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SOFT-DIET FEEDING AFTER WEANING AFFECTS BEHAVIOR IN MICE: POTENTIAL INCREASE IN VULNERABILITY TO MENTAL DISORDERS

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Abstract—Mastication is one of the most important oral functions, and the period during which mastication is acquired overlaps with the term of rapid development and maturation of the neural systems. In particular, the acquisition period after weaning is related to the potential onset of mental disorders. However, the roles of mastication during this period for brain development remain largely unknown. Therefore, we used a series of standard behavioral analyses, assessment of hippocampal cell proliferation, and the expression of brain-derived neurotrophic factor (BDNF), TrkB, and Akt1 in the hippocampus and frontal cortex of mice to investigate the effects of post-weaning mastication on brain function. We fed 21-day-old C57BL6/J male mice either a hard or a soft diet for 4 weeks and conducted a series of standard behavioral tests from 7 weeks of age. Further, histological analysis with bromodeoxyuridine was performed to compare hippocampal cell proliferation at 7 and 14 weeks of age. Real-time polymerase chain reaction was performed to compare *BDNF*, *TrkB*, and *Akt1* expression in the hippocampus and frontal cortex of 14-week-old mice. Compared to mice fed a hard diet (HDM), soft-diet mice (SDM) showed behavioral impairments, including decreased home cage activity, increased open field test activity, and deficits in prepulse inhibition. These results were similar to those observed in mouse models of schizophrenia. However, no effects were observed on anxiety-like behaviors or memory/learning tests. Compared to HDM, SDM showed significantly decreased hippocampal cell proliferation and hippocampal *BDNF* and *Akt1* gene expression at 14 weeks of age. A soft diet after weaning may have resulted in histological and molecular changes in the hippocampus and influenced outcomes of behavioral tests related to mental disorders. Our findings suggest that soft-diet feeding after weaning may affect both physical and mental development of mice, and may increase vulnerability to mental disorders.

Key words: soft-diet feeding, prepulse inhibition; behavioral analysis; mental disorder; neurogenesis; brain-derived neurotrophic factor.

INTRODUCTION

Mastication is one of the most important oral functions. Infancy is an extremely important period for acquiring the complex ability to masticate, which consists of the actions of chewing and swallowing (Bosma, 1976; Gisel, 1991; Qureshi et al., 2002). Epidemiological studies of human infants have examined mastication acquisition, which is comprised of chewing, swallowing, and coordinating the timing of breathing and chewing rhythm. Such studies indicated that the acquisition of masticatory ability, which occurs simultaneously with anatomical development of the brain, is made possible by the interaction of mastication experience with central nervous system (CNS) development and maturation (Morris, 1989; Gisel, 1991; Fucile et al., 2005).

Additional studies have been conducted to investigate masticatory motor development in other mammals. These studies indicated that masticatory ability is acquired through various factors, such as craniofacial development, CNS maturation, peripheral sensory nerve input, and motor learning (Iriki et al., 1988; Westneat and Hall, 1992; Huang et al., 1994). In particular, it has been reported that the development of proper masticatory function is inhibited by soft-diet feeding (Liu et al., 1998; Okayasu et al., 2003).

Mastication has been reported to be related to maxillofacial development, particularly the growth and

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Abbreviations: ANOVA, analysis of variance; ASR, acoustic startle response; BDNF, brain-derived neurotrophic factor; Brd-U, bromodeoxyuridine; CCD, charge-coupled device camera; CNS, central nervous system; DG, dentate gyrus; fMRI, functional magnetic resonance imaging; HDM, hard diet mice; OCT, optimal cutting temperature; PBS, phosphate-buffered saline; PCR, polymerase chain reaction; PPI, prepulse inhibition; PTSD, post-traumatic stress disorder; RT, reverse transcriptase; RT-PCR, real-time polymerase chain reaction; SDM, soft-diet mice.

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development of the mandible (Beecher and Corruccini, 1981; Kiliaridis et al., 1999; Luca et al., 2003; Maki et al., 2003). Our previous studies in mice fed a soft diet indicated that mastication after weaning influences gene expression in mandibular condylar cartilage (Watahiki et al., 2004) and produces major differences in mandibular morphology (Enomoto et al., 2010). Mastication has recently been reported to influence not only craniofacial development, but also brain function. For example, mastication has been reported to be involved in improving memory and learning in adults (Wilkinson et al., 2002). In addition, studies using functional magnetic resonance imaging (fMRI) suggested that mastication may simultaneously activate the prefrontal cortex and parietal cortex and may contribute to higher cognitive function (Takada and Miyamoto, 2004; Hirano, 2008).

Furthermore, human studies showed that reduced bite force and the number of teeth lost are related to the onset and progression of dementia and Alzheimer's disease (Okimoto et al., 1991; Shigetomi et al., 1998; Okamoto et al., 2010).

In an animal study in which senescence-accelerated model SAMP8 mice were fed a long-term soft diet, significant declines were observed in behavioral tests of memory and learning ability (Yamamoto and Hirayama, 2001). Yamazaki et al. (2008) also reported that tooth-extracted rats showed significantly reduced performance on behavioral tests that evaluate spatial memory (Yamazaki et al., 2008). In addition, it has been reported that rats from which the molar teeth have been removed show accumulation of amyloid-β in the hippocampus, which is related to decreased hippocampal neurogenesis (Ekuni et al., 2011a,b).

The studies mentioned above clearly demonstrated that a long-term soft diet and tooth loss influence brain functions related to memory and learning, and may also be related to the onset of dementia and Alzheimer's disease.

Previous work has focused primarily on the relationship between mastication and brain function in senescence. However, there have been no reports regarding the relationship between mastication and brain function during growth and development, particularly the relationship between masticatory alterations and mental disorders.

Mental disorders, including schizophrenia, are multifactorial diseases that result from the interaction of complex genetic and environmental factors. All periods of CNS formation, including the fetal stage, the perinatal period, and infancy, are crucial periods in the onset of schizophrenia (Weinberger, 1987; Lillrank et al., 1995). Epidemiological studies have revealed many environmental factors that exacerbate the incidence rate of schizophrenia (Lewis et al., 1992; Mortensen et al., 1999; Cannon et al., 2002). Many aspects of the relationship between environmental factors and the prodromal stage lasting from infancy to adolescence remain unclear. Therefore, many studies using animal models have been conducted to examine the relationships between environmental factors and onset of mental disorders (Deminière et al., 1992; Eyles et al., 2003).

As behaviors are assumed to express internal mental activity, behavioral assessment is likely to be an effective means of studying mental disorders in animal models. Prepulse inhibition (PPI) is a behavioral test procedure that is widely used to assess sensorimotor gating (a type of information processing). PPI is typically observed in healthy subjects, while a decrease in PPI reflects deficits in sensorimotor gating that may indicate impaired information processing in schizophrenia and other mental disorders (Braff et al., 1978; Braff, 2001; Ludgewig, 2003; Geyer, 2006). In addition, decreased PPI has often been reported in behavioral analyses of genetically modified animals related to schizophrenia and other mental disorders (Swerdlow et al., 1994; Lipska and Weinberger, 2000; Powell et al., 2009).

Along with the behavioral measurements, anatomical and molecular analyses of the nervous system are also essential to understand mental disorders. Reduced hippocampal volume and cell count are frequently observed in MRI and histological analyses of the brains of patients with mental disorders (schizophrenia, bipolar disorder, depression, and post-traumatic stress disorder [PTSD]; Saddath, 1990; Bremmner, 2008). Hippocampal neurogenesis has also been reported to occur in adulthood in both humans and animals (Altman and Das, 1965; Cameron et al., 1993; Eriksson et al., 1998; Gage, 2000). Strong relationships between hippocampal neurogenesis and vulnerability to mental disorders have been reported in animal models (Weinberger, 1987; Lillrank et al., 1995; Harrison, 2004; Watanabe et al., 2007; Maekawa et al., 2009). In addition, decreased levels of neurotrophin brain-derived neurotrophic factor (BDNF) were reported to be related to decreased hippocampal neurogenesis and may be involved in dementia (Durany et al., 2001; Szeszko et al., 2005; Tan et al., 2005). Other studies have also suggested that long-term soft-diet feeding may be related to decreased hippocampal neurogenesis (Mitome et al., 2004; Tsutsui et al., 2007). Furthermore, mastication ability is related to BDNF levels in adult mice or senescence-accelerated mice fed a soft diet (Yamamoto and Hirayama, 2001; Aoki et al., 2005; Yamamoto et al., 2008; Yamazaki et al., 2008).

We focused on the observation that the period of masticatory acquisition coincides with that of brain development related to the onset of mental disorders. We hypothesized that masticatory alterations after weaning may affect emotional development and potentially increase vulnerability to mental disorders. To verify this hypothesis, we examined the relationships between mastication after weaning and mental disorders in mice fed either a hard or soft diet.

EXPERIMENTAL PROCEDURES

Animals

Male C57BL6/J mice (CLEA Japan Inc., Tokyo, Japan) were used in this study, and the experiment was started