dysfunctional mastication on cognitive function

Dysfunctional mastication is associated with impaired cognitive function. Several studies in mice and rats using various learning tests, e.g., Morris water maze¹¹⁻¹⁷, passive avoidance¹⁸,¹⁹, and radial arm maze¹⁰⁻²², indicate that extraction of molar teeth (molarless) and long-term soft-diet feeding result in learning and memory deficits. Studies using the Morris water maze demonstrated that molarless condition-induced learning deficits in aged (8–9 mo-old) senescence-accelerated prone (SAMP8) mice were induced relatively quickly (within approximately 2 wk), but the learning deficits in young-adult mice (1–2 mo-old) required a longer period of time to develop (approximately 5–6 mo)¹¹⁻¹⁰. SAMP8 mice undergo normal maturation up to 6 months of age, but then exhibit accelerated aging (median life span 12 months compared with 2–3 years for other strains). At 6 months of age, SAMP8 mice exhibit clear learning and memory deficits.
Masticatory dysfunction also leads to various morphologic changes in the hippocampus and cerebral cortex, e.g., the molarless condition and soft-diet feeding decrease the number of pyramidal cells, dendritic spines, and synapses in the hippocampus and parietal cortex, as well as neurotrophic receptor expression in hippocampal CA1 and CA3 regions. Hypertrophy and hyperplasia of glial fibrillary acid protein-labeled astrocytes in the CA1 region and suppressed cell proliferation in the hippocampal dentate gyrus also occur in mice with learning deficits. These behavioral and hippocampal morphologic changes are similar to the changes associated with advanced age, and masticatory dysfunction may therefore accelerate the aging process in the hippocampus. Consistent with this hypothesis, molarless mice also exhibit reduced Fos induction after spatial learning, fewer choline acetyltransferase-positive neurons in the septal nucleus, lower acetylcholine concentrations in the cerebral cortex and hippocampus, and reduced release of acetylcholine and dopamine in the hippocampus in response to extra-cellular stimulation.

These masticatory dysfunction-related behavioral and morphologic changes seem to result mainly from reduced activity of the sensorimotor pathways, chronic stress, or both. A quantitative change in afferent impulses from the sensory receptors to the central nervous system may produce alterations in neuroanatomic pathways. Physical training promotes axonal sprouting and synaptogenesis and enhances the formation of neurons and their survival in the hippocampus. In contrast, tooth extraction and pulp extirpation cause degenerative changes in the trigeminal ganglion cell bodies of the primary sensory neurons innervating the teeth and ganglionic degeneration in secondary neurons in the trigeminal spinal tract nucleus. Hence, cognitive impairment associated with masticatory dysfunction might result, in part, from diminished activity of the sensory pathways caused by reduced mastication. In elderly patients, the hippocampus does not receive sufficient inputs to maintain hippocampal function due to reduced locomotor activity and decreased input/function of the peripheral sensory organs compared to young subjects, thereby leading to a gradual decline in learning and memory. Thus, sensory input from masticatory organs appears to have an important role in maintaining cognitive function, especially in the aged hippocampus.

The molarless condition induces an increase plasma corticosterone levels, and decrease in glucocorticoid receptors (GR) and glucocorticoid receptor messenger ribonucleic acid (GRmRNA) in the hippocampus. The hippocampus is a highly targeted region of the effects of the stress hormone corticosterone. The masticatory-related hippocampal changes described above are similar to the hippocampal changes induced by chronic stress or long-term exposure to excessive corticosterone. Taken together, these findings suggest that increased plasma corticosterone levels due to chronic stress induced by the molarless condition contribute to the learning and memory deficits.

Recent neuroimaging studies using fMRI and positron emission tomography in humans indicate that several regions of the brain are activated during mastication, including the primary somatosensory cortex, primary motor cortex, supplementary motor area, premotor area, prefrontal cortex, insula, posterior cortex, thalamus, striatum, and cerebellum. Functional MRI evaluation of the effects of chewing on neuronal activity in the brain during a working memory task indicated that chewing increases the blood oxygen level-dependent (BOLD) signals in the right premotor cortex, prefrontal cortex, thalamus, hippocampus, and inferior parietal lobe. Furthermore, Onozuka et al. reported that chewing significantly enhances memory in aged subjects. These results in humans suggest that aggressive chewing activates a variety of brain areas and enhances learning.

It is not yet clear how the effects of reduced input activity due to masticatory dysfunction differ from the effects of a reduction in other types of sensory stimuli in the aging hippocampus. To elucidate the mechanisms underlying the specific effects of masticatory dysfunction in aging hippocampus, it will be necessary to compare the impact of mastication and environmental enrichment or physical exercise on hippocampal function.

Effects of occlusal disharmony on cognitive function

Occlusal disharmony also affects cognitive function. In SAMP8 mice, raising the bite by approximately 0.1 mm using dental materials (bite-raised condition) induces age-dependent deficits in spatial learning in the Morris water maze. Especially in aged SAMP8 mice, the bite-raised condition decreases neuron number and increases hypertrophy and hyperplasia of glial fibrillary acid protein-labeled astrocytes in the hippocampal CA3 region, suggesting that the bite-raised condition accelerates the hippocampal aging process. In rodents and monkeys, application of dental materials to the upper molars, attaching acrylic caps to the incisors, or inserting occlusal splints in the maxilla to raise the bite increases urinary cortisol excretion rates and plasma corticosterone levels by inducing
acute and chronic stress. In monkey, the increased urinary cortisol levels induced by occlusal splints return to basal values when the splints are removed. Furthermore, in aged SAMP8 mice with deficits in spatial learning, plasma corticosterone levels are markedly increased and expression of GR and GRmRNA is significantly decreased. Chronic stress and glucocorticoid exposure also impair maze learning performance and hippocampal neuronal degeneration. The corticosterone synthesis inhibitor metyrapone prevents bite-raised induced behavioral and hippocampal morphologic impairments. It is very possible that, under occlusal disharmony, the hippocampal degeneration and impaired spatial performance are caused by increased glucocorticoid levels through impairment of the hypothalamic-pituitary-adrenal axis due to the downregulation of GR and GRmRNA.

Similar to dysfunctional mastication, occlusal disharmony inhibits input activities from the masticatory organs to the hippocampus. The bite-raised condition in aged SAMP8 mice decreases Fos induction following a learning task and decreases the number of spines in the hippocampus.

Occlusal disharmony also affects catecholaminergic activities. Placing an acrylic cap on the lower incisors increases dopamine and noradrenaline levels in the hypothalamus and/or frontal cortex. Occlusal disharmony also reduces tyrosine hydroxylase, GTP cyclohydrolase I, and serotonin immunoreactivity in the cerebral cortex, caudate nucleus, substantia nigra, locus coeruleus and nucleus raphe dorsalis. These catecholaminergic changes are similar to changes induced by chronic stress. Because the hippocampus is innervated by noradrenergic and serotonergic systems, the changes in the catecholaminergic and serotonergic systems induced by occlusal disharmony may affect hippocampal function.

Otsuka et al. measured BOLD signals during clenching in a malocclusion model using a custom-made splint in humans and reported that malocclusion affects emotion-related neuronal processing in the brain, such as in the anterior cingulate cortex and amygdala.

The occlusal disharmony-induced changes in the hippocampus are due largely to stress responses. Why the effects of occlusal disharmony are specific to hippocampal function compared with other physical or psychologic stressors should be clarified. Because the changes induced by occlusal disharmony are similar to those that occur with dysfunctional mastication, any differences between dysfunctional mastication and occlusal disharmony should also be explained.

Effect of mastication on stress-induced impairment of cognitive function

Chewing under stressful conditions may affect cognitive function. Extensive rodent and human research demonstrates that the hippocampus is not only crucially involved in memory formation, but is also highly sensitive to aging and stress. Chewing during a stressful event ameliorates the stress-induced impairment of plasticity and memory. Stress and/or increases in corticosterone levels suppress synaptic plasticity, which is involved in learning and memory. These findings suggest that chewing under stressful conditions ameliorates the stress-induced impairment of cognitive function.

Mastication under stressful conditions modulates the hypothalamic-pituitary-adrenal-axis, the autonomic nervous system, and the immune system. In rats and mice, chewing on a wooden stick during restraint stress suppresses the restraint-induced increase in corticotrophin releasing factor expression, c-fos induction, phosphorylation of extracellular signal-regulated protein kinase 1/2, oxidative stress, and nitric oxide in the paraventricular nucleus of the hypothalamus. These findings suggest that chewing under some stress-inducing conditions decreases plasma corticosterone levels through reduced expression of the adrenocorticotropic hormones. Further, chewing during stress attenuates changes in blood pressure, core temperature, and plasma adrenaline levels, suggesting that the automatic nervous system response is attenuated. Mastication also suppresses the increase in plasma interleukin-1beta, interleukin-6 and leptin levels that occur during stress.

Masticatory function may involve inactivation of histamine neurons through the ventromedial hypothalamus and the mesencephalic trigeminal sensory nucleus. The histamine system may contribute to modulate of the activity of the septohippocampal cholinergic system. Hence, the change in acetylcholine release induced by chewing may be a key factor impacting memory processes.

Aggressive biting under immobilization stress or novelty stress increases stress-induced noradrenaline release in the amygdala and Fos-immunoreactivity in the right medial prefrontal cortex, decreases Fos-immunoreactivity in the right central nucleus of the amygdala, and attenuates the dopamine response in the medial prefrontal cortex. The prefrontal cortex has a pivotal role in a variety of cognitive, affective, and physiologic processes and the central nucleus of the amygdala regulates dopamine neurotransmission in the medial prefrontal nucleus. These findings suggest that chewing during stressful conditions may modulate catecholaminergic neurotransmission in the central nervous system involved in stress, leading to changes in cognitive and affective function. Indeed, chewing under restraint stress decreases anxiogenic behavior in animals, based on findings obtained in the elevated plus-maze after restraint stress exposure.

Similar results are reported in humans. Chewing gum alleviates a negative mood reduces cortisol during acute laboratory-induced psychologic stress, and helps...
reduce perceived levels of everyday stress. These findings suggest that chewing gum in humans may also ameliorate the stress-induced response. At this stage, how aggressive chewing under stressful condition ameliorates the stress reaction is not clear. To elucidate this issue, more studies focused mainly on the hippocampus and amygdala are necessary. Chewing gum is simple and easy to implement; therefore, the practice of chewing gum may help to prevent dementia and decrease the effects of stress.

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