J. Gifu. Dent. Soc
Vol. 33, No. 2, 111～115
October, 2006

Effect of Masticatory Dysfunction on the Rate of Aging and Life Span in Senescence-Accelerated Mice (SAMP 8).

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We examined the effect of masticatory dysfunction on the rate of aging and life span in senescence-accelerated mice (SAMP 8). Aging scores of molarless mice were significantly higher compared to those of age-matched controls. The average life span of molarless mice was significantly shorter than that of control mice. These results suggest that masticatory dysfunction in SAMP 8 mice accelerates the aging process, leading to a shortened life span.

Key words: Masticatory dysfunction, Aging, Life span, SAMP 8

INTRODUCTION

There is currently great interest in masticatory function in relation to aging. For example, elderly patients in need of dental care that have lower activities of daily living (ADL) levels, dental treatments that allow for increased ability to ingest food orally result in higher ADL levels[1,2]. In addition, masticatory dysfunction in aged mice (SAMP 8) induces spatial memory deficits with various pathologic changes in the hippocampus, such as degeneration of hippocampal CA1 pyramidal cells[3], decreased Fos induction in the CA1 region[4], and a decreased number of spines on CA1 pyramidal cells[5]. Masticatory dysfunction also increases plasma corticosterone levels[6] and the number of hippocampal CA1 astroglial cells[7], and induces a decline in the septo-hippocampal cholinergic system[8], suggesting that masticatory dysfunction contributes to hippocampal pathology and stress.

In rats, repeated daily restraint stress results in atrophy of hippocampal pyramidal neurons[9] and suppression of the immune system[10]. In addition, restraint stress in SAMP 8 mice accelerates the rate of senescence and shortens life span[11]. These results suggest that chronic stress shortens life span.

We hypothesized that molar tooth extraction induces chronic stress like restraint and might therefore accelerate the aging process. In this study, we examined the effect of molar tooth extraction on senescence and life span in SAMP 8 mice.

METHODS AND MATERIALS

Two-month-old male SAMP 8 mice (n=30) were used in this study. The features of this mouse strain were previously described in detail[12,13]. The animals were treated in accordance with the principles approved by the Council of the Japanese Neuroscience Society. Mice were bred and maintained under conventional conditions and housed one in plastic cages under temperature- and humidity-controlled conditions (23±1℃, 55%±2%) with free access to food and water. Mice were maintained on a 12h light/ dark cycle.

Mice were anesthetized with sodium pentobarbital (35mg/kg) and their upper molar teeth (maxillary molars) were extracted (molarless condition) as previously described[5]. Control animals underwent the same surgical procedure except for the removal of the molars. After the operation, the mice were allowed free access to chow pellets and water.

The postoperative body weight of each mouse and amount of food consumed in each cage were monitored daily for 7 d after the operation. After the recovery period, body weight and food consumption were measured once a week.

The degree of senescence of each mouse was evaluated weekly using a grading score system[12,13]. Health conditions and the number of deaths were checked daily. These investigations continued until all the mice died. The data were statistically analyzed using a t-test or Mann-Whitney's U test. A P value of less than 0.05 was considered statistically significant.

RESULTS

1) Body weight

The time course of changes in body weight for both control and molarless mice is shown in Fig.1. Although the postopera-

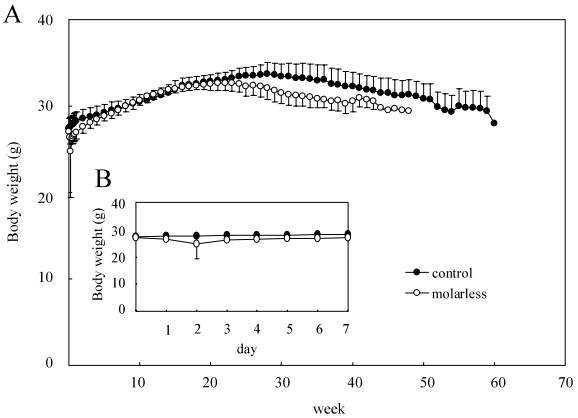

Fig.1. Changes in body weight in molarless and control mice.
(A) Body weights throughout the experimental period.
(B) Body weights for 7 d after the operation. Each value represents the mean± SD.

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(*Accepted August 22, 2006*)

tive body weight of the molarless mice initially decreased, it recovered to preoperative levels within 1wk. After 4wk, there was no significant difference in body weight between molarless and control mice. There was a significant difference in body weight between molarless and control mice, however, from 24wk to 39 wk (24, 26, 38, 39wk, $P<0.05$; other wk, $P<0.01$). Thereafter, the difference was not significant.

2) Food consumption

Postoperative food consumption by the molarless mice initially decreased and then recovered to preoperative levels within 3 d (Fig.2). From 3 d to 22wk and from 36wk to 41wk after the operation, there was no significant difference in food consumption between molarless and control mice, but from 23wk to 35wk and after 42wk, there was a significant difference between the two (23, 32, 35, 36, 44wk, $P<0.05$; other wk, $P<0.01$).

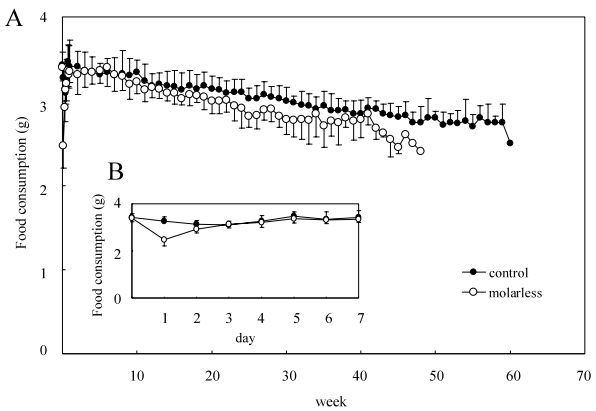

Fig. 2. Changes in food consumption in molarless and control mice.
(A) Food consumption throughout the experimental period.
(B) Food consumption for the 7 d after the operation. Each value represents the mean ± SD.

3) Grading score

For both molarless and control mice, the grading score increased with advancing age (Fig.3). The grading scores for both control and molarless mice began to increase from 15wk and 17wk, respectively, after the operation. After 18wk, there was a statistically significant difference between the grading scores of molarless and control mice (18, 20, 41, 42wk, $P<0.05$; other wk, $P<0.01$).

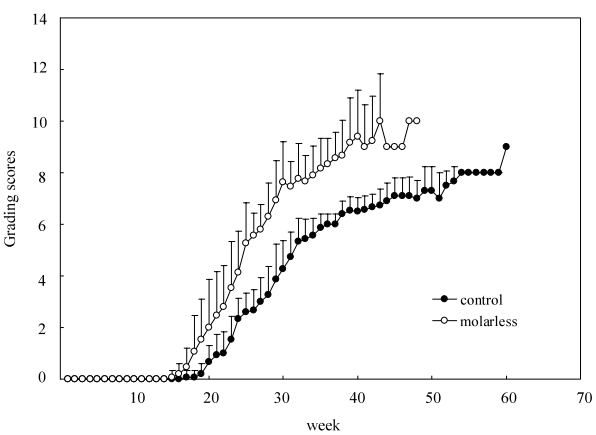

Fig.3. Changes in grading score. The grading score increased steadily with advancing age in both molarless and control mice, but the increase in molarless mice was more marked than that of control mice after 18wk. Each value represents the mean ± SD.

4) Life span

There was a significant difference in the mean life span of molarless mice (37.2±6.1wk) and that of control mice (53.1 ±6.4wk; $P<0.01$).

5) Survival curve

The pattern of survival differed somewhat between molarless and control mice, as shown in Fig.4. The pattern of survival in molarless mice was not a simple parallel shift to the left of control mice. In molarless mice, survival rates declined precipitously with advancing age compared to control mice.

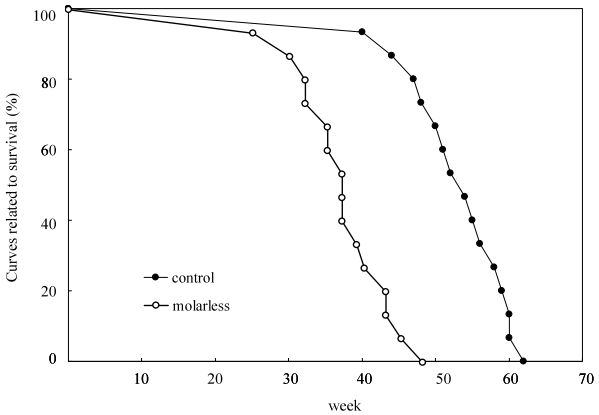

Fig.4. Survival curves of molarless and control mice.

DISCUSSION

The present study demonstrates that molar tooth extraction in SAMP 8 mice accelerates the rate of senescence and shortens life span. The effects of molar tooth extraction are similar to those of restraint stress in SAMP 8 mice[11], feeding of fine-grained diets in SAMP 1 mice[14], and extraction of molar teeth in SAMP 1 mice[15]. The mechanism by which molar extraction accelerates senescence and reduces life span is purely speculative at the present time. Indirect effects on senescence-related impairment, however, can be proposed.

One possibility is that the molarless condition reduces masticatory sensory input from the oral area and face to the somatic sensory cortex. The hippocampus receives inputs through the entorhinal area from cerebral association areas[16~18]. Granule cells in the hippocampal dentate gyrus primarily receive perforant pathway projections from the entorhinal area, thus providing a key interconnection between the neocortex and the hippocampus[21,22]. This circuit is highly vulnerable and is invariably devastated by abnormal neuropathologic formations in Alzheimer's disease and aging[23]. The afferent fibers projecting to the septohippocampal system are thought to have an important role in spatial memory[19,20]. In the hippocampus, the cholinergic system is related to spatial cognition and undergoes a variety of age-dependent changes[24,25]. Indeed, in previous experiments using aged SAMP 8 mice, the molarless condition resulted in deficits in spatial memory with a reduction in the density of Fos-positive cells in the hippocampal CA1 region[4], a loss of pyramidal cells in the hippocampal CA1 region[3], and a decrease in the number of spines on CA1 pyramidal cells[5]. The molarless condition also contributes to senile progression in the hippocampus

and a decline in the septohippocampal cholinergic system in SAMP8 mice[26]. Furthermore, the act of chewing increases neuronal activity and blood flow in various cortical regions, including the primary sensory cortex[27]. Chewing results in a bilateral increase in blood oxygenation level-dependent signals in the sensorimotor cortex, supplementary motor area, insula, thalamus, and cerebellum[28,29]. These results suggest that chewing causes regional increases in neuronal activity in the brain. Therefore, a reduction in masticatory sensory input might reduce activity in the central nervous system, thereby leading to accelerated aging and shortened life span.

The molarless condition might also influence the hypothalamic-pituitary-adrenal (HPA) axis. Long-term suppression of glucocorticoids results in impaired hippocampal function, such as spatial learning[30], a decline in local cerebral blood flow[31], and neuronal damage similar to that found in aged hippocampus[32]. Plasma corticosterone levels rise with age[33], suggesting that glucocorticoids are associated age-related changes in the brain[34,35]. The increase in plasma corticosterone levels with aging might lead to neuronal degeneration of the hippocampus and impaired HPA negative-feedback inhibition, and subsequent cognitive impairment. Indeed, molarless mice have significantly higher plasma corticosterone levels than molar-intact control mice[6]. The molarless condition enhances age-dependent decreases in both learning ability and the number of neurons in the hippocampal CA1 subfield[3], as well as age-dependent increases in the number and hypertrophy of glial fibrillary acidic protein-labeled astrocytes in the same subfield[7]. These findings are similar to age-related changes in the brain suggesting that the molarless condition enhances senescence-related impairment.

Finally, restraint stress induces atrophy of the thymus and spleen, decreased antibody production, decreased natural-killer cell activity, and decreased macrophage phagocytosis; electric shock stress reduces blastogenesis of spleen lymphocytes and natural-killer cell activity[10]. The molarless condition is a form of chronic stress and might therefore induce immune system suppression. Thus, the molarless condition might impair the HPA axis and suppress the immune system, thereby accelerating the aging process and shortening life span.

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岐　歯　学　誌
33巻2号　111～115
2006年10月

咀嚼障害が加齢変化と寿命に及ぼす影響

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咀嚼障害が老化と寿命に及ぼす影響を老化促進モデルマウス（SAMP8）を用いて検討した．咀嚼障害のあるマウスの老化度はコントロールマウス群のそれに比較して有意に高かった．また，咀嚼障害のあるマウスの寿命はコントロール群に比較して有意に短かった．これらのことから，咀嚼障害は老化促進マウスの老化を促進させる結果，寿命を短縮させることが示唆された．

キーワード：咀嚼障害，老化，寿命，SAMP 8

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