Chapter 5

The Relationship Between Mastication and Cognition

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Additional information is available at the end of the chapter

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1. Introduction

Although mastication is primarily involved in food intake and digestion, it also promotes and preserves general health, including cognitive function. Functional magnetic resonance imaging (fMRI) and positron emission topography studies recently revealed that mastication leads to increases in cortical blood flow and activates the somatosensory, supplementary motor, and insular cortices, as well as the striatum, thalamus, and cerebellum [1]. Masticating immediately before performing a cognitive task increases blood oxygen levels (BOLD) in the prefrontal cortex and hippocampus, important structures involved in learning and memory, thereby improving task performance [1]. Thus, mastication may be a drug-free and simple method of attenuating the development of senile dementia and stress-related disorders that are often associated with cognitive dysfunction. Previous epidemiologic studies demonstrated that a decreased number of residual teeth, decreased denture use, and a small maximal biting force are directly related to the development of dementia, further supporting the notion that mastication contributes to maintain cognitive function [2].

Here we provide further evidence supporting the interaction between mastication and learning and memory, focusing on the function of the hippocampus, which is essential for the formation of new memories. We first summarize recent progress in understanding how mastication affects learning and memory. We then describe the impaired function and pathology of the hippocampus in an animal model of reduced mastication using senescence-accelerated prone (SAMP8) mice, and discuss human studies showing that mastication enhances hippocampal-dependent cognitive function. We then describe how occlusal disharmony is a potential chronic stressor that impedes or suppresses hippocampal-mediated learning and memory, suggesting that normal occlusion is essential for producing the ameliorative effects of mastication on stress-induced changes in the hippocampus. Finally, we focus on the ameliorative effects of mastication on stress-induced suppression of learning and

memory functions in the hippocampus and on systemic stress responses in both animals and humans.

2. Dysfunctional mastication and cognitive function

Dysfunctional mastication affects cognitive function, and reduced mastication contributes to senile dementia, Alzheimer's disease, and a declining quality of life in the elderly. In particular, the systemic effects of tooth loss are an epidemiologic risk factor for Alzheimer's disease [2]. Missing teeth, due to dental caries and periodontitis are common in the elderly, and reduce their ability to masticate. We created a molarless senescence-accelerated prone (SAMP8) mouse model of dysfunctional mastication by extracting or cutting the upper molar teeth (molarless). SAMP8 mice mature normally for up to 6 months of age, but then exhibit accelerated aging (with a median life span of 12 months compared with 2- to 3 years for other strains). SAMP8 mice show clear aging-related impairments in learning and memory at 6 months of age [3, 4], and these mice are often used in aging studies. Molarless SAMP8 mice exhibit age-dependent deficits in spatial learning in the Morris water maze [5-10] (Fig. 1). The duration of the molarless condition in aged SAMP8 mice correlates with the level of impaired learning [7], and restoring lost molars with artificial crowns attenuates the molarless-induced increases in the learning and memory deficits [9]. Masticatory stimulation is also impaired by a soft-food diet [11], which leads to learning impairment [11]. Together, these findings indicate that masticatory stimulation is closely related to learning and memory.

Several morphologic changes are observed in the hippocampus of molarless mice, including a decreased number of pyramidal cells [6], hypertrophied glial fibrillary acid protein-labeled astrocytes [7, 10] and decreased dendritic spines in the CA1 region [8], suppressed cell proliferation in the dentate gyrus [12]. These behavioral and morphologic changes are very similar to aging-related changes in the hippocampus [13]. The decreased masticatory stimulation resulting from a soft-food diet results in similar morphologic features [14, 15]. Thus, masticatory dysfunction appears to accelerate the aging process in the hippocampus.

Although the relationship between dysfunctional mastication and these behavioral and morphologic changes in the hippocampus is unclear, there are several possible mechanisms.

Decreased mastication decreases the information input from the oral area to the central nervous system, which leads to the degeneration of target cells [16], as exercise promotes axonal sprouting and synaptogenesis [17] and enhances neurogenesis in the hippocampus [18]. Tooth loss or extraction causes degenerative changes in the trigeminal ganglion cell bodies of the primary sensory neurons innervating the teeth [19] and transganglionic degeneration in the secondary neurons in the trigeminal spinal tract nucleus [20]. Hence, the impairment in cognitive function due to masticatory dysfunction might be related to the decreased activity of the sensory pathways of the oral areas. Further, dysfunctional mastication leads to increased decreased cholinergic activity. The number of choline acetyltransferase-positive neurons in

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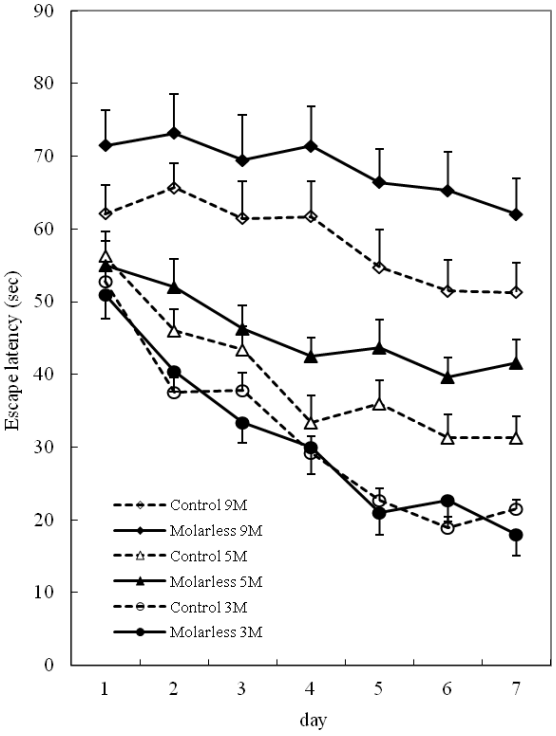

Figure 1. Effect of molarless condition on spatial learning in the Morris water maze test. The results are expressed as the mean score (mean ± SE, n=6 for each group) of four trials per day. Note that 9-month-old molarless mice required a significantly longer time than age-matched controls to reach the platform.

the septal nucleus is decreased in molarless mice [24], and decreased acetylcholine concentrations are observed in the cerebral cortex and hippocampus [24], as well as decreased acetylcholine release [24] in the hippocampus in response to extracellular stimulation. In rodents, spatial memory is associated with acetylcholine levels in the hippocampus [25]. Therefore, the decreased cholinergic activity induced by the molarless condition could contribute learning impairments.

Decreased mastication may also lead to increases in the plasma corticosterone levels. The molarless condition in aged SAMP8 mice increases plasma corticosterone levels [5], and downregulates glucocorticoid receptors (GRs) and GR messenger ribonucleic acid (GR

mRNA) in the hippocampus [21]. The hippocampus contains a high density of GR and is involved in the negative feedback mechanism with the hypothalamo-pituitary-adrenal axis via GR, making it very sensitive to corticosterone [22]. The morphologic and behavioral changes in the hippocampus due to chronic stress or long-term exposure to excessive corticosterone are similar to the changes observed with reduced mastication [23]. In support of this notion, treatment with the corticosterone synthesis inhibitor metyrapone prevents molarless-induced learning impairments and neuron loss in the hippocampus [5]. Thus, chronic stress induced by masticatory dysfunction could lead to learning and memory impairments.

Recent fMRI and positron emission tomography studies in humans revealed that several brain regions are activated during mastication [26, 27]. We performed fMRI studies in humans to evaluate the areas of the brain that are activated in association with chewing. In these studies, subjects were asked chew gum with no odor or taste components and perform rhythmic chewing at a rate of approximately 1 Hz. Bilateral increases in activity were observed in several brain areas, including the primary somatosensory cortex, primary motor cortex, supplementary motor area, premotor area, prefrontal cortex, insula, posterior cortex, thalamus, striatum, and cerebellum [26, 27]. Age-dependent changes in the chewing-induced BOLD signals were observed in the primary sensorimotor cortex, cerebellum, and thalamus [26, 27]. The right prefrontal cortex showed the highest increase in activity in elderly persons compared to both young adults and young persons [1] (Fig. 2). The prefrontal cortex is involved in cognitive function [28], and neuronal activity between the right prefrontal cortex and hippocampus might contribute to cognitive function. An fMRI evaluation of the effects of chewing on brain activity during a working memory task showed an increase in BOLD signals in the right premotor cortex, precuneus, thalamus, hippocampus, and inferior parietal lobe [29]. In another fMRI experiment examining the effect of chewing on hippocampal activity in a spatial cognition task [1], subjects were shown 16 photographs followed by the same number of pictures of a plus character (+) on a green background during each cycle. Each picture or photograph was projected every 2 s during the cycle and the subjects were asked to remember as many of the photographs as possible. The hippocampal BOLD signals in young subject were strongly increased but no significant difference was seen before and after chewing, whereas hippocampal activation in aged subject was quite small compared to that in young subject. The activation area and the intensity of the fMRI signals were, however, increased by chewing [1] (Fig. 3 and 4). Memory acquisition in aged subjects is also significantly enhanced by chewing, whereas chewing had no effect in young subject [1] (Fig. 5). These findings in humans support a link between increased hippocampal BOLD signals and enhanced memory acquisition.

Further studies are needed to clarify how the reduced oral input activity to the aging hippocampus resulting from masticatory dysfunction differs from reduced activity of other types sensory pathways.

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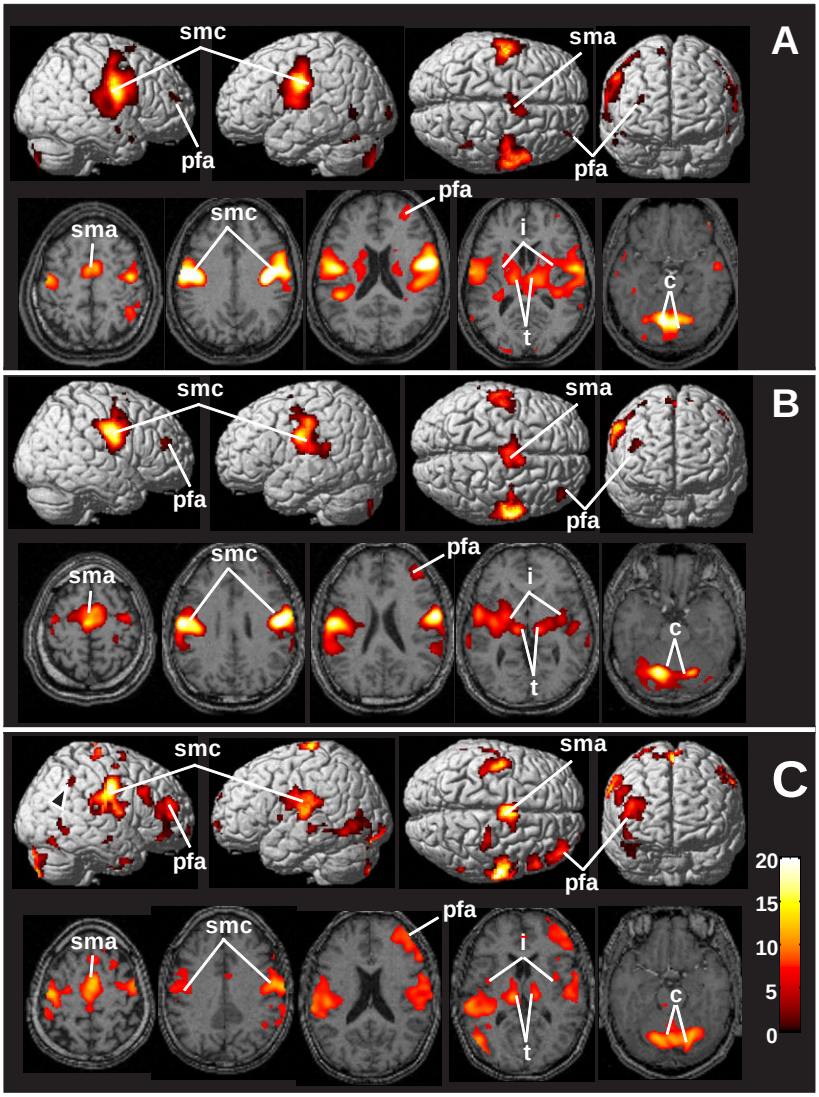

Figure 2. Effects of aging on brain regional activity during chewing. Significant signal increases associated with gum chewing in a young adult subject (A), middle-aged subject (B), and an aged subject (C). Upper section: activated areas superimposed on a template (P<0.05, corrected for multiple comparisons). Lower section: activated regions superimposed on a T1-weighted MRI scan (P<0.01, uncorrected for multiple comparisons). pfa, prefrontal area; sma, supplementary motor area; smc, primary sensorimotor cortex; c, cerebellum; i, insula; t, thalamus. Color scale: t value (degree of freedom=87.12). (Onuzuka et al., 2008, [1] with permission)

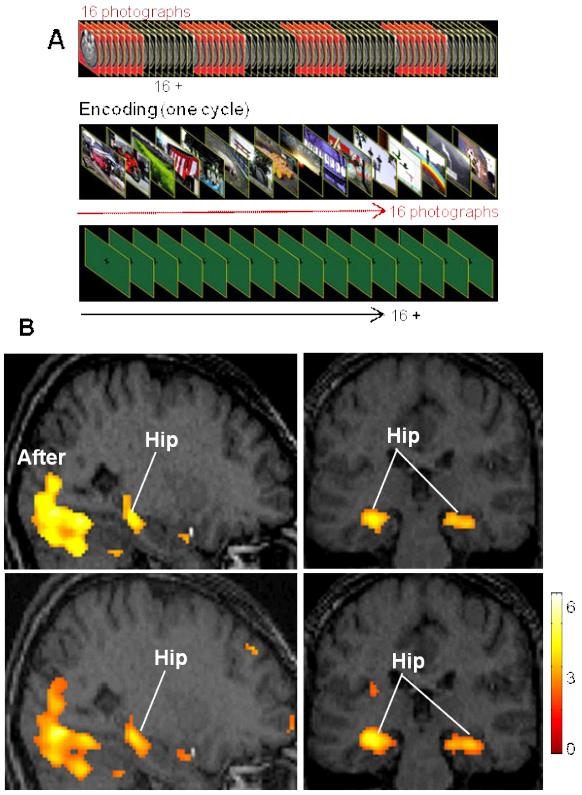

Figure 3. Hippocampal activities in young subject. A Task paradigm. B Significant signal increases associated with photograph encoding before and after gum chewing. Hip, hippocampus. Color scale: t value. (Onozuka et al., 2008, [1] with permission)

3. Occlusal disharmony and cognitive function

Occlusal disharmony, such as loss of teeth and increases in the vertical dimension of crowns, bridges, or dentures, causes bruxism or pain in the masticatory muscles and temporomandibular joints, and general malaise [30, 31]. Studies in SAMP8 mice also show that occlusal disharmony impairs learning and memory. Using SAMP8 mice, we created a model of occlusal disharmony by raising the bite by approximately 0.1 mm using dental materials, referred to as the bite-raised condition. Animals in the bite-raised condition show age-dependent deficits in spatial learning in the Morris water maze [32-39] (Fig. 6). Raising the bite in aged SAMP8 mice decreases the number of pyramidal cells [34] as well as the number of their dendritic spines [39], and increases hypertrophy and hyperplasia of grail fibrillary acid protein-labeled astrocytes [38] in the hippocampal CA1and CA3 regions, suggesting that occlusal disharmony

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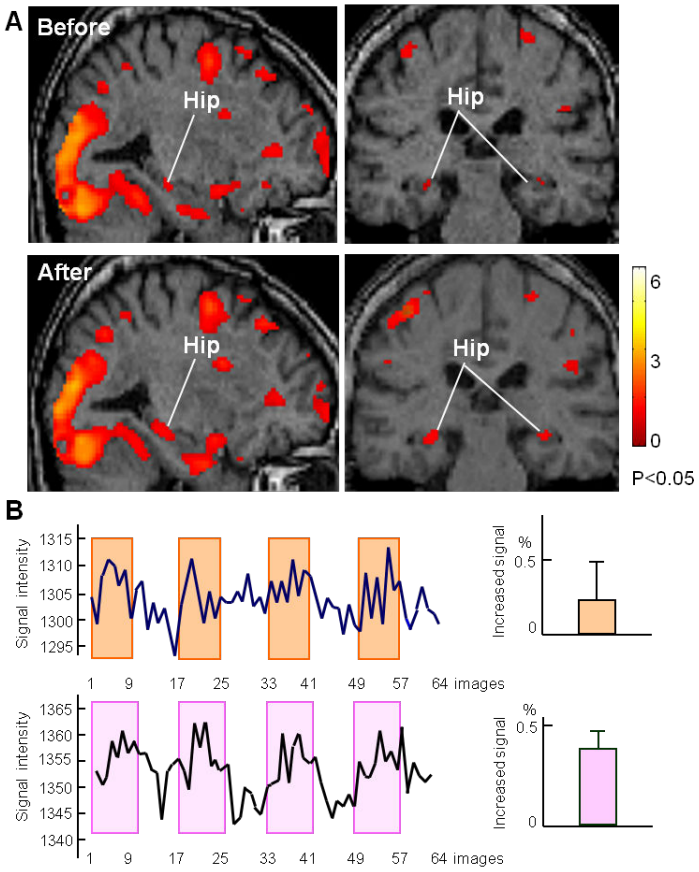

Figure 4. Hippocampal activities in an aged subject. A, Significant signal increases are associated with photograph encoding before and after gum chewing. Color scale: t value. B, Changes in signal intensity on an image-by image basis for 64 successive images during four cycles of encoding of photographs: brown (without chewing) and pink (with chewing) boxes; plus (+) characters (without boxes) (Onozuka et al., 2008, [1], with permission)

resulting from the bite-raised condition also enhances aging-related changes in the hippocampus.

In rodents and monkeys, alterations of the bite alignment induced by attaching acrylic caps to the incisors [40-42] or inserting occlusal splints in the maxilla [43, 44] are associated with increases urinary cortisol levels and plasma corticosterone levels, suggesting that occlusal disharmony is also a source of stress. In support of this notion, aged bite-raised SAMP8 mice with learning deficits exhibit marked increase in plasma corticosterone levels [33, 36, 37] and downregulation of hippocampal GR and GR mRNA [33]. The behavioral and morphologic changes observed in animals with occlusal disharmony closely resemble the changes induced

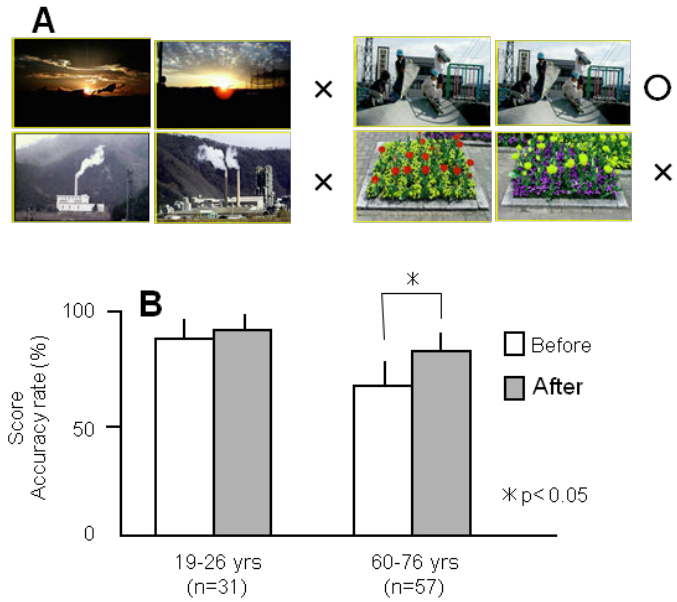

Figure 5. Memory acquisition before and after gum chewing for 2 min. A recall test was carried out 20 min after the encoding experiments. In the recall test, we used 64 photographs at random: 32 of the photographs were repeated from the encoding test, and the other 32 photographs were newly added. The subject had to judge whether each photograph had been seen before. (Onozuka et al., 2008, [1], with permission)

by chronic stress and/or long-term exposure to glucocorticoid exposure [23, 100]. The hippocampus is very sensitive to corticosterone [22]. These hippocampal behavioral and morphologic impairments induced by occlusal disharmony are also attenuated by administration of the corticosterone synthesis inhibitor metyrapone [37]. These findings suggest that occlusal disharmony-induced changes in learning behavioral and hippocampal morphology due to increases in the glucocorticoid levels in association with the downregulation of GR and GR mRNA.

Occlusal disharmony, like masticatory dysfunction, decreases hippocampal activity resulting from the activity of masticatory organ pathways. In bite-raised aged SAMP8 mice, both induction of Fos in the hippocampus following a learning task [36] and the number of spines in hippocampal CA1 pyramidal cells are decreased [39]. Further, the bite-raised condition leads to a decreased number of choline acetyltransferase-positive neurons in the septal nucleus, and reduction in extracellular stimulation-induced acetylcholine release [45].

Occlusal disharmony also affects catecholaminergic activity. Altering the bite by placing an acrylic cap on the lower incisors leads to increases in both dopamine and noradrenaline levels in the hypothalamus and/or frontal cortex [40-42], and decreases in tyrosine hydroxylase, GTP cyclohydroxylase I, and serotonin immunoreactivity in the cerebral cortex, caudate nucleus,

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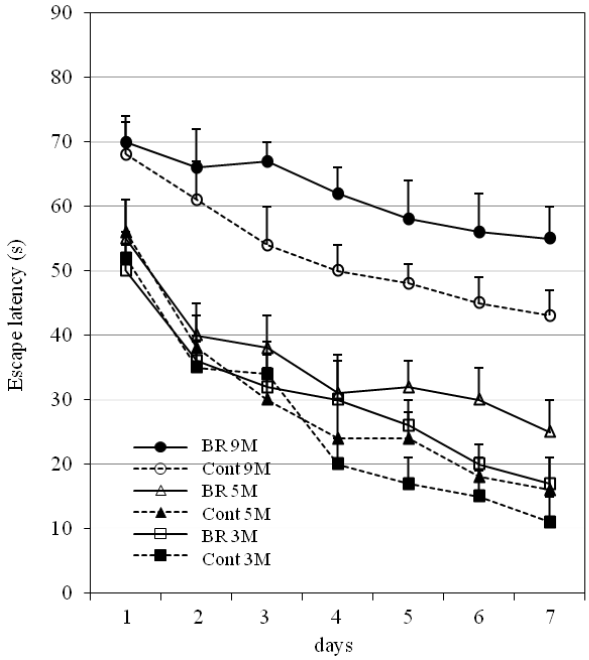

Figure 6. Effect of bite-raised condition on spatial learning in the Morris water maze test. The results are expressed as the mean score (mean ± SE, n=6 for each group) of four trials per day. 9m BR, 9-month-old bite-raised mice; 9m Cont, 9-month-old control mice; 5m BR, 5-month-old bite-raised mice; 5m Cont, 5-month-old control mice; 3m BR, 3-month-old bite-raised mice; 3m Cont, 3-month-old control mice. Note that 9-month-old bite-raised mice required a significantly longer time to reach the platform than age-matched controls. (Kubo et al., 2007, [34])

substantia nigra, locus coeruleus, and nucleus raphe dorsalis [46], which are similar to the changes induced by chronic stress [47]. These changes in the catecholaminergic and serotonergic systems induced by occlusal disharmony likely affect the innervations of the hippocampus. The bite-raised condition impairs neurogenesis and leads to apoptosis in the hippocampal dentate gyrus and decreases the expression of hippocampal brain derived neurotrophic factor, all of which could contribute to the learning impairments observed in animals with occlusal disharmony.

These findings in animal models were extended to humans. In humans, we used a custom-made splint that forced the mandible into a retrusive position and a splint without modification as a control in order to measure BOLD signals during clenching in a malocclusal model [48]. Several regions were activated by clenching, including the premotor cortex, prefrontal cortex, sensorimotor cortex, and insula. In the malocclusion model, which also induces psychologic discomfort, clenching further increased BOLD signals in the anterior cingulate cortex and the amygdala [48]. These findings suggest that clenching under malocclusal conditions induces emotional stress and/or pain-related neuronal processing in the brain.

Together these findings suggest that changes in the hippocampus induced by occlusal disharmony result from increased stress. Occlusal disharmony, like masticatory dysfunction leads to alterations in the central nervous system, especially the hippocampus. Further studies are needed to elucidate differences in the effects of dysfunctional mastication and occlusal disharmony.

4. Mastication and stress coping

The act of chewing, or masticatory stimulation, during stressful conditions may attenuate the effects of stress on cognitive function. To examine the effect of mastication on stress-induced behavioral and morphologic changes, we placed mice in a ventilated plastic restraint tube in which they were only able to move back and forth, but not turn around, to induce restraint stress. Half of mice were given a wooden stick (diameter, ~2mm) to chew during restraint [12]. As mentioned above, the hippocampus plays a crucial role in memory formation and is highly sensitive to aging [49, 50] and stress [51]. Increased plasma corticosterone levels suppress synaptic plasticity in the hippocampus [52] and cell proliferation in the hippocampal dentate gyrus [12] (Fig. 7). Chewing during a stressful event, on the other hand, attenuates stress-induced impairments of plasticity in the hippocampus by activating stress-suppressed N-methyl-D-aspartate-receptor function [53, 54]. Chewing under stress conditions also blocks the stress-induced suppression of cell generation in the hippocampal dentate gyrus [12]. In adults, neurogenesis in the hippocampus is required for hippocampus-dependent learning and memory [55]. Thus, chewing during stress may attenuate stress-induced impairments in cognitive function.

Rodents permitted to chew on a wooden stick during restraint stress showed attenuated restraint-induced increase in plasma corticosterone levels [12] and corticotrophin releasing factor expression [56], c-Fos induction [57], and phosphorylation of extracellular signal-regulated protein kinase 1/2 [58], oxidative stress [59], and nitric oxide [60, 61] in the paraventricular nucleus of the hypothalamus, compared with controls not provided with a wooden stick. Thus, chewing under stressful conditions appears to attenuate stress-induced increase in plasma corticosterone levels by inhibiting the hypothalamo-pituitary-adrenal-axis.

Mastication may also activate histamine neurons through the ventromedial hypothalamus and mesencephalic trigeminal sensory nucleus [62]. The histamine system could modulate the activity of the septohippocampal cholinergic system, which is involved in learning and memory [63]. Chewing under stress conditions increases the release of histamine in the hippocampus by activating H1 receptors [64]. Therefore, chewing may induce changes in the amounts of acetylcholine released, thereby attenuating stress-induced impairments in memory function.

In animals that aggressively chew on a wooden stick during immobilization stress, the stress-induced release of noradrenaline in the amygdala [65] and Fos-immunoreactivity in the right medial prefrontal cortex are increased [66], whereas Fos-immunoreactivity in the right central nucleus of the amygdala [66], and the dopamine response in the medial prefrontal cortex are decreased [67]. The prefrontal cortex has a crucial role in several cognitive, affective, and

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physiologic processes, and the central nucleus of the amygdala regulates dopamine neurotransmission in the medial prefrontal nucleus [60, 61]. These findings suggest that chewing during stressful conditions modulates catecholaminergic neurotransmission in the central nervous system, leading to changes in cognitive function.

Clinical studies have shown that offspring of mothers who suffer social, emotional or hostile experiences displayed enhanced susceptibility to some mental disorders, including depression, schizophrenia and cognitive deficits [68]. Maternal stress is a suggested risk factor for impaired brain developmental and anxiety, depressive-like behavior and learning deficits in rodents pups [69-71], and maternal stress model is often used in studies for depression and cognitive deficits in pups. We recently evaluated whether chewing during maternal restraint stress prevents stress-induced anxiety-like behavior and learning impairment in pups. Pregnant mice were exposed to restraint stress beginning on day 15 and continuing until delivery. Mice were placed in a ventilated plastic restraint tube in which they were only able to move back and forth, but not turn around, to induce restraint stress. Half of the dams were given a wooden stick (diameter, ~2mm) to chew on during the restraint stress. The pups were raised to adulthood and behavioral and morphologic changes were assessed. Restraint stress during pregnancy caused anxiety-like, impaired learning and suppressed cell proliferation in the hippocampal dentate gyrus. Chewing during restraint stress, however, attenuated the anxiety-like behavior, impaired learning, and suppressed cell generation induced by restraint stress. These findings suggest that maternal chewing contributes to prevent stress-induced anxiety-like behavior, learning impairment, and morphologic changes in hippocampus in pups.

In humans, chewing gum alleviates a negative mood, reduces cortisol levels during acute laboratory-induced psychologic stress [72], and reduces perceived levels of daily stress [73]. These findings indicate that the stress response in human is also ameliorated by chewing.

Additional studies are needed to investigate the mechanisms by which aggressive chewing under stress conditions attenuates stress-induced changes to the brain.

5. Conclusion

Masticatory dysfunction resulting from tooth loss or extraction, feeding on a soft-diet or occlusal disharmony, induces pathologic changes in the hippocampus and deficits in learning and memory. Aggressive biting or chewing activates several regions in the central nervous system, including the right prefrontal cortex, which is strongly involved in learning and memory. Chewing under stressful conditions attenuates stress-induced changes in the brain. These findings together indicate that masticatory function is important for maintaining cognitive function, and chewing during exposure to stress might be a useful method of coping with stress. Chewing gum may thus be a simple method to attenuate or delay the development of dementia and to ameliorate the effects of stress on the brain.

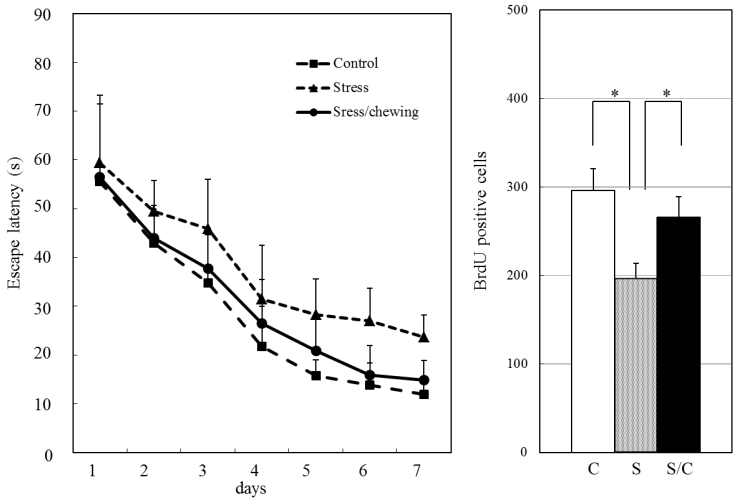

Figure 7. Effect of chewing during prenatal stress on learning ability and cell proliferation in the hippocampal dentate gyrus. Spatial learning in the water maze test (A) and BrdU-positive cells (B). The results are expressed as the mean score (mean ± SD, n=6 for each group) of four trials per day (A). The results are presented as the mean ± SD (n=5 for each group). C, control; S, restraint stress; S/C, restraint/chewing. *P<0.05 (B). Note that prenatal stress induced learning and memory deficits, and decreased cell proliferation in the hippocampal dentate gyrus. Maternal chewing during stress inhibits the stress-induced learning and memory deficits, and suppression of cell generation.

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