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The effects of bilateral lesions of the mesencephalic trigeminal sensory nucleus on nocturnal feeding and related behaviors in mice

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ABSTRACT

Aims: The mesencephalic trigeminal sensory nucleus (Me5), which receives signals originating from oral proprioceptors and projects its fibers to the hypothalamus, regulates mastication and modulates satiation. Because the Me5 neurons display circadian rhythms in circadian *mPer1* gene expression and bilateral Me5 lesions change feeding and exploratory behavior profiles, we speculated that Me5 may influence the daily timing of feeding. Therefore, we explored the effects of bilateral caudal Me5 lesions on the circadian profiles of feeding and its related behaviors.

Main methods: We measured the activities of feeding, drinking, and locomotion for 24 h using an automated feeding behavior measurement apparatus and analyzed the mRNA expression levels of hypothalamic orexigenic and anorexigenic signaling molecules in both Me5-lesioned and sham-operated mice.

Key findings: Food and water intake and locomotor activity decreased significantly in Me5-lesioned mice during the dark phase without affecting these total indexes when measured over the entire day. Analysis of the mRNA expression levels of hypothalamic orexigenic and anorexigenic signaling molecules showed that prepro-orexin (orexin) mRNA in the perifornical area was significantly decreased during the dark phase only in Me5-lesioned mice.

Significance: Bilateral caudal Me5 lesions alter the nocturnal properties of food and water intake and locomotor activity in mice and decrease the mRNA expression level of orexin in the perifornical area during the dark phase. These results suggest that Me5 activity may influence the nocturnal properties of feeding and its related behaviors by adjusting the activity of orexin neurons in the perifornical area.

Introduction

The mesencephalic trigeminal sensory nucleus (Me5) receives proprioceptive sensory afferents of the trigeminal nerve from the jaw-closing muscle spindles and the periodontal ligaments, and innervates the motor trigeminal nucleus, which is related to the jaw-jerk reflex (Corbin and Harrison, 1940; Harrison and Corbin, 1942). The Me5 also receives histaminergic and orexinergic hypothalamic innervation that facilitates masticatory behavior (Stoyanova and Lazarov, 2005; Wada et al., 1991). The Me5 also projects its fibers to the tuberomammillary nuclei (TMN) in the posterior hypothalamus (Ericson et al., 1989, 1991), and Me5 lesions change feeding behavior profiles and inhibit exploratory behavior (Ishii et al., 2005). A limited population of histaminergic neurons is exclusively located in the TMN, the neurons of which project extensively to multiple cerebral regions and are implicated in the regulation of numerous brain functions such as locomotion, drinking, feeding, and synaptic plasticity (Wada et al., 1991; Haas and Panula, 2003). Therefore, the Me5 may participate in feeding control and related behaviors (Lazarov and Gratzl, 2006; Sakata et al., 2003) and may modulate satiation (Fujise et al., 1993, 1998) through the Me5–TMN and the above pathways. The histaminergic neuronal subpopulation in the TMN innervates the arcuate nucleus of the hypothalamus (Umehara et al., 2011, 2012), which is adjacent to the third ventricle and contains first-order orexigenic neuropeptide Y (NPY)/agouti-related protein (AGRP) neurons and anorexigenic pro-opiomelanocortin (POMC) neurons. In response to the circulating adiposity signals of insulin and leptin (Schwartz et al., 2000), these orexigenic and anorexigenic neurons control food intake. Recently, Hiler et al. (2008) showed that Me5 cells display circadian rhythms with elevated expression of the circadian *mPer1* gene in culture, corresponding to the lights-off phase before entering the lights-on phase. Because Me5 lesions change feeding and exploratory behaviors and also affect spatial memory that is involved in food-seeking behavior (Ishii et al., 2005, 2006, 2010), we examined the effects of bilateral caudal Me5 lesions on the daily timing of feeding and its related behaviors and also on mRNA expression

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levels of orexigenic and anorexigenic signaling molecules in the arcuate nucleus during the light and/or dark phase. In addition, we examined the effects of bilateral caudal Me5 lesions on the mRNA expression level of orexin in the perifornical area and the lateral hypothalamic area, which receive signals from the arcuate nucleus, leading to stimulation of food intake via their activation (Schwartz et al., 2000). Our results suggest that Me5 activity may influence the daily timing of feeding and its related behaviors probably via an unknown neuronal pathway other than the Me5–TMN–arcuate nucleus pathway to a specific hypothalamic area such as the perifornical area.

Materials and methods

Animals

Male *ddY* mice were maintained under controlled temperature and lighting conditions with a 12-h light/12-h dark cycle (lights on at 0700) and allowed ad libitum access to food and water. Mice were housed in groups of 2–3 per cage. All procedures for the care and use of experimental animals were approved by the Animal Research Committee at Obihiro University of Agriculture and Veterinary Medicine and were conducted in compliance with the Guiding Principles for the Use of Animals in Toxicology that were adopted by the Society of Toxicology in 1989. The animals were humanely euthanized with an overdose of anesthetic ether at the end of the experiment.

Me5 lesions

Bilateral electrolytic caudal Me5 lesions were made in 8-wk-old mice anesthetized with Avertin® (0.36 g/kg). Using a stereotaxic apparatus, a 0.2-mm-diameter stainless steel electrode was positioned 5.3 mm posterior to bregma, 0.9 mm lateral to the midsagittal suture, and 3.2 mm below the surface of the skull. As previously described, anodal electrolytic lesions were produced by passing a 1.3-mA current through the electrode three times for 1 s each (Ishii et al., 2005, 2006, 2010). All successful Me5 lesions were restricted to the caudal level of the Me5. Sham-operated mice underwent an identical operation but without application of a current. At the end of the experiment, mice were sacrificed, brains were fixed with 4% neutral-buffered paraformaldehyde solution, and serial brain sections (40 μm thick) were cut and stained with hematoxylin–eosin or for Nissl substance with a solution of 0.1% Cresyl Violet and 0.04% acetic acid to check the placement of the Me5 lesions. Out of 26 mice that underwent lesioning, 16 showed successful bilateral Me5 lesions, one showed a unilateral Me5 lesion, and nine showed lesions in peri-Me5 regions. Only data from the mice with successful bilateral Me5 lesions were used.

Behavioral analyses

Total locomotor activity and food and water intake in a day were measured using an automated feeding behavior measurement apparatus (Feedam apparatus) equipped with sensors to simultaneously detect these activities for 24 h (Feedam: model V1.0.10; Melquest, Toyama, Japan). Locomotor activity was monitored using a detector, the activity sensor module of Feedam, which was attached to the top of the apparatus. The training task was conducted by placing individual mice in the Feedam apparatus cage for 3 consecutive days to allow adaptation to the test environment. Following training, the tests were conducted by recording the activities of feeding, drinking, and locomotion in mice that were continuously housed in the Feedam apparatus cage (Me5-lesioned mice: n = 6; sham-operated mice: n = 6) for 24 h. The mice were allowed ad libitum access to food and water.

RNA extraction and reverse transcriptase-polymerase chain reaction (RT-PCR)

Three hours after the onset of the light or dark period, the mice were anesthetized with ether and decapitated. The brains were removed and cut into 1-mm thick coronal sections including the mid-hypothalamus (Me5-lesioned mice: n = 10; sham-operated mice: n = 10). The isolated sections extended rostrally to just behind the optic chiasma and caudally just anterior to the mammillary bodies, occupying the central region of the hypothalamus. The tissues were transferred to cold phosphate-buffered saline and dissected into the arcuate nucleus, the perifornical area, and the lateral hypothalamic area regions with the aid of prominent landmarks (fornix, third ventricle, and optic tract) under a dissecting microscope. The perifornical area was taken from the medial and ventral areas of the fornix and distinguished from the lateral hypothalamic area that was taken from the lateral and dorsal areas of the fornix. The tissue pieces were frozen in liquid nitrogen and used for RT-PCR. Total RNA was isolated from the tissue pieces using TRIzol Reagent (Invitrogen, Carlsbad, CA) and quantified by measuring the absorbance at 260 nm. RNA integrity was confirmed with denaturing agarose gel electrophoresis. The mRNA expression levels of NPY, NPY Y1 receptor (NPY1R), AGRP, POMC, prepro-orexin (orexin), and the housekeeping gene β-actin were quantified with RT-PCR. Total RNA (25 ng) was reverse-transcribed using an oligo (dT) primer and AMV reverse transcriptase with a Takara RNA LA PCR™ Kit (AMV) v.1.1 (Takara Shuzo Co., Kyoto, Japan) according to the manufacturer's instructions. First-strand cDNA products were amplified using specific primers for mouse (Table 1). The PCR reaction was carried out in a Bio-Rad I cycler (Bio-Rad, Tokyo, Japan).

Analysis of NPY, NPY1R, AGRP, POMC, orexin, and β-actin cDNAs

Amplified cDNAs were separated on 3.0% agarose gels, stained with SYBR Green (Takara Shuzo Co., Kyoto, Japan), and quantified using an Epi-Light UV FA500 analyzer (Aisin Seiki, Aichi, Japan). The mRNA levels were determined as the ratio of the fluorescence intensity for the gene in question to that for β-actin cDNA.

Statistical methods

Multiple group comparisons were assessed using one-way analysis of variance (ANOVA), followed by post-hoc Tukey's test when significant main effects or interactions were detected. Comparisons between two-group data were analyzed using Student's *t*-test. Statistical differences were considered significant when $P < 0.05$. All statistical analyses were performed with SPSS 16.0 software (SPSS Japan Inc., Tokyo, Japan).

Table 1
PCR primers.

Transcript	Primers (5′–3′)		Product size (bp)
β-Actin	Sense	ATTGCCGACAGGATGCAGAAG	202
	Antisense	TAGAAGCATTTGCGGTGGACG	
NPY	Sense	ACTCTCACAGGCTGTCTTAC	103
	Antisense	ATAGTCTCGTAGTCGTCGTC	
NPY1R	Sense	TCAGACCTCTTAATGAAGGAAAGCA	436
	Antisense	GAGAACAAGTTTCATTTCCCATCA	
AGRP	Sense	CAGAAGCTTTGGCGGAGGT	80
	Antisense	AGGACTCGTGCAGCCTTACAC	
Orexin (prepro-orexin)	Sense	GCTCCGTGCAACAGTTCGTA	72
	Antisense	CAGCAAGCCTCTGCCCGACTG	
POMC	Sense	CTGCTTCAGACCTCCATAGATGTG	120
	Antisense	CAGCGAGAGGCGAGTTTGC	

Results

Quantitative estimates of locomotor activity and food and water intake in a day

We examined whether bilateral caudal Me5 lesions affect the total locomotor activity and total water and food intake in a day. Fig. 1 shows that there were no significant differences in total locomotor activity or in water and food intake per day between Me5-lesioned and sham-operated mice (Fig. 1 *inset 2* shows representative profiles of feeding behavior in sham-operated (top) and Me5-lesioned (bottom) mice during the dark and light phases for 24 h). The pattern of feeding frequency (feeding counts in 24 h) in each bin of food intake (range of food intake in 5 min: 0.01–0.09, 0.10–0.19, 0.20–0.29, and >0.29 g/5 min) did not show any significant differences between sham-operated and Me5-lesioned mice (Supplemental Fig. S1). Moreover, no significant difference was seen in mean body weight between Me5-lesioned and sham-operated mice (Fig. 1 *inset 1*, also see our previous reports (Ishii et al., 2005, 2006, 2010)).

Differences in quantitative estimates of locomotor activity and food and water intake during the light and dark phases

In sham-operated mice, as was expected for nocturnal animals, all activities of locomotion and water and food intake were significantly higher during the dark phase than during the light phase. However, this circadian pattern of activities disappeared in Me5-lesioned mice, and no significant differences were noted in activity between the dark phase and the light phase (Fig. 2A–C, left). The 12-h dark/12-h light ratio of locomotor activity and food intake in the Me5-lesioned mice approached 1 and was significantly lower than that in sham-operated mice (Fig. 2A and C, right, also see Fig. 1 *inset 2*). Although the difference in the 12-h dark/12-h light ratio of water intake between sham-operated and Me5-lesioned mice was not significant, Me5-lesioned mice showed significantly less water intake than sham-operated mice during the dark phase (Fig. 2B, left and right).

To determine the influence of Me5 lesions on the ingestion of food, we examined the effect of Me5 lesions on 24-h fast-induced food intake. Food consumption soon after a 24-h fast in the Me5-lesioned mice did

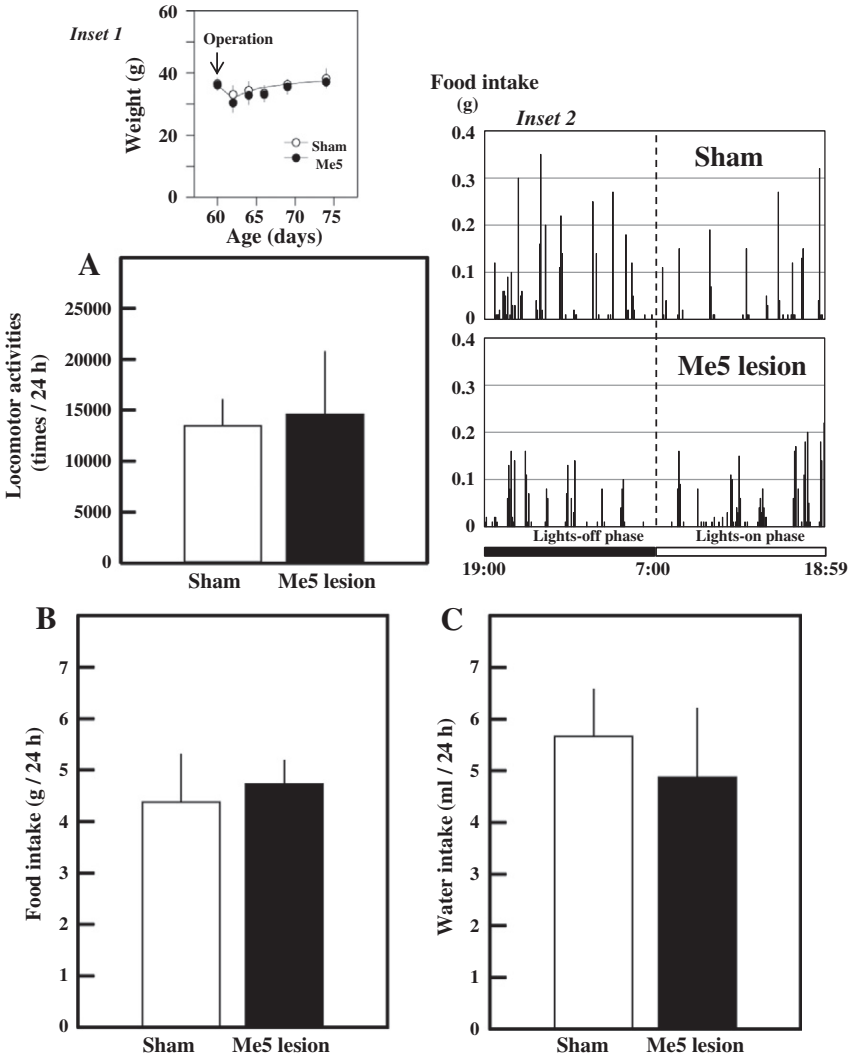

Fig. 1. Locomotor activity and ingestion activity over 24 h in Me5-lesioned mice compared to sham-operated mice. Total locomotor activity (A), food intake (B), and water intake (C) in a day were measured using an automated feeding behavior measurement apparatus. *Inset 1*, changes in body weight after bilateral Me5 lesions. *Inset 2*, representative profiles of feeding behavior in sham-operated (top) and Me5-lesioned (bottom) mice during the lights-off and lights-on phases for 24 h. Mice were housed individually in the apparatus cage for 24 h. Results are the mean ± SD. No significant differences were observed between Me5-lesioned and sham-operated mice.

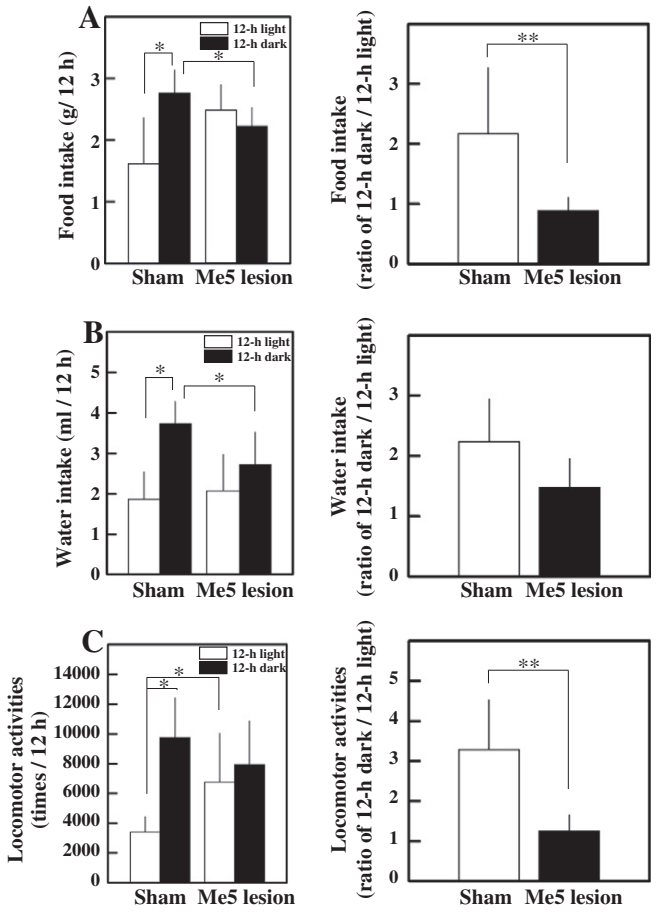

Fig. 2. Quantitative estimates of food and water intake and locomotor activity during the light and dark phases in Me5-lesioned and sham-operated mice. Food intake (A), water intake (B), and locomotor activity (C) during the light and dark phases were measured using an automated feeding behavior measurement apparatus. Mice were housed individually in the apparatus cage for 24 h. Right panels show the 12-h dark/12-h light ratio of food and water intake and locomotor activity. Results are the mean ± SD. $^{*}P < 0.05$ (left panels: one-way ANOVA followed by post-hoc Tukey's test) and $^{**}P < 0.01$ (right panels: Student's *t*-test).

not significantly differ from that in sham-operated mice (Supplemental Fig. S2). Thus, caudal Me5 lesions do not appear to affect the activity of ingesting and/or chewing and motivation to eat.

Analysis of mRNA expression levels of orexigenic NPY, NPY1R, and AGRP in the arcuate nucleus, and orexin in the perifornical area and the lateral hypothalamic area after onset of light and dark phases in sham-operated and Me5-lesioned mice

After the onset of light and dark phases, relative NPY and NPY1R mRNA expression levels in the arcuate nucleus did not show any significant differences between sham-operated and Me5-lesioned mice (Fig. 3A and B). Similarly, orexigenic AGRP mRNA expression levels in the arcuate nucleus did not show significant differences between sham-operated and Me5-lesioned mice, after the onset of light and dark phases (Fig. 3C). In contrast, the mRNA expression level of orexin in the perifornical area, but not in the lateral hypothalamic area, in the Me5-lesioned mice was significantly decreased in the dark phase compared to the sham-operated mice (Fig. 3E and F). Moreover, the level of orexin in the perifornical area in the dark phase was significantly lower than that in the light phase (Fig. 3E).

Analysis of mRNA expression levels of anorexigenic POMC in the arcuate nucleus after onset of light and dark phases in sham-operated and Me5-lesioned mice

Anorexigenic POMC mRNA expression levels in the arcuate nucleus did not show any significant differences between sham-operated and Me5-lesioned mice after the onset of the light or dark phase (Fig. 3D).

Discussion

In this study, we examined the circadian pattern of drinking, feeding and locomotor activity in Me5-lesioned mice relative to sham-operated mice. The major findings of the study indicate that caudal Me5 lesions alter both locomotor and food ingestion activities during the light and/or dark phase and affect nocturnal properties of feeding and its related behaviors in mice.

The Me5 receives signals from the jaw-closing muscle spindles and the periodontal ligaments, regulates motor control of mastication, and sends sensory signals to the hypothalamus (Corbin and Harrison, 1940; Ericson et al., 1989, 1991; Harrison and Corbin, 1942). Recently, Me5 cells in explant cultures were reported to display circadian rhythms of elevated expression of the circadian *mPer1* gene (Hiler et al., 2008). The Me5 projects its fibers to the TMN in the posterior hypothalamus (Lazarov and Gratzl, 2006; Sakata et al., 2003) and modulates satiation through this pathway (Fujise et al., 1993, 1998). It was reported that depletion of histamine within axons projecting to the Me5, by bilateral microinfusion of a specific suicide inhibitor of histidine decarboxylase, increased feeding duration in mice, and this effect was probably because of a decrease in the time to reach satiety and/or slower chewing (Fujise et al., 1993, 1998). In the present study, however, no significant difference was seen in food consumption soon after a 24-h fast between Me5-lesioned and sham-operated mice (Supplemental Fig. S2). This result suggests that caudal Me5 lesions do not affect the activity of ingestion and/or chewing or motivation to eat. The Me5 is likely to be most stimulated by jaw movement during the dark phase, the most active feeding period, exactly corresponding to circadian rhythms in the animal's nocturnal activity (Hunter et al., 2001; Pedroarena et al., 1999). Therefore, the Me5 may play an important role in the daily timing of feeding and its related behavior by coordinating its own circadian rhythms with input stimuli derived from mastication.

The histaminergic neuronal subpopulation of the TMN innervates the arcuate nucleus of the hypothalamus (Umehara et al., 2011, 2012). Therefore, we examined the effect of bilateral caudal Me5 lesions on the mRNA expression levels of neuropeptides implicated in the control of energy homeostasis in the arcuate nucleus. Me5-lesioned mice did not show any significant differences in the mRNA levels of orexigenic NPY, NPY1R, or AGRP or anorexigenic POMC after the onset of either the light or the dark phase compared to sham-operated mice. On the other hand, the mRNA expression level of orexin in the perifornical area, but not in the lateral hypothalamic area, in the Me5-lesioned mice was significantly decreased during the dark phase compared with the sham-operated mice. Both the perifornical area and the lateral hypothalamic area receive signals from first-order neurons such as NPY/AGRP and POMC neurons in the arcuate nucleus and contain second-order neurons such as orexin and melanin-concentrating hormones (Schwartz et al., 2000). However, an alteration in mRNA expression levels in orexigenic signaling molecules was observed only in the perifornical area and not in the lateral hypothalamic area or the arcuate nucleus. These results suggest that signals from the Me5–TMN pathway directly influence orexin neurons in the perifornical area without affecting the first-order neurons in the arcuate nucleus.

Histaminergic neurons in the TMN are morphologically subdivided into five groups (E1–E5) (Inagaki et al., 1988) and innervate several brain regions, including the hypothalamus, nucleus basalis magnocellularis, nucleus accumbens, striatum, and prefrontal cortex

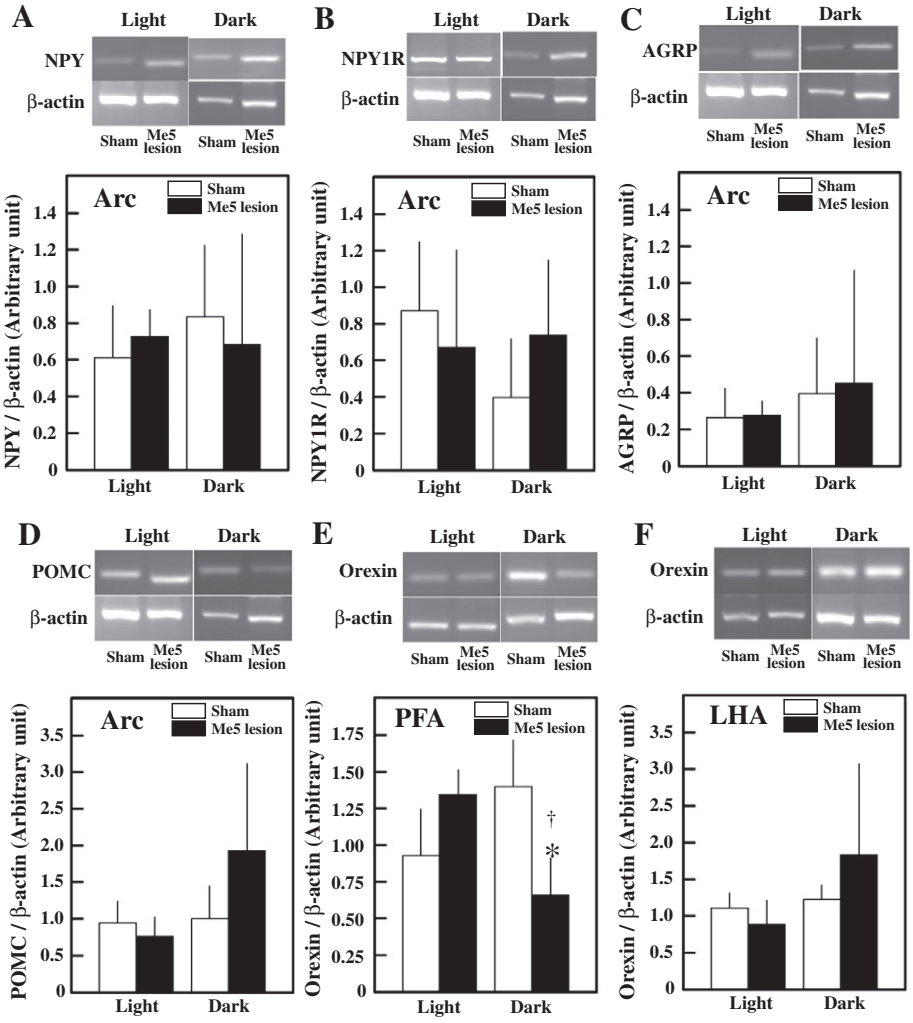

Fig. 3. The effects of bilateral Me5 lesions on mRNA expression levels of orexigenic and anorexigenic signaling molecules during the light and dark phases in the arcuate nucleus (Arc), the perifornical area (PFA), and the lateral hypothalamic area (LHA). The mRNA levels of NPY (A), NPY1R (B), AGRP (C), and POMC (D) in the Arc and orexin in the PFA (E) and LHA (F) were measured with RT-PCR 3 h after the onset of light and dark phases. The mRNA levels of these peptides are shown as the signal relative to that for β-actin. Results are the mean ± SEM. $^{*}P < 0.05$ and $^{\dagger}P < 0.05$ vs. the dark phase in sham-operated mice and the light phase in Me5-lesioned mice, respectively (one-way ANOVA followed by post-hoc Tukey's test).

(Inagaki et al., 1988; Panula et al., 1989). Among the subdivisions, the E3 group was recently found to innervate arcuate nucleus neurons (Umehara et al., 2012) and is activated by deprivation of anticipated food during scheduled feeding with corresponding activation of arcuate nucleus neurons (Umehara et al., 2011, 2012). Such concomitant activation in the TMN and arcuate nucleus neurons by food deprivation suggests that both the TMN and arcuate nucleus functionally interact with each other to maintain energy homeostasis. Although the details remain unknown, one hypothesis is that heterogeneous subpopulations in the TMN innervate distinct brain regions to regulate particular functions such as the sleep–wake cycle, appetite, nociception, cognition, and emotion (Brown et al., 2001; Haas and Panula, 2003; Passani et al., 2004). For example, the E2 group receives excitatory input from the orexin-containing neurons in the perifornical area, which are involved in sleep and/or arousal regulation (Bayer et al., 2001). Indeed, orexin is also thought to contribute to the onset and maintenance of sleep as well as feeding behavior (Schwartz et al., 2000). Moreover, histamine-containing neurons in the perifornical area and the E2 group are activated before mealtime (Umehara et al., 2011), suggesting that histaminergic neurons are present in the perifornical area and are activated when animals become hungry. In Me5-lesioned mice, the mRNA expression level of orexin in the perifornical area in the dark phase was significantly lower than that in the light phase (Fig. 3E). This result suggests that caudal Me5 lesions induce lower activity in orexin neurons in the perifornical area during the dark phase and may be insufficient for motivated arousal for feeding. Consequently, caudal Me5 lesions may lead to changes in the nocturnal properties of locomotion, feeding, and its related behaviors. Thus, Me5 may transmit the sensory signals derived from mastication and/or its own circadian signals to the perifornical area via an unknown neuronal pathway and control the daily timing of feeding and its related behaviors by adjusting the arousal state for feeding.

The circadian pacemaker of the hypothalamic suprachiasmatic nucleus (SCN) controls much of the circadian timing system of mammals by transmitting external light cycles through retinal ganglion cells (Morin and Allen, 2006). On the other hand, the Me5 with an endogenous circadian pacemaker operates via a different sensory mode than the SCN, which receives photic signals from the retina, and contains neurons with different bursting firing patterns and much higher spontaneous firing rates than SCN neurons (Enomoto et al., 2006; Herzog et al., 1997). Further studies will be needed to determine how the circadian

pacemaker modulates Me5 sensory responses to optimize its sensitivity, the motor trigeminal nucleus that is related to the jaw-jerk reflex, or satiation of food intake during the night to coincide with nocturnal behaviors.

Conclusion

The Me5 receives signals from the jaw-closing muscle spindles and the periodontal ligaments, regulates motor control of mastication, and also sends sensory signals to the hypothalamus. Indeed, the Me5 projects its fibers to the TMN in the posterior hypothalamus and modulates satiation through this pathway. The Me5 is likely to be mostly stimulated by jaw movement during the dark phase, exactly corresponding to circadian rhythms in the animal's nocturnal activity. As demonstrated in this study, bilateral caudal Me5 lesions alter the nocturnal behavior of food and water intake and locomotor activity in mice and decrease the mRNA expression levels of orexin in the perifornical area during the dark phase. Based on our results, Me5 activity corresponding to input stimuli derived from mastication may influence nocturnal properties of feeding and related behaviors by adjusting the activity of orexin neurons in the perifornical area.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.lfs.2013.09.015.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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