



Novel stress increases hypothalamic-pituitary-adrenal activity in mice with a raised bite



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ABSTRACT

Background and objective: In humans, occlusal disharmony may cause various physical complaints, including head and neck ache, stiffness in the shoulder and neck, and arthrosis of the temporomandibular joints. Occlusal disharmony induced by raising the bite in rodents, increases plasma corticosterone levels, which leads to morphologic changes in the hippocampus and altered hippocampus-related behavior. The paraventricular nucleus (PVN) of the hypothalamus regulates the hypothalamic-pituitary-adrenal system. Chronically stressed animals exposed to a novel stress exhibit higher adrenocorticotrophic hormone levels than naive control animals. We hypothesized that there would be different response of the corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP) to a novel acute stress with occlusal disharmony.

Design: In order to investigate how exposure of mice with occlusal disharmony to a novel acute stress (restraint stress) affects the PVN, we induced occlusal disharmony by raising the vertical dimension of the bite (bite-raised condition) and examined the expression of corticotrophin releasing hormone (CRH) mRNA and arginine vasopressin (AVP) mRNA in mouse PVN.

Results: CRH mRNA expression was increased in the PVN of the bite-raised group 90 min after the bite-raising procedure, but the expression was recovered to the control level at 14 days. AVP mRNA expression in the PVN was normal at 90 min, and increased significantly 14 days after the bite-raising procedure. Exposure to restraint stress in the bite-raised mice induced a significant increase in CRH mRNA expression in the PVN.

Conclusions: The bite-raising procedure induced a rapid CRH mRNA response and a slower AVP mRNA response in the parvocellular PVN of the hypothalamus. Exposure to a novel stress following the bite-raising procedure further reinforced the CRH stress response. Thus, occlusal disharmony, such as that induced by raising the bite, may be a risk factor for hypersensitivity to a novel stress.

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1. Introduction

Occlusal disharmony resulting from tooth loss and periodontitis, or an inadequate vertical dimension of crowns, bridges, or dentures has physical, psychologic, and social effects on quality of life (Bernabé, Sheiham, & de Oliveira, 2009; Christensen, 1970; Uemoto, Tsukiyama, & Koyano, 1998). Ekuni et al. (2011) reported

that malocclusion contributes to psychologic stress in young Japanese adults. Occlusal disharmony induced by raising the bite in rodents increases plasma corticosterone levels, which leads to spatial learning deficits, and concomitant decreases in pyramidal cells and cell proliferation in the hippocampus (Ichihashi et al., 2007; Kubo et al., 2007; Mori, Katayama, Miyake, Fujiwara, & Kubo, 2013), which is consistent with previous chronic stress-induced hippocampal changes (Fuchs & Flugge, 1998; Sapolsky, Krey, & McEwen, 1985). These findings suggest that chronic stress resulting from occlusal disharmony induces hippocampal behavioral and morphologic changes.

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Corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) are secreted by parvocellular neurons in the paraventricular hypothalamus nucleus (PVN), and regulate adrenocorticotrophic hormone (ACTH) secretion in the pituitary corticotroph, which stimulates glucocorticoid release from the adrenal cortex (Antoni, 1993). AVP alone only weakly induces the secretion of ACTH, but it has synergistic actions with CRH and helps to sustain pituitary responsiveness during chronic stress (Aguilera, 1998; Antoni, 1993). The PVN contains two populations of CRH neurons, one containing CRH alone and the other in the parvocellular region of the PVN that colocalizes with AVP (Whitnall, Smyth, & Gainer, 1987).

Secretion of both CRH and AVP is stimulated by acute stress (Ma & Lightman, 1998). In repeated or chronic stress conditions, however, cells in which CRH and AVP colocalize preferentially secrete VP (Bartanusz et al., 1993; Ma & Aguilera, 1999; Ma & Lightman, 1998). Chronic stress causes the hypothalamo-pituitary-adrenal (HPA) axis to desensitize to the homotypic stressor (Dallman et al., 1992; Ma & Lightman, 1998). On the other hand, exposure to a novel acute stress in a chronically stressed animal induces greater ACTH response than that observed in naive control animals (Aguilera, 1998; Bhatnager & Dallman, 1998). The relative contribution of the CRH and AVP to acute stress with chronic stress due to occlusal disharmony is unclear. Therefore, our objective of this study is to clarify the response of both CRH and AVP with occlusal disharmony induced by raising the bite in mice. We also examined the CRH alteration induced by novel acute stress in the animals with a raised bite.

2. Materials and methods

We used 8-month-old male senescence-accelerated prone 8 (SAMP8) mice ($n=68$). The detailed characteristics of this strain were previously described (Flood & Morely, 1998). Briefly, SAMP8 mice mature normally up to the age of 6 months, and then exhibit accelerated aging (median life span of 12 months compared with 2–3 years for other strains). The SAMP8 mouse is a proposed experimental model of human senile dementia (Flood & Morely, 1998). The ethics committee of Asahi University School of Dentistry approved the experimental protocol and the animals

were treated according to the principles approved by the Council of the Japanese Neuroscience Society. The mice were bred and maintained under conventional conditions and housed in groups of five in plastic cages under temperature- and humidity-controlled conditions ($23 \pm 1^\circ\text{C}$, $55 \pm 25\%$) and a 12-h light cycle (light period, 6:00–18:00; dark period, 18:00–6:00). After the bite-raising procedure (described below), the mice were allowed free access to water and pelleted chow (hard type, CE-2, Tyubu Kagaku Shizai Co., Ltd.).

The mice ($n=68$) were divided into two groups, mice in the bite-raised condition ($n=34$), and controls ($n=34$). For the bite-raising procedure, anesthesia was induced by injection with sodium pentobarbital (35 mg/kg), and the vertical dimension of the bite was increased by ~ 0.1 mm by applying ultraviolet-ray polymerization resin (UniFil[®] Lo Flo, GC Corporation, Tokyo, Japan) to the upper molars (maxillary molars) after treatment with a Single Bond Dental Adhesive System (3 M Dental Products, St. Paul, MN), as described previously (Ichihashi et al., 2007). Control mice underwent the same anesthetic procedure, but no resin was applied.

The experimental design is shown in Fig. 1. Control and bite-raised mice were anesthetized and perfused as described below at either 90 min ($n=6$ /group) or 2 weeks ($n=6$ /group) after the operation. Additional groups of five control and five bite-raised mice were anesthetized and perfused as described below either without being exposed to restraint stress ($n=5$ /group) or 60 min after exposure to restraint stress ($n=5$ /group). For restraint stress, the mice were placed in a ventilated plastic restraint tube with an inner diameter of 3.5 cm, in which they could move back and forth but not turn around, under exposure to bright light.

For *in situ* hybridization analysis of CRH and AVP mRNA in the PVN, mice in each group were anesthetized with pentobarbital sodium (40 mg/kg) and perfused transcardially with 30 ml of saline at 37°C , followed by 100 ml of 4% paraformaldehyde in 0.1 M phosphate buffer (PB), pH 7.4. The brains were removed and placed in 2% paraformaldehyde fixative overnight at 4°C . The *in situ* hybridization method used in this study was reported previously (Ichihashi et al., 2007). Briefly, deparaffinized sections (3 μm thick) were placed in xylene and then in a descending ethanol series, and treated with 2 $\mu\text{g}/\text{ml}$ proteinase K (Roche Diagnostics) for 15 min

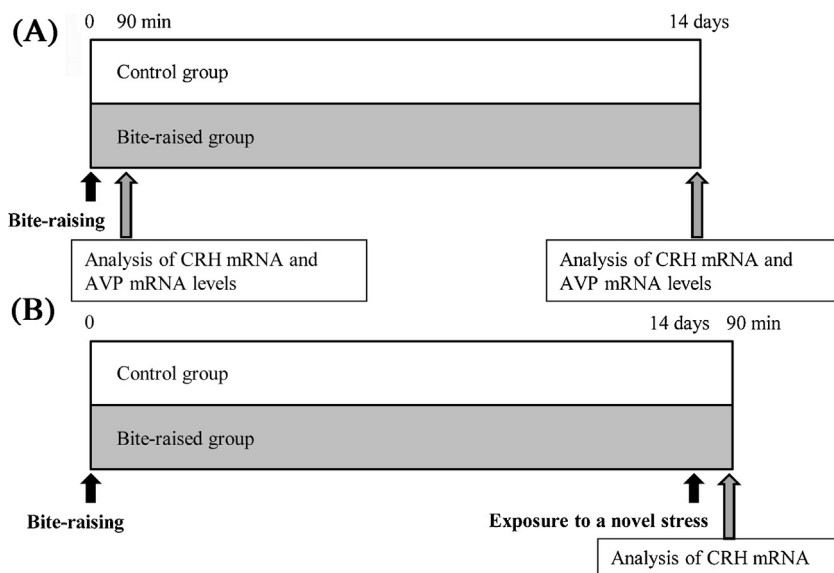


Fig. 1. Experimental design.

Effects of bite-raising on CRH mRNA and AVP mRNA expression (A) in the PVN and effects of novel stress on CRH mRNA expression in the PVN under the bite-raised condition (B).

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