Journal of Oral Rehabilitation

Journal of Oral Rehabilitation 2010 **37**; 624–640

Review Article

Occlusion and brain function: mastication as a prevention of cognitive dysfunction

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SUMMARY **Research in animals and humans has shown that mastication maintains cognitive function in the hippocampus, a brain area important for learning and memory. Reduced mastication, an epidemiological risk factor for the development of dementia in humans, attenuates spatial memory and causes hippocampal neurons to deteriorate morphologically and functionally, especially in aged animals. Active mastication rescues the stress-attenuated hippocampal memory process in animals and attenuates the perception of stress in humans by suppressing endocrinological and autonomic stress responses. Active mastication further improves the performance of sustained cognitive tasks by increasing the activation of the hippocampus and the prefrontal cortex, the brain regions that are essential for cognitive processing. Abnormal mastication caused by experimental occlusal disharmony in animals produces chronic stress, which in turn suppresses spatial learning ability. The negative correlation between mastication and corticosteroids has raised the hypothesis that the suppression of the hypothalamic–pituitary–adrenal (HPA) axis by masticatory stimulation contributes, in part, to preserving cognitive functions associated with mastication. In the present review, we examine research pertaining to the mastication-induced amelioration of deficits in cognitive function, its possible relationship with the HPA axis, and the neuronal mechanisms that may be involved in this process in the hippocampus.**

KEYWORDS: corticosteroids, hippocampus, HPA axis, learning and memory, mastication, occlusion

Accepted for publication 6 February 2010

Introduction

Mastication has been shown to promote and preserve general health, especially the cognitive function of the brain, beyond its primary functions of food intake and digestion (1–4). Recent studies in functional magnetic resonance imaging (fMRI) and positron emission topography (PET) revealed that mastication increases cortical blood flow (5) and widely activates various cortical areas of the somatosensory, supplementary motor, and insular cortices, as well as the striatum, thalamus and cerebellum (6, 7). Mastication immediately before cognitive task acquisition further increases blood oxygen levels in the prefrontal cortex (PFC) and the hippocampus during the task, which is essential for the learning and memory processes, and improves performance of the tasks (8, 9). These data suggest that mastication is a medication-free and simple way to prevent senile dementia and stress-related disorders, which are often associated with cognitive dysfunctions such as impaired spatial memory and amnesia. That masticatory stimulation maintains cognitive function is also obvious from epidemiological studies showing that a decreased number of residual teeth, decreased use of

doi: 10.1111/j.1365-2842.2010.02079.x

dentures, and a small maximal biting force are directly related to the development of dementia (1, 10–12).

Here, we provide an overview of the interaction between mastication and the cognitive processes of learning and memory, focusing on the function of the hippocampus, which plays a pivotal role in the formation of new memories. First, we review recent progress in understanding how changes in the amount of mastication affect learning and memory abilities. We describe the impaired function, as well as the pathology of the hippocampus in an animal model of reduced mastication, and following that we describe human studies that show that mastication enhances hippocampal-dependent cognitive function. Second, we focus on the ameliorative effect of mastication on the stress-suppressed learning and memory functions in the hippocampus and on the systemic stress responses in both animals and humans. Third, we describe an occlusal disharmony as a possible chronic stressor that impedes or suppresses hippocampal learning and memory, suggesting that normal occlusion is necessary in order for mastication to provide the ameliorative effect. In the current review, we define 'normal' occlusion as a state in which one can masticate without any pain or discomfort, regardless of the use of prosthetic appliance. Finally, we discuss pathways that convey masticatory information to the hippocampus. The authors discuss mastication as a common mediator of the above modulatory effects of hippocampal function, by, at least in part, suppressing the blood concentrations of corticosteroid stress hormones (cortisol in humans and corticosterone in rodents) that are increased by advancing senility or by stressful stimuli.

Masticatory modulation of learning and memory

Lack of masticatory stimulation impairs learning and memory in the senile hippocampus

Loss of functionality of molar teeth, because of either extraction or reduction of crowns, and long-term soft-diet feeding are both causes of reduced mastication in rodents, and these rodents are less able to learn and to memorise (Table 1). These rodents are still able to chew; however, the occlusal hypofunction causes degenerative and abnormal changes in the periodontal mechanoreceptors (13), suggesting suppressed sensory feedback from periodontal ligaments upon chewing. Studies using the Morris water maze and the radial-arm maze, both of which are behavioural procedures used to test hippocampal-dependent spatial memory, indicate that adult rats suffer a loss of learning ability somewhere between 2 and 30 months after the extraction of molar teeth (14–16). Acute pain or stress associated with surgery can be ruled out as a cause of the learning ability, because the learning impairment arises several months after extraction, long after the period of acute pain or stress, and because soft-diet feeding from the weanling onwards also suppresses

Table 1. Learning and memory deficits in model animals of reduced or abnormal masticatory input

Type of treatment	Strain	Age at the operation	Age at the examination	Type of behavioural test	Reference
Molar extraction	Wistar	3 month	6 month	Habituation learning, radial-arm maze	(14)
		11 week	135 week after operation	Radial-arm maze	(15)
		25 week	40 week	Passive avoidance	(19)
		8 week	7 week after operation	Radial-arm maze	(16)
	SAMP8	10 month	10 day after operation	Morris water maze	(22, 24)
		6 month, 10 month	10 day after operation	Morris water maze	(23)
		5 month, 9 month	1 week after operation	Morris water maze	(26)
Reduction of crown	SAMP8	10 month	10 day after operation	Morris water maze	(21, 25)
Soft-diet feeding	Wistar	3 week	7 week	Passive avoidance	(20)
	B6C3Fe-a/a	20 day	360 day	Morris water maze	(17)
	SAMR1, SAMP8	3 week	6 month	Radial-arm maze	(18)
Bite rise	SAMP8	9 month	8 day after operation	Morris water maze	(118–120)
		9 month	8 day, 15 day, 22 day after operation	Morris water maze	(117)

spatial learning ability at between 6 and 12 months (17, 18). The molarless condition also affects fear-conditioned passive avoidance learning (19, 20), which involves both the hippocampus and the amygdala, suggesting that reduced mastication suppresses the overall learning function of the hippocampus.

For the above young adult animals, a molarless period greater than 2 months is required for them to develop deficits in spatial learning. However, aged animals rapidly lose their learning ability after their molars have been extracted. Senescence-accelerated SAMP8 mice, whose median life span is 13 months, showed learning impairment 7–10 days after extraction or reduction of molar teeth if extraction or reduction took place after 5 months of age (21–26), while learning impairment was not observed in extraction experiments where the surgery took place at 3 months of age (21, 23, 26). These results suggest that regular sensory stimulation from the masticatory organ is critical to maintaining the learning and memory functions in the senile hippocampus. Of clinical importance is the reversibility of the hippocampal deficit that is induced by the molarless state; restoring the missing molars with artificial crowns results in recovery of learning ability even in the aged mice (25).

Reduced mastication also affects the morphology and the function of hippocampal neurons (Table 2), which are essential in the learning processes. Reduced

Table 2. Organic and functional deficits in model animals of reduced or abnormal masticatory input

Type of treatment	Strain	Type of deficit (decrease in amount, unless otherwise stated)	Site	Reference
Molar extraction	Wistar	ACh responsiveness	Parietal cortex	(15)
		ACh synthesis	Cortex, hippocampus	(19)
		trkB-mRNA expression	Hippocampal CA1	(16)
		Density of neurons	Hippocampal CA1	(16)
	C57BL/6	Cell proliferation	Hippocampal DG	(30)
	SAMP8	Astroglial responsiveness	Hippocampal CA1	(22)
		Increased density and hypertrophy of glial fibrillary acidic protein (GFAP)-labelled astroglia	Hippocampal CA1	(23)
		Number of spines	Hippocampal CA1	(26)
		Number of ChAT-positive neurons	Diagonal band/medial septal nucleus	(28)
		ACh responsiveness, ChAT activity	Hippocampus	(28)
Reduction of crown	Wistar	Number of ChAT-positive neurons	Diagonal band/medial septal nucleus	(27)
		ACh concentration	Hippocampus	(27)
	SAMP8	Number of neurons	Hippocampal CA1	(21)
		Fos expression induced by spatial learning	Hippocampal CA1	(25)
Soft-diet feeding	Wistar	DA responsiveness	Hippocampus	(20)
		Cell proliferation	Hippocampal DG	(29)
	B6C3Fe-a/a	Number of neurons	Hippocampal CA1 and CA3	(17)
	SAMR1, SAMP8	Amount of synaptophysin	Cortex	(18)
		Synaptic formation	Hippocampus and parietal cortex	(18)
Bite rise	SAMP8	Expressions of GR and GR mRNA	Hippocampus	(118, 120)
		Number of neurons	Hippocampal CA3	(117, 119, 120)
		Increased corticosterone level	Plasma	(119, 120)
		Fos expression induced by spatial learning	Hippocampus	(120)
		Increased DA level	Frontal cortex and hypothalamus	(121)
		Increased NA level	Frontal cortex	(121)
			Hypothalamus	(122)

mastication affects the *Cornu Ammonis* (CA) 1 and CA3 subfields in the hippocampus, where spatial encoding is processed, in several ways. It decreases the number of pyramidal neurons (16, 17, 21) and spines (26), and it decreases the amount of synaptic formation (18) and neurotrophic receptor expression (16). The function of the affected neurons is also impaired, which show suppressed c-Fos expression after spatial learning (25), reduced acetylcholine synthesis (19, 27, 28), and decreased release of acetylcholine (15, 28) and dopamine (20) in response to extracellular stimulation. Reduced mastication not only impairs spatial learning, but it also suppresses cell proliferation in the dentate gyrus (DG) as well (29, 30).

The hypertrophy of astrocytes can be demonstrated by labelling them with glial fibrillary acidic protein (GFAP). Such hypertrophy shows that glial cells are inflamed and degenerating. With reduced mastication, hypertrophied astrocytes are evident in the CA1 subfield (22, 23), implying that the reduced mastication increases the production of cytokines such as interleukins from the microglia to cause the above morphological and functional degeneration of hippocampal astrocytes and neurons. Interestingly, such hypersecretion of interleukins and the consequent inflammatory responses in the astrocytes and neurons are frequently observed in the senile hippocampus, and it is a possible cause of age-related cognitive impairment (31, 32). This evidence, taken together with the evidence that the astrocytes release various factors that modulate synaptic transmission as well as neuronal morphology to maintain learning and memory function (33), suggests that reduced mastication suppresses the protection and support provided by glial cells and hastens the ageing process of the hippocampal neurons.

Generally, the more the hippocampus processes peripheral sensory inputs received from the surrounding environment, the better hippocampal function is maintained. Indeed, increased sensory stimulation through environmental enrichment or physical exercises has been shown to improve hippocampal cognitive function (34, 35). The authors hypothesise that regular sensory input from the masticatory organ is essential to maintain cognitive functions, especially in the senile hippocampus. Reduced mastication at a young age may not affect hippocampal function in the short term, as the hippocampus receives rich sensory inputs continuously through vigorous locomotor activity and well-working peripheral sensory organs to maintain its function. In old age, however, reduced locomotor activity (36, 37) and senesced peripheral organs do not provide sufficient sensory input (38) to maintain the hippocampal function, leading to a gradual decline (39, 40). At this stage, elimination of sensory input from the masticatory organ may accelerate the senile process in the hippocampus. As the hippocampus is one of the target brain regions of stress hormone corticosteroids regulating its negative feedback system (41), the attenuated hippocampal function may further cause a lack of control in the secretion of corticosteroids. Indeed, the extraction of molar teeth in aged mice increases plasma corticosterone levels, which is associated with deterioration of hippocampal neurons, glial cells and spatial memory (22–24). As it is well established that excessive corticosterone suppresses hippocampal-dependent learning and memory (41, 42), an increase in circulating corticosterone levels following reduced mastication may be a reason for declining spatial memory in the molarless aged animals.

Reduced mastication might alter cognitive function via malnutrition especially in case of extraction. Loss of functional teeth for months impairs digestive and absorptive function by altering the maxillomandibular relationship (43, 44) and by reducing secretion of saliva and gastric acid (45, 46), even though having teeth extracted does not cause the rodents to consume less food (13). However, recent evidence suggests that moderately restricting calories acts to protect against age-related hippocampal deficits (47–50). Likewise in human studies, loss of teeth or disuse of dentures was the factor inducing malnutrition; however, these did not account for the association with cognitive impairment (11). Malnutrition therefore may not be a major cause of impaired hippocampal function associated with reduced mastication. The effect of reduced salivary secretion on hippocampal function remains to be shown, because some evidence suggests the existence of salivary-derived neurotrophic factors (51, 52) that maintain learning ability in the hippocampus (53, 54, and see the section 'Humoral connections').

At the current stage, we cannot determine whether motor events themselves or the loss of sensory inputs to the central nervous system (CNS) during mastication is critical to suppress hippocampal function in the rodents with reduced mastication, as loss of hippocampal memory still occurs with ablation of the unilateral masseteric nerve as well as in cases of molar extraction and reduction of crowns (Onozuka *et al.*, unpublished

observation). Considering that in the oral cavity there is an enormous number of periodontal mechanosensitive neuron terminals and Merkel cells that are activated during mastication (55), reduced mastication and the consequent hypofunction of the mechanoreceptors likely reduce the number of working mechanoreceptors (13, 56). The accumulating evidence suggests that sensory feedback from the oral cavity plays an essential role in maintaining cognitive function in the hippocampus.

Note that the hippocampus receives sensory feedback from all locomotor activity and that consequently there are many confounding factors that must be adequately characterised before we can conclude that there is a direct relationship between masticatory input and the cognitive function of the hippocampus. The specificity of reduced mastication compared to other types of reduced sensory stimuli on the function of the senile hippocampus should be clarified. Further studies combining reduced mastication with other modulators of hippocampal function, such as environmental enrichment or physical exercise, may confirm the impact of reduced mastication on the senile hippocampus.

Does masticatory stimulation facilitate human cognitive function?

If mastication has a direct link to the maintenance of hippocampal function, active chewing may enhance learning and memory. Indeed, in several psychological studies using human subjects, it has been shown that chewing (57–61) or even sucking (58) a piece of sugar-free, spearmint flavoured, chewing gum improved the score of immediate or delayed word recall, the sensitivity index of the spatial working-memory task, and the reaction time of the numeric working-memory task. Together with the results of PET imaging showing chewing increased blood flow in various cortical and cerebellar regions (5), they suggest that chewing increases the availability of blood-borne glucose, thereby improving cognitive performance (62). Stephens and Tunney (59) examined this hypothesis using a within-subjects design where subjects were tested under the combined condition of either chewing gum or sucking a mint tablet after consuming either glucose drink or water. Their results confirmed that chewing gum and the consumption of glucose had additive effects on improving the scores of several working memory tasks. Wilkinson *et al.* (57) also reported that chewing increases heart rate, suggesting enhanced sympathetic activity to increase blood glucose level and/or arousal level during a cognitive task. However, none of these studies includes a direct observation of blood glucose levels and its relationship with cognitive performance. Whether or not gum chewing improves human cognitive function remains an open discussion. Researchers at other laboratories claim that, although gum chewing helps to sustain attention and arousal, it has no effect on learning and memory abilities (63–66) or even worsens them (67).

Recent studies using functional brain imaging support the hypothesis that mastication enhances brain function, particularly the performance of sustained cognitive tasks. Hirano *et al.* (9) used fMRI to examine mastication-induced change in brain activity during a working-memory task. Subjects experienced three consecutive sessions of a delayed-match task in which they chewed a piece of gum without any taste or smell between the second and the third sessions. Gum chewing restored the accuracy subjects had in doing the task to the same level as in the first trial, even though the accuracy of the subjects on the second trial had decreased significantly compared to the first trial. The increased proficiency of task performance was associated with increased intensity of the BOLD signal in the dorsolateral PFC, a brain region associated with attentional selection during working-memory acquisition. As other physical activities performed to increase cerebral blood flow, such as a hand exercise, failed to prevent rundown of task performance in the continuous acquisition of working-memory trials (68), there may exist some mastication-specific neuronal mechanism contributing to the maintenance or the improvement in learning and memory functions. One possible mechanism involved in the effect of gum chewing is the maintenance of the concentration level via activation of reticular formation arousal centres through masticatory sensory input. Indeed, gum chewing increased the mean frequency of the spontaneous alpha wave activity, showing increased arousal level (69). Moreover, in the attention task of an auditory oddball paradigm, gum chewing reduces the reaction time, as well as the duration of the event-related potential for the target stimuli (70). Takada *et al.* (71) reported a fronto-parietal network that is activated by actual gum chewing, but not by mechanical jaw movement without gum, suggesting a mastication-specific neuronal network that accelerates cognitive processing.

The authors speculate that the difference in experimental results about the effect of chewing on cognitive function is, at least in part, because of the subjects, which were limited to young adult to middle age subjects in the above studies. The reduced mastication studies in rodents suggest that the effect of masticatory stimulation on accelerating the cognitive process is small in the young, highly functioning hippocampus. Gum chewing may be effective on the aged hippocampus by supplying additional sensory inputs that serve to improve hippocampal function, which deteriorates with ageing. Indeed, Onozuka *et al.* (8) reported that active gum chewing improved the performance of memory recall in elderly (60–76 years) subjects, but did not show an effect in the young adult (19–26 years) subjects. Furthermore, the improved memory recall was associated with an increased volume of the activated region in the hippocampus during encoding. Behavioural and neurophysiological investigations, similar to those already performed with young healthy subjects, should be done with elderly populations as well, to further characterise the ameliorative effect of mastication on cognitive function.

Execution of cognitive tasks requires coordinate activation of various cortical and subcortical regions that are connected with the hippocampus. The PFC is one of these cortical areas, and it plays an especially important role in learning arbitrary associations between sensory cues and determining voluntary actions to accomplish a task (72). As both animal and human studies indicate that the primary motor area for the face undergoes neuroplastic changes in association with oro-facial motor learning or an altered oral environment (73), mastication might modulate the PFC as well as the hippocampus to improve cognitive function. Indeed, gum chewing facilitates both of these brain regions during working memory task in young subjects (9). Even gum chewing alone, without a specific cognitive task, increases the intensity of the BOLD signal in the right PFC regardless of age (6, 7). However in aged subjects, this increase was four times larger than that seen in young subjects (7). Grady (74) reported that the augmented activation in the PFC and the hippocampus during memory acquisition was selectively associated with the aged subjects who preserved memory performance over 8 years of the experimental period, while their acquisition-related activity in the other brain regions showed longitudinal decrease. Together, these results suggest that mastication facilitates recruitment of the PFC and the hippocampus in the aged brain, compensating for the cognitive performance decline that accompanies ageing. The neuronal connections by which mastication selectively activates the PFC in the aged brain should be further elucidated.

Masticatory modulation of stress-impaired learning and memory

Mastication ameliorates stress perception in rodents

The hippocampus is sensitive to stress**,** as well as to the ageing process**,** and is one of the first regions to be structurally and functionally modified by severe and inescapable stress (75). Excessive or prolonged stress stimulates the hypothalamic–pituitary–adrenal (HPA) axis, causing the adrenal cortex to secrete corticosterone. The elevated concentration of corticosterone suppresses synaptic plasticity, the ability to change the electrical connectivity between neurons in the hippocampus, which is thought to be the cellular mechanism of learning and memory (76). Recently, we observed in rats that active chewing of a wooden stick during immobilisation stress ameliorates the stress-impaired synaptic plasticity (77, 78).

One mechanism that may affect this ameliorative effect is the inhibition of systemic stress responses by mastication, which has been shown in various psychological and physical types of stress stimuli such as immobilisation, novelty exposure and tail pinch (Table 3). First, mastication suppresses stress-related increases in core body temperature (79), blood pressure (79) and the level of plasma adrenaline (80), suggesting that mastication ameliorates the compromised functioning of the stress-activated sympathetic-adrenal-medullary system. Second, mastication during stress prevents immune activation of interleukin-1β and interleukin-6 (79). These systemic inhibitions of stress responses contribute to preventing development of stress ulcers in the stomach (80–83). Third, and most important, mastication suppresses the stress-activated expression of corticotropin releasing factor (CRF) (84) and c-Fos (85), the phosphorylation of extracellular signal-regulated kinases 1 and 2 (86), oxidative stress (87), and the production of nitric oxide (88, 89) in the paraventricular nucleus (PVN) of the hypothalamus, at which aversive sensory stimuli converge to trigger the HPA axis responses. The reduced expression of the above brain markers correlates well with the decrease

Table 3. Masticatory alteration of stress-related physiological responses

Parameter	Stress type	Reaction to stress	Effect of mastication	Reference
Brain markers				
BDNF	IMO	−	Suppression	(92)
Cl^- uptake	RES	−	Suppression	(100)
CRF	IMO	+	Suppression	(84)
DA	Novelty	+	Suppression	(101)
	Tail pinch	+	Suppression	(102)
Fos	IMO	+	Suppression	(85)
	Novelty	+	Acceleration in right mPFC, suppression in right CeA	(100)
Free radicals	IMO	+	Suppression	(87)
NA	IMO	+	Suppression	(83, 91)
	Cold + IMO	+	Suppression	(82)
NO	IMO	+	Suppression	(88, 89)
NT-3	IMO	−	Suppression	(92)
pERK	IMO	+	Suppression	(86)
Blood levels				
ACTH	Shock-induced fighting	+	Suppression	(94)
	IMO	+	Suppression	(77, 92)
Adrenaline	IMO	+	Suppression	(80)
CORT	Novelty	+	Suppression	(90)
	IMO	+	Suppression	(91, 92)
Cortisol	RES	+	Suppression	(93)
	IMO	+	Suppression	(80)
IL-1β	IMO	+	Suppression	(79)
IL-6	IMO	+	Suppression	(79)
Leptin	IMO	+	Suppression	(79)
Neutrophils	IMO	+	Suppression	(80)
TSH	IMO	−	Suppression	(79)
Blood pressure	IMO	+	Suppression	(79)
Body temperature	IMO	+	Suppression	(79)
Spleen weight	IMO	−	Suppression	(80)
Stomach ulcer	IMO	+	Suppression	(80, 83)
	Cold + IMO	+	Suppression	(81, 82)
Thymus weight	IMO	−	Suppression	(80)

IMO, immobilisation (with four limbs fixed in supine position); RES, restraint; CRF, corticotropin releasing factor; ACTH, adrenocorticotropic hormone.

in circulating corticosterone (90–92), cortisol (80, 93) and their secretagogue, adrenocorticotropic hormone (ACTH) (77, 92, 94). The functions of the HPA axis and the masticatory apparatus might be reciprocally regulated, because the hyperactivation of the HPA axis has been implicated as a cause of temporomandibular disorders and oro-facial pain (95, 96).

Another possible mechanism of rescuing hippocampal function is the increased brain histamine (HA) by mastication, which facilitates N-methyl-D-aspartate receptor function to restore stress-attenuated synaptic plasticity in the hippocampal neurons. Fujise *et al.* (97) and Sakata *et al.* (98) reported that activation of the mesencephalic trigeminal nucleus (Me5) by mastication stimulates histaminergic neurons in the tuberomammillary nuclei (TMN) in the posterior hypothalamus, increasing extracellular concentration of HA in the lateral hypothalamus to control satiety. As the electrical stimulation of the TMN also facilitates extracellular HA in the hippocampus (99), a mastication-induced increase in

the HA level may restore the stress-attenuated hippocampal memory processes. Our recent *in vitro* study shows that the blockade of histamine H1 receptor antagonises the effect of chewing on synaptic plasticity (78), suggesting that H1 receptors mediate the amelioration of stress-attenuated hippocampal memory in the chewing rats. Further examination using behavioural procedures, possibly combined with the inhibition of systemic stress responses such as the production of glucocorticoid receptor antagonists, would confirm the contribution of the histaminergic system. The varieties of physiological changes that are caused by mastication suggest that multiple neuronal mechanisms, including both mastication-specific and non-specific mechanisms, mediate the ameliorative effect of mastication on hippocampal function in a complex manner.

The benefits that mastication confers on stress perception are also apparent in rodents. Biting attack during immobilisation stress prevents stress-induced noradrenaline release in the amygdala, the limbic area that processes fear and other forms of aversive information (82, 83, 91). Using Fos-immunoreactivity (Fos-IR) as a measure of neuronal activation, Stalnaker *et al.* (100) found that the chewing of inedible objects during novelty-exposure stress suppressed Fos-IR expression in the right central nucleus of the amygdala (CeA) and increased expression in the right medial prefrontal cortex (mPFC), in which they have previously shown chewing-attenuated dopaminergic response to stress (101). As the mPFC also plays a pivotal role in cognitive and affective processes and as its dopaminergic neurotransmission is regulated by the CeA, these results suggest that chewing suppresses neuronal transmission in the amygdala to further attenuate stress-related dopamine release in the mPFC. Chewing during tail-pinch stress has also been reported to quickly return the nigrostriatal dopaminergic activity to the resting level (102). These results clearly indicate that mastication modulates catecholaminergic neurotransmission in the brain areas that regulate the perception of stress, possibly altering affective states, such as fear, and behaviour, such as aggression. Indeed, chewing during acute restraint decreases anxiogenic behaviour in the elevated plus-maze after stress exposure (103). A question that remains open at the present time is whether or not the alteration of stress perception by active mastication affects aversive learning, which involves both the hippocampus and the amygdala.

Mastication as an active strategy by which humans cope with stress

The active mastication in rodents exposed to stress reduces physiological stress responses, suggesting mastication as an active strategy by which to cope with stressful conditions. Ruf *et al.* (104) reported increased activation of masticatory muscles during chewing and biting in dental students under emotional stress (mid-term examination). Moreover, in accordance with the results from animal experiments, mastication during stressful conditions in humans has also been shown to attenuate stress responses. Using a multi-tasking procedure to elicit laboratory stress, Scholey *et al.* (105) recently reported that gum chewing improved alertness and reduced state anxiety, stress, and salivary cortisol. In addition, for subjects who are subjected to a loud unpleasant sound, simulated bruxing suppresses the production of salivary chromogranin A (106), a marker of mental stress that reflects sympathetic activity (107, 108). Chewing or light clenching immediately after stress is applied effectively and quickly returns salivary cortisol to the resting level (109). Zibell and Madansky (110) used the State-Trait Anxiety Inventory to further investigate the effect of gum chewing on quantitative measures of everyday stress. Each participant either chewed gum or abstained from chewing (except for normal mealtimes) for a number of sequential days, then switched to the opposite behaviour for the same number of days. They completed the inventory at the end of the each period. Particular stress-specific emotions such as 'not feeling relaxed' and 'feeling tense' were reported to have significantly increased when participants abstained from chewing gum and to have decreased when they chewed. Together, these results suggest that gum chewing reduces the perception of daily stress as well as experimental stress produced in the laboratory. Mastication possibly reduces the risk of senile cognitive deficit by reducing stress, because an increase in the cortisol level in elderly persons accompanies cognitive impairment (111, 112).

The authors further propose that the increase in the serotonin level that is produced by the rhythmic movement of chewing (113) plays a role in a neuronal mechanism by which mastication reduces stress perception. Chewing and other oral-buccal movements activate serotonin neurons in the dorsal raphe nucleus (114, 115). Serotonin receptors densely populate the hypothalamus as well as the hippocampus, and they

regulate the circulating corticosteroids (116). Moreover, selective serotonin reuptake inhibitors are typically used as antidepressants in the treatment of depression and anxiety disorders. The combined evidence suggests that mastication activates the serotonergic nervous system, which regulates both stress-induced corticosteroids and stress-related anxiety. Functional PET imaging of serotonin receptors is required to further elucidate the effect of mastication on the serotonergic neuronal system.

Occlusal disharmony disrupts learning and memory

Abnormal sensory input as a result of occlusal disharmony has been reported to suppress learning and memory ability as in the case of reduced mastication. Raising the bite by approximately 0.1 mm using dental adhesive significantly disrupts hippocampal-dependent spatial learning in aged SAMP8 mice. Such disruption had become observable in experimental mice within 8 days of the bite-altering procedure (117–120). In one experiment, a significant decrease in learning-induced c-Fos expression in the hippocampal neurons was associated with bite-raising (120). This occlusal disharmony has been thought to represent a chronic stress, in that the longer the occlusal disharmony continued, the worse their learning ability became (117).

Experimental occlusal disharmony in rodents and in monkeys, produced by applying adhesive to the molar teeth (117–120), attaching acrylic caps at the incisors (121–123), or inserting occlusal splints in the maxilla (124, 125), quickly increases plasma corticosterone (122–124) and urine cortisol (124, 125) as acute stress responses. These stress responses persists for weeks (119, 120, 124, 125). Budtz-Jørgensen (125) showed that the increased cortisol levels return to basal values when the occlusal disharmony is returned to the normal state. These results suggest that occlusal disharmony induces chronic activation of the HPA axis, and increase in corticosterone that follows further suppresses the learning ability in the hippocampus. Indeed, blocking corticosterone synthesis by administrating metyrapone prevented learning deficits after the bite was raised in mice (120). Furthermore, the hippocampus of the rodents with occlusal disharmony shows a significant decrease in glucocorticoid receptors in the CA1 subfield and DG (118, 120), resulting in a prolonged corticosterone response to the subsequent new stress (123). These results support the idea that a sustained increase in plasma corticosterone levels by occlusal disharmony impairs the negative feedback system of the HPA axis in the hippocampus. The suppressed negative feedback system of the HPA axis further enhances the secretion of corticosterone, which suppresses neuronal excitability or leads to neuron death (41). The bite-raised condition has been shown to decrease the number of neurons in the hippocampal CA3 subfield (117, 119, 120) in a duration-dependent manner (117).

Occlusal disharmony also affects stress markers other than corticosteroids, especially monoaminergic responses. Attachment of incisor caps elevated dopamine and noradrenaline levels in the hypothalamus (121, 122) and disrupted the circadian rhythm of noradrenaline release (122). While the direct effect that monoamines, increased by occlusal disharmony, have on learning and memory ability has not been examined in detail, both dopaminergic and noradrenergic systems innervate with the hippocampus, possibly affecting the hippocampal functions. Another indirect pathway by which monoamines affect hippocampal functions may be that increased monoamines in the hypothalamus accelerate the stress response of the HPA axis to secrete more corticosteroids.

Using custom-made splints that place the mandible into either a retrusive or a normal position, Otsuka *et al.* (126) studied changes in brain activity in human subjects with experimental occlusal disharmony. Regardless of the position of the mandible, clenching with splints activated four brain regions: the insula, the premotor, prefrontal and sensorimotor cortices. Additional neuronal activity was found in the amygdala and the anterior cingulate cortex when they clench in a retrusive position of the mandible, with a significant increase in subjective discomfort scores. Both regions process aversive and nociceptive information, and they are activated by a variety of stressors such as cold stress and aversive visual stimuli (127–129). These results suggest that occlusal disharmony is a stressor in human subjects as well, even though their experimental design is an acute occlusal disharmony in which subjects use splints only during the recording of data.

Clearly, occlusal disharmony is not an acute stress, but rather a chronic stress persisting for weeks. Enhanced secretion of corticosteroids or other stress-activated neuronal responses by occlusal disharmony may trigger cognitive impairments, especially in the

elderly (111, 112). Special care should be taken in clinical treatment such as in denture design. Mastication with normal occlusion may maintain or preserve cognitive functions of learning and memory in the elderly, but that with malocclusion may adversely impair those functions.

Possible pathways from the oral cavity to the hippocampus

The details of underlying pathways from the oral cavity to the hippocampus are not fully clarified, although mastication and malocclusion clearly affect the CNS as discussed earlier. To date, direct interactions between these two areas have not been demonstrated. However, there are two possible indirect pathways: neuronal and humoral. It is important to note that brain systems are interconnected with complexity. Therefore, when one system is affected, others are likely to be affected as well.

Neuronal connections

The trigeminal sensory system conducts sensory information from the oral cavity to the CNS. Trigeminal primary sensory neurons have unique profiles compared with other primary sensory neurons. The trigeminal primary sensory somata are localised not only in the trigeminal ganglion, which is equivalent to the spinal ganglia, but also in the mesencephalic trigeminal nucleus located within the CNS. Proprioceptive and nociceptive sensation is transmitted to the CNS through these somata in the trigeminal ganglion and mesencephalic trigeminal nucleus. In general, central axons of the trigeminal ganglion reach the trigeminal sensory nuclei, the spinal and principal sensory nuclei of the trigeminal nerve (130), and those of mesencephalic trigeminal neurons terminate on the supra- and intertrigeminal regions, and trigeminal motor nuclei, which are responsible for voluntary mastication (Fig. 1a). In addition, these mesencephalic primary sensory neurons also project their afferent fibres to the trigeminal sensory nuclei, the cerebellum, the solitary and hypoglossal motor nuclei, and the brainstem reticular formation (131, 132). The latter reticular formation is believed to regulate or control sensory input to the higher brain centres as an ascending reticular activating system. The reticular formation and the ascending reticular activating system are necessary for arousal of the brain for attention, perception and conscious learning. Therefore, sensation of the oral cavity may influence the maintenance of sufficient attention and perception for learning (Fig. 1b).

Sensory information from secondary sensory neurons located in the trigeminal sensory nuclei reaches the contralateral thalamus (mainly to the ventral posterior thalamic nucleus and sparsely to the posterior thalamic nuclear group and medial thalamic nuclei). In addition to these projections, these secondary sensory neurons also send branches to the reticular formation and the hypothalamus (133, 134). The hypothalamus is known to control the pituitary gland by releasing various releasing and inhibiting factors targeting the pituitary hormones, such as CRF. Corticotropin releasing factor stimulates the pituitary gland through the pituitary portal system as a humoral factor and accelerates the release of ACTH. Adrenocorticotropic hormone leads to the secretion of glucocorticoids from the adrenal cortex. The glucocorticoid binds to the glucocorticoid receptors in the hippocampus, which triggers the negative feedback system of the HPA axis (Fig. 1c).

Trigeminal sensory input is also delivered to the hippocampus via cortical connections. Nerve fibres bearing oral cavity information from the ventral posterior thalamic nucleus terminate on the ipsilateral somatosensory cortex (Fig. 1a). The somatosensory cortex receives input from the contralateral homonym cortex through the corpus callosum and the ipsilateral primary motor cortex. The neurons of the somatosensory cortex project their axons to the ipsilateral ventral posterior thalamic nucleus, inferior parietal cortex and the somatosensory association area. The latter association area has reciprocal projection with the entorhinal cortex. The entorhinal cortex is a major afferent source to the DG of the hippocampal formation. Thus, sensations in the oral cavity may influence hippocampal functions through the thalamus and cortices (Fig. 1d).

The hippocampal formation is composed of the hippocampus, the DG and the subiculum. Within the hippocampal formation, there are well-known main pathways, including mossy fibres from the DG to the hippocampal CA3 subfield, the Schaffer collateral pathway from the CA3 to the hippocampal CA1 subfield, projections from the CA1 to the subiculum, and perforant fibres from the subiculum to the DG. In addition to these circuits, the hippocampal formation receives projections of cholinergic fibres from the septal nucleus, noradrenergic fibres from the locus coeruleus,

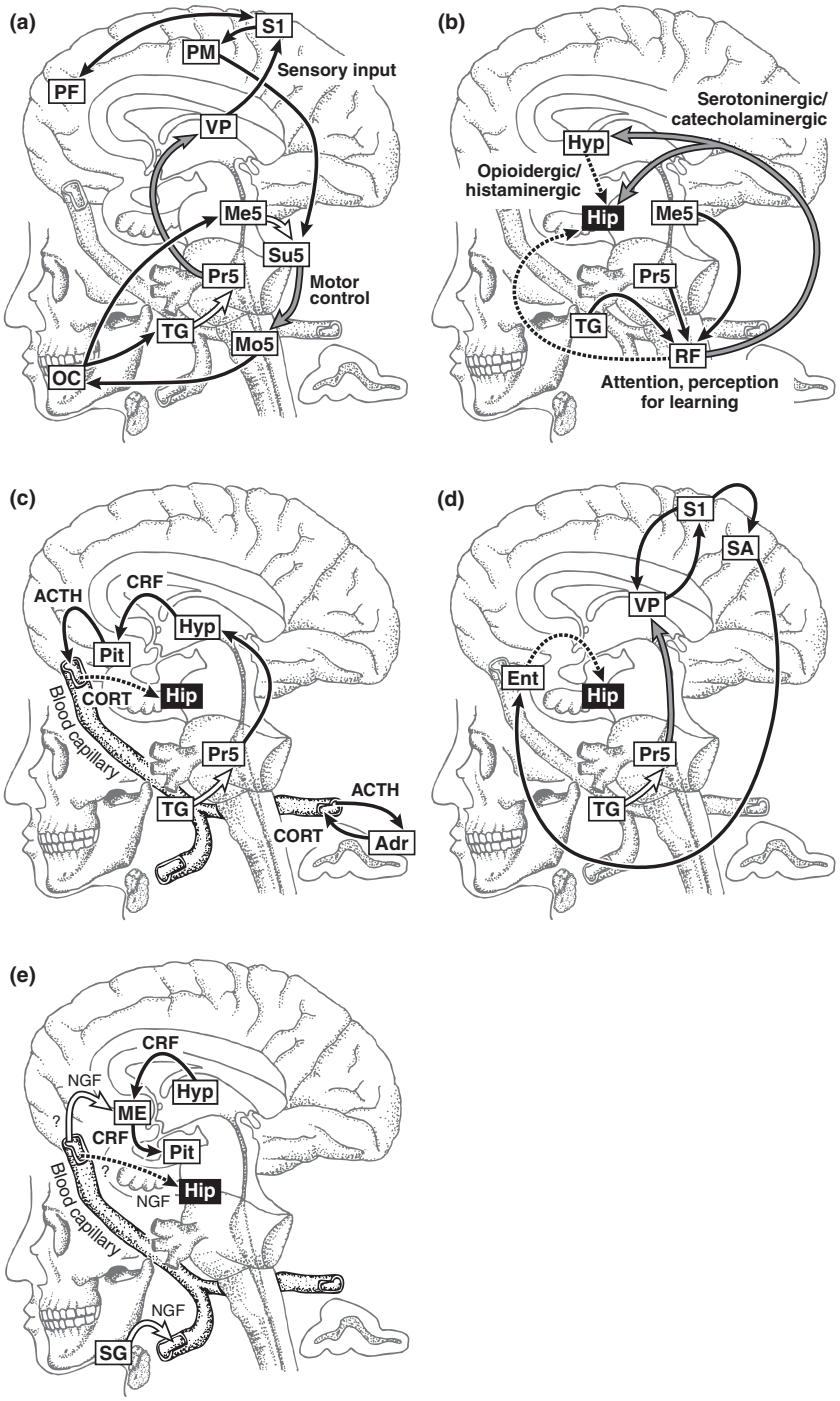

Fig. 1. Possible neuronal and humoral pathways from the oral cavity to the hippocampus. Arrows indicate neuronal or humoral connections. (a) Major signalling pathways of somatosensory stimuli from the oral cavity. (b) Modulation of the hippocampus via reticular formation. (c) Modulation of the hippocampus via HPA axis activation. (d) Modulation of the hippocampus via cortical sensory pathway. (e) Modulation of the hippocampus via saliva-derived NGF. Note that only focussed pathways are represented. ACTH, adrenocorticotropic hormone; Adr, adrenal cortex; CORT, corticosteroids; CRF, corticotropin releasing factor; Ent, entorhinal cortex; Hip, hippocampus; Hyp, hypothalamus; PF, prefrontal cortex; PM, premotor cortex; Me5, mesencephalic trigeminal nucleus; ME, median eminence; Mo5, trigeminal motor nucleus; NGF, nerve growth factor; OC, oral cavity; Pit, pituitary; Pr5, principal sensory trigeminal nucleus; RF, reticular formation; S1, primary somatosensory cortex; SA, somatosensory association area; Su5, supratrigeminal nucleus; SG, salivary gland; TG, trigeminal ganglion; VP, ventral posterior thalamic nucleus.

serotonergic fibres from the raphe nuclei and dopaminergic fibres from the ventral tegmental area. The latter three areas are a part of the ascending reticular activating system. Therefore, it is possible that mastication and malocclusion affect the hippocampus via the reticular formation even without involvement of the hypothalamus (Fig. 1b).

Finally, the hypothalamus receives input from the reticular formation and projects to the hippocampal formation directly as opioidergic and histaminergic fibres (Fig. 1b). As a result, the sensations from the oral cavity may influence hippocampal functions through the hypothalamus without humoral control via activation of the pituitary gland.

Humoral connections

In addition to the humoral pathway in the HPA axis, various growth factors, such as nerve growth factor (NGF) and epidermal growth factor, are produced in the salivary glands (135–137), and mastication increases their secretion (138). Malocclusion may change the levels of these growth factor secretions. Although NGF is thought to not cross the blood-brain barrier (139), subcutaneous injection of NGF increases brain noradrenaline levels (140). Interestingly, the permeability of NGF in the hippocampus, though much lower than insulin, is higher than those of other brain areas such as the cortex and brainstem, suggesting the presence of an NGF-specific delivery mechanism in the hippocampus (141).

Another possibility is that NGF originating the salivary glands affects the CNS. The median eminence, where CRF-containing fibres are localised (142), lacks a blood-brain barrier. If the CRF fibres have NGF receptors, NGF from the salivary glands may interfere with the HPA axis at the level of the median eminence. In fact, the presence of NGF receptors in the median eminence has been reported (143), although it is not clear whether these receptors belong to CRF fibres in the median eminence. In any case, we cannot exclude a possible connection between the oral cavity and the hippocampus through the salivary glands (Fig. 1e).

Therefore, the effects of mastication and malocclusion on the CNS may not be attributable to a single pathway, but to the multiple pathways discussed earlier.

Conclusion

Accumulating evidence suggests that mastication is effective in sending an enormous amount of sensory information to the brain and in maintaining learning and memory functions of the hippocampus. The ameliorative effect of mastication on cognitive function may be negligible in the young, highly functioning hippocampus, but it becomes evident in the hippocampus whose function is attenuated by ageing or by stress inducement. Of particular interest is the mastication-induced modulation of the HPA axis controlling stress hormones. Direct and indirect neuronal pathways by which mastication interferes with the HPA axis should be clarified in future studies. As occlusal disharmony as well as reduced mastication are also possible stressors attenuating hippocampal function, maintaining normal occlusion and preserving masticatory function as long as possible during the whole life span may potently contribute to the general health from the standpoint of dentistry. At the present time, more concrete evidence is available from animal experiments than from human experiments, possibly because we have much less control over other some of the variables that affect cognitive function besides mastication. However, a number of the scientific papers we have reviewed here clearly indicate the significant correlation between mastication and cognitive function in humans. Further longitudinal work is needed to confirm a causal relationship between occlusion and brain function.

Acknowledgment

The Ministry of Education, Culture, Sports, Science and Technology (MEXT) supported this work with KAKENHI 21791815, KAKENHI 21390562, and an Open Research Center subsidy for the Research Center of Brain and Oral Science, Kanagawa Dental College.

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