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Relationship between the Early Toothless Condition and Hippocampal Functional Morphology

Mitsuo Iinuma[1*], Hiroko Kondo[1], Minori Kurahashi[1], Mika Ohnishi[1], Yasuo Tamura[1], Huayue Chen[2] and Kin-ya Kubo[3]

[1]*Department of Pediatric Dentistry, Division of Oral Structure, Function and Development, Asahi University, School of Dentistry, Japan*

[2]*Department of Anatomy, Gifu University Graduate School of Medicine, Japan*

[3]*Seijoh University Graduate School of Health Care Studies, 2-172 Fukinodai, Tokai, Aichi, 476-8588, Japan*

[*]**Corresponding author**: Mitsuo Iinuma, Department of Pediatric Dentistry, Asahi University, School of Dentistry, Japan, Tel: (+81)58-329-1130; Fax: (+81)58-329-1493; E-mail: iinuma@dent.asahi-u.ac.jp

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Abstract

Hippocampus is important for learning and memory. This article reviews the recent progress of the relationship between the toothless condition and the hippocampal functional morphology. Tooth loss early in life was generated by extracting the upper molars shortly after tooth eruption in mice or rat. Morphological and physiological studies showed that early toothlessness, acting as a chronic stress, induced constantly elevated levels of corticosterone, leading to morphological and molecular alterations in hippocampus, accompanied by deficits in spatial learning and memory. The early toothlessness may be a risk factor of cognitive impairment. Adequate dental treatments such as denture or dental implants for defective part of teeth are considered to be important for maintaining the hippocampal functions. The possible mechanism of the hippocampal alterations induced by early toothless condition is also discussed.

Keywords: Early tooth loss; Chronic stress: Hippocampus; Spatial memory; Brain derived neurotrophic factor; TrkB

Introduction

With the aging of the population, the burden of dementia is rapidly expanding. Worldwide, millions of people are suffering from dementia and this number is expected to increase sustainably. Dementia has become an increasingly important health and socioeconomic issues [1]. It has been demonstrated that mastication is of great importance not only for food intake, but also for psychological, physical, and cognitive function [2]. Teeth, especially molars play an important role for maintaining masticatory function. The systemic effect of tooth loss is suggested to be an epidemiologic risk factor for dementia, physical and mental impairment, and mortality [3]. People with cognitive impairment have more oral health problem, including lingual ulcers, mucosal hyperplasia, stomatitis, xerostomia, poorer periodontal condition and more coronal and root caries [4]. The physical activity and masticatory function are related to quality of life (QOL) [5].

The repeated or continuous stress, such as restraint stress, induces the spatial cognitive impairments associated with multiple morphological and molecular alterations in rodent hippocampus. Prolonged exposure to stress has been shown to promote dendritic atrophy, diminish cell proliferation, and impair synaptic plasticity of the hippocampal neurons in mice and rats [6-13]. Recent studies showed that chronic stress produced a downregulation of memory-related signaling pathways and genes in the hippocampal neurons, including brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin-related kinase B (TrkB) [14-19]. These findings indicate that the toothless condition in aged mice causes serious behavioral and morphologic changes in the hippocampus via chronic stress. New evidence suggests that long-lasting toothless condition severely impairs the hippocampal function, leading to learning deficits. The present paper summarizes the influence of the early tooth loss on morphology and function of the hippocampus.

Early Toothlessness and Chronic Stress

It was reported that there were two kinds of animal models for dysfunctional mastication, the molarless by extracting the upper molar teeth on both sides [8-11] and soft-diet feeding [20,21]. Impaired masticatory ability due to tooth loss affects the functional structure of the hippocampus and the cognitive function. Permanent loss of teeth decreases the somatosensory stimuli from the oral cavity, inducing sustained increase of circulating corticosterone concentration. Several studies demonstrated that loss of molar teeth for a long period of time in rodents induces a chronic psychological stress [22-24]. Higher plasma corticosterone levels have been shown in animal as early as 10 days after molar extraction [8,23,25]. We extracted the bilateral maxillary molars at the age of 1 month in senescence accelerated mouse prone 8 (SAMP8) [26-29]. SAMP8 mice undergo normal maturation up to the age of 6 months, and then exhibit accelerated aging (median life span 12 months compared with 2 or 3 years for other strains). SAMP8 mice are a proposed experimental murine model for human senile dementia [30]. The plasma corticosterone level was measured 8 days (young), 4 months (mature), and 8 months (old) after tooth extraction [26]. The results showed that the plasma corticosterone level increased with age both in the control and toothless animals (Figure 1). There were no significant differences of the plasma corticosterone levels between the young control and the toothless mice. The plasma corticosterone level was significantly higher in the mature and old toothless mice than that of the age-matched controls. As the chronic stress causes a significant increase in the plasma corticosterone levels [8,23,25], we consider that early toothlessness may act as chronic stress in adult and aged SAMP8.

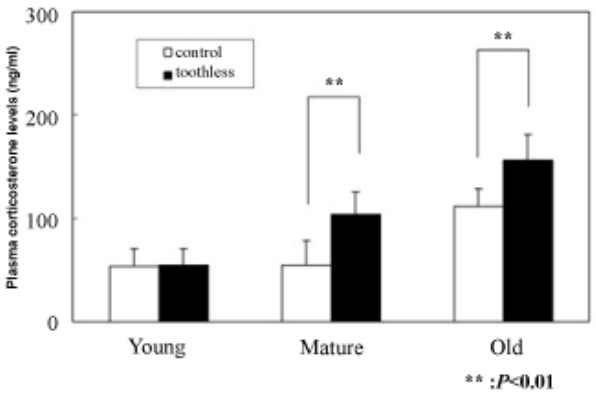

Figure 1: Effects of early toothless condition on plasma corticosterone levels. Each data is presented as mean ± SE (n=5). The plasma corticosterone level increased with age both in the control and toothless animals. In the adult and aged toothless mice, the plasma corticosterone level was significantly higher than that of the age-matched controls [33]

Early Toothlessness and Spatial Cognitive Function

Hippocampus plays a crucial role in cognitive function. Morris water maze test is conducted to evaluate the short-term memory and spatial cognitive ability by measuring number of errors entering non-exists and the escape latency duration [26]. The result of Morris water maze test showed that the time required to reach the platform was significantly long with age in both control and toothless mice (Figure 2). The time to reach the platform in the adult and aged toothless mice were significantly longer than that of the age-matched controls, though there was no significant difference between the young toothless and control mice [26]. Similar results were obtained in toothless rats [15,22]. Open field test is carried out to investigate general locomotive activity in rodents. It was demonstrated that the toothless animals were indistinguishable from their control counterparts in locomotive activity [17,24,31]. These results are fairly consistent with the changes of the plasma corticosterone level. The similar learning deficits were also observed in the soft-diet feeding mice [20,21]. Mounting evidence suggests that hippocampal functions are particularly influenced by glucocorticoids [18]. We consider that early toothlessness may enhance the age-dependent deficits in the spatial cognitive ability via increased plasma corticosterone levels.

The cognitive deficits induced by early toothlessness might be attributed to the reduced activity of the sensorimotor pathways. A quantitative change in the afferent impulses from sensory receptors to the central nervous system may produce alter the neuroanatomical alterations in their pathways [31]. The moderate amount of prolonged physical training could promote axonal sprouting and synaptogenesis [32], and enhance the formation of neurons and their survival in the hippocampal formation [33]. In contrast, the tooth extraction or pulp extirpations caused degenerative changes in the trigeminal ganglion cell bodies of the primary sensory neurons innervating the teeth [34], and trans-synaptic degenerative changes in second-order neurons in the trigeminal spinal tract nucleus [35]. These findings supports the hypothesis that stress-induced release of corticosteron, causes changes in hippocampus, thereby influencing cognitive processing [11,31]. The toothless condition caused a reduction in the number of Fos-positive cells in the hippocampus linked to the learning ability [11], decreased the dendritic spine number in the hippocampal pyramidal cells [36-38], and enhanced an age-related decline in the septohippocampal cholinergic system [25]. Taken together, the morphological changes observed in the early toothlessness mice seem to be involved in the activity of sensorimotor pathways and/or chronic stress.

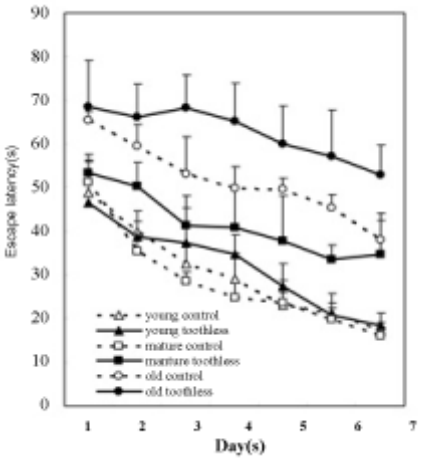

Figure 2: Effects of early toothless condition on spatial learning in the Morris water maze test. Each data point is presented as mean ± SE (n=5). Note the old toothless mice required a significantly longer time to reach the platform than age-matched controls [33]

Early Toothlessness and Hippocampal Morphology

Hippocampus can be divided into three main regions, i.e., CA1, CA3 and dentate gyrus (DG). Neurons derived from these regions are connected by synaptic pathways. In rodent model, prolonged exposure to stress or oral corticosterone administration has been shown to promote dendritic atrophy in hippocampus, particularly in CA3 region [7,36,37]. Treatment with corticosterone caused apical dendrites of CA3 pyramidal neurons to decrease in length and branching [**7**,36]. This pattern of apical dendritic atrophy was also observed in the tree shrew after chronic psychosocial stress [**39**]. Chronic immobilization stress also caused significant atrophy in basal dendrites, eliciting structural changes in both apical and basal dendrites [7,36]. Several chronic stress paradigms in rodents showed diminished the spine number and cell proliferation of hippocampal neurons [16,26,28,37]. We investigated effects of early toothless condition on neuron number in hippocampal CA1, CA3 and DG regions (Figure 3). The pyramidal neuron number in CA3 region of the mature and old toothless mice was significantly decreased, when compared with the age-matched controls. The reduction in neuron number of the hippocampus is closely related to age-related deterioration in learning and memory, which appears in patients with senile dementia [40,41] and experimental animals with impaired cognition [42,43].

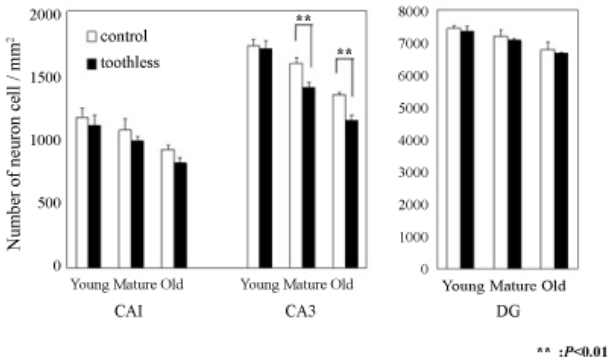

Figure 3: Effects of early toothless condition on neuron number in hippocampal CA1, CA3 and dentate gyrus. Each data is presented as mean ± SE (n=5). The neuron number in CA3 region of the mature and old toothless mice was significantly lower than that of age-matched controls [33]

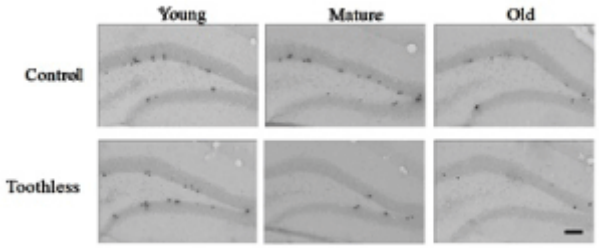

Figure 4A: Representative light micrographs showing BrdU-positive cells in hippocampal dentate gyrus

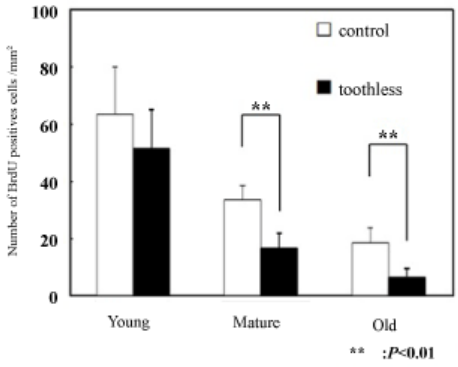

Figure 4B: Effects of early toothless condition on BrdU-positive cell number in dentate gyrus (B). Scale bars=500 μm. Each data is presented as mean±SD (n=5). As compared with the controls, the number of BrdU-positive cells in the mature and old toothless mice significantly decreased [35]

In most brain regions, neurons are produced only during a discrete period of development. However, in the DG region, granule neurons continue to be produced throughout adulthood in animals, including humans [44]. These neurons derive from a pool of precursor cells that reside within the DG region, and play a markedly significant role in retention of the hippocampal-mediated learning and memory [44,45]. The hippocampal granule neurons are susceptible to various hormonal and environmental stimuli. The plasma corticosterone levels play an important role in regulating the hippocampal neurogenesis [46]. Chronic stress experience is considered to inhibit the neurogenesis in the hippocampal DG region [28,47]. The neurogenesis in the DG region can be confirmed using *bromodeoxyuridine* (*BrdU*) labeling [28]. The number of BrdU-positive cells decreased with age both in the control and early toothless mice (Figure 4A and 4B). The number of BrdU-positive cells showed no significant differences between the young control and early toothless mice. However, the number of BrdU-positive cells in the mature and old toothless mice markedly decreased (Figures 4A and 4B). Several chronic stress paradigms, such as subordination stress in primates and social stress in rodents showed diminished cell proliferation in the DG rigion [48]. These results coincided with the changes in spatial learning ability. The suppression of the hippocampal neurogenesis was also observed in soft-diet feeding mice [20,21]. Based on the previous findings [13,31], it was suggested that learning deficits induced by early toothlessness have a positive correlation with the suppression of the hippocampal neurogenesis via the elevated corticosterone levels. Similar phenomena were also investigated in toothless transgenic mice [16].

High levels of corticosterone, as well as stressful conditions, may be correlated with accelerated damage and finally loss of hippocampal pyramidal neurons [16]. The pyramidal neurons in the hippocampus are important sites for corticosterone action as they contain high concentrations of corticosterone receptors [48-50]. The impairments of spatial learning ability induced by early toothlessness in adult and aged mice were explained at least in part by an impairment of hippocampal neurons, resulting from constantly elevated levels of corticosterone.

We investigated the influence of early toothless condition on GFAP-positive cells, a specific protein to astrocytes [27,29]. No significant differences were found in the number of GFAP-positive cells in the hippocampal CA1, CA3, and DG regions between the young control and toothless mice. As compared with the controls, the number of GFAP-positive cells in the CA3 region were significantly increased in the mature and old toothless mice (Figure 5), accompanied by the decrease of pyramidal neurons. GFAP is an intermediate filament protein, expressed by numerous cell types of the central nervous system, including astrocytes [51]. Glial proliferation is also observed as a physiological function during normal aging process. Following damage in the central nervous system, astrocytes shows identical features of gliosis. Damage or loss of neurons is associated with the increase in GFAP that is manifested morphologically by an increase in fibrous astrocytes [51]. Increased gliosis in the central nervous system, particularly in the hippocampus, is related to aging process and sustained stress [52]. The increase in GFAP-positive astrocytes observed in mature and old toothless mice is considered to compensate for the loss of hippocampal neurons.

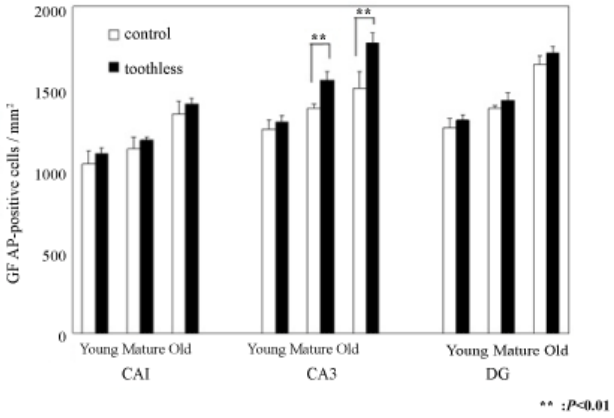

Figure 5: Effects of early toothless condition on GFAP-positive cells in hippocampal CA1, CA3 and dentate gyrus. Each data is presented as mean ± SE (n=5). GFAP-positive cell number in CA3 region of the mature and old toothless mice was significantly higher than that of age-matched controls [34]

The Possible Molecular Pathogenesis of the Hippocampal Alterations Induced by Early Toothless Condition

Hippocampus is the main site in the brain for corticosterone, as it has the highest concentration of glucocorticoid receptor [53]. Elevated glucocorticoid level induced by chronic stress has profound effects on the excitation-inhibition balance within hippocampus. Chronic stress significantly decreased long-term potentiation (LTP) in rat hippocampal CA1 neurons [15,17,22,54]. It is suggested that thytotropin-releasing hormone (Trh), tenascin XA (Tnxa), neuronatin (Nnat), and S100a9 genes may affect memory in rats [14]. Trh is a neuropeptide originally discovered for its function as a hypothalamic factor controlling the synthesis and release of thyrotropin from the pituitary. Spatial learning has been shown to increase Trh levels in the hippocampus. Reduced levels of S100a9 in toothless rats may be a compensatory effect for the decrease in spatial memory. The expression of S100a9 may be affected by occlusal support. These findings demonstrate that Trh, Tnxa, Nnat and S100a9 genes may affect memory in rats [14].

Brain-derived neurotrophic factor (BDNF) is a small dimeric protein belonging to the nerve growth factor family of neurotrophins and is widely expressed in the brain, including hippocampus [15,54]. BNDF is mainly secreted by astrocytes. It binds to tropomyosin-related kinase B (TrkB) and activates down-stream protein kinases to phosphorylate substrates [15,17-19]. BDNF has been shown to play a key role as a mediator of activity-induced LTP in hippocampus. The effect of BDNF on hippocampal neuronal LTP is mediated by TrkB receptor. BDNF-TrkB binding, as a mediator of hippocampus-dependent learning and memory, plays a critical role in activity-dependent synaptic plasticity. It was reported that both BDNF and TrkB expressions in hippocampal neurons were markedly reduced in the complete molarless mice. It may be partially due to reduced cerebral blood flow induced by the masticatory dysfunction [15,17]. The spatial memory impairment in rodents could have a close relationship with the decrease in BDNF-TrkB levels of the pathways located from trigeminal nerve area to hippocampus. A possible explanation for the mechanism is that tooth loss reduces sensory input linked to mastication and temporomandibular joint movements.

Conclusions

This article shows that early tooth loss not only cause masticatory disorders, but also act as a chronic stress, induces constantly elevated levels of corticosterone. As hippocampus contains high level of glucocorticoid receptor, it is the main target for corticosterone. Elevated corticosterone has a negative effect on memory-related genes and signaling proteins in the hippocampus, especially BDNF-TrkB signaling system, impairs hippocampal synaptic plasticity and hippocampus-dependent spatial memory. Long-term toothless condition may be a risk factor for cognitive impairment. Adequate dental treatments such as denture or dental implants for defective part of teeth are considered to be important for maintaining the hippocampal functions.

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