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Direct projection from the lateral habenula to the trigeminal mesencephalic nucleus in rats

Haruka Ohara[a,b], Yoshihisa Tachibana[a], Takashi Fujio[a], Rieko Takeda-Ikeda[a,b], Fumihiko Sato[a], Ayaka Oka[a,b], Takafumi Kato[a], Etsuko Ikenoue[a], Takashi Yamashiro[b], Atsushi Yoshida[a,*]

[a]Department of Oral Anatomy and Neurobiology, Osaka University Graduate School of Dentistry, Suita, Osaka 565-0871, Japan

[b]Department of Orthodontics and Dentofacial Orthopedics, Osaka University Graduate School of Dentistry, Suita, Osaka 565-0871, Japan

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ABSTRACT

Trigeminal mesencephalic nucleus (Vmes) neurons are primary afferents conveying deep sensation from the masticatory muscle spindles or the periodontal mechanoreceptors, and are crucial for controlling jaw movements. Their cell bodies exist in the brain and receive descending commands from a variety of cortical and subcortical structures involved in limbic (emotional) systems. However, it remains unclear how the lateral habenula (LHb), a center of negative emotions (e.g., pain, stress and anxiety), can influence the control of jaw movements. To address this issue, we examined whether and how the LHb directly projects to the Vmes by means of neuronal tract tracing techniques in rats. After injections of a retrograde tracer Fluorogold in the rostral and caudal Vmes, a number of neurons were labeled in the lateral division of LHb (LHbl) bilaterally, whereas a few neurons were labeled

Abbreviations: ABC, avidin-biotin-peroxidase complex; ATg, anterior tegmental nucleus; Aq, cerebral aqueduct; BDA, biotinylated dextranamine; CG, central gray matter; CL, central lateral nucleus of the thalamus; CM, central medial nucleus of the thalamus; DR, dorsal raphe nucleus; DTg, dorsal tegmental nucleus; FG, Fluorogold; fr, fasciculus retroflexus; IV, trochlear nucleus; IMD, intermediodorsal nucleus of the thalamus; KF, Kölliker-Fuse nucleus; LC, locus coeruleus; LDTg, laterodorsal tegmental nucleus; LHb, lateral habenula; LHbl, lateral division of LHb; LHbm, medial division of LHb; MD, mediodorsal nucleus of the thalamus; MHb, medial habenula; ml, medial lemniscus; mlf, medial longitudinal fasciculus; OPC, oval paracentral nucleus of the thalamus; PAG, periaqueductal gray matter; Pb, parabrachial nucleus; PB, phosphate buffer; PBS, phosphate-buffered saline; PC, paracentral nucleus of the thalamus; Po, posterior nucleus of the thalamus; PV, paraventricular nucleus of the thalamus; Rt, reticular nucleus of the thalamus; RtTg, reticulotegmental nucleus; scp, superior cerebellar peduncle; sm, stria medullaris of the thalamus; SPF, subparafascicular nucleus of the thalamus; TH, tyrosine hydroxylase; VM, ventromedial nucleus of the thalamus; Vmes, trigeminal mesencephalic nucleus; Vmest, trigeminal mesencephalic tract; Vmo, trigeminal motor nucleus; Vp, trigeminal principal nucleus; VPL, ventral posterolateral nucleus of the thalamus; VPM, ventral posteromedial nucleus of the thalamus; VPPC, parvicellular part of the ventral posterior nucleus of the thalamus; Vsup, supratrigeminal nucleus; ZI, zona incerta of the thalamus.

*Corresponding author at: Department of Oral Anatomy and Neurobiology, Osaka University Graduate School of Dentistry, 1-8 Yamadaoka, Suita, Osaka 565-0871, Japan. Fax: +81 6 6879 2880.
E-mail address: yoshida@dent.osaka-u.ac.jp (A. Yoshida).

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Negative emotion
Pain

in the medial division of LHb (LHbm) bilaterally. After injections of an anterograde tracer, biotinylated dextranamine (BDA) in the LHbl, a small number of labeled axons were distributed bilaterally in the rostral and caudal levels of Vmes, where some labeled axonal boutons contacted the cell body of rostral and caudal levels of Vmes neurons bilaterally. After the BDA injection into the LHbm, however, no axons were labeled bilaterally in the rostral and caudal levels of Vmes. Therefore, the present study for the first time demonstrated the direct projection from the LHbl to the Vmes and the detailed projection patterns, suggesting that jaw movements are modulated by negative emotions that are signaled by LHbl neurons.

1. Introduction

Trigeminal mesencephalic nucleus (Vmes) neurons are primary afferents innervating the muscle spindles of jaw-closing muscles or the periodontal mechanoreceptors around teeth (Byers et al., 1986; Corbin and Harrison, 1940; Jerge, 1963; Luo et al., 1991; Matesz, 1981), and are, thus, homologous to the ganglion neurons whose cell bodies are located in the dorsal root ganglion or trigeminal ganglion. Vmes neurons give off a large number of axon fibers terminating mainly in the jaw-closing motoneuron area of the trigeminal motor nucleus (Vmo) and in the supratrigeminal nucleus containing premotoneurons that project to the trigeminal motoneurons (Dessem and Taylor, 1989; Hugelin and Bonvallet, 1957; Nakamura et al., 1967; Shigenaga et al., 1988; Yabuta et al., 1996). Therefore, Vmes neurons conveying deep sensation from jaw-closing muscle spindles and periodontal ligaments are considered to play an important role in the feedback control of jaw-movements (Cody et al., 1972; Jerge, 1963; Taylor and Davey, 1968).

Compared to the ganglion neurons, the Vmes neurons are very unique primary afferents in that their cell bodies are located in the central nervous system, suggesting the possibility that the cell bodies receive inputs from other brain structures. Electron microscopic studies have revealed a large number of synapses on the cell bodies of Vmes neurons (Hinrichsen and Larramendi, 1970; Honma et al., 2001; Imamoto and Shimizu, 1970; Liem et al., 1991; Paik et al., 2012). The cell bodies are known to receive direct projections from several subcortical structures such as the hypothalamus (Moga et al., 1990; Nagy et al., 1986; Yamamoto et al., 1988), amygdala (Krettek and Price, 1978; Lazarov et al., 2011; Shirasu et al., 2011), raphe nuclei (Copray et al., 1991; Lazarov and Chouchkov, 1995; Li et al., 2000; Tashiro et al., 1989), locus coeruleus (LC) (Takahashi et al., 2010) and pontine reticular formation (Minkels et al., 1991; Ter Horst et al., 1991). On the other hand, our group has reported that the cell bodies of Vmes neurons receive strong direct projections from the medial prefrontal cortex and lateral prefrontal cortex (insular cortex), but rarely from the somatic sensorimotor cortex (Iida et al., 2010). These studies suggest that the neuronal activity of Vmes neurons can be modulated by multiple limbic structures. However, it remains unknown how negative emotions (e.g., orofacial pain, stress, anxiety and disappointment) can influence the jaw movements. With this respect, we hypothesized that the lateral habenula (LHb) can be a source of projections conveying the information of negative emotions on Vmes activity.

The habenula is an epithalamic structure. The LHb neurons encode disappointment and expectation of negative conditions (Shepard et al., 2006; Ullsperger and von Cramon, 2003). Pioneering electrophysiological studies have elegantly shown that the primate LHb neurons are excited by the omission of rewards and the aversive stimuli/outcomes (Matsumoto and Hikosaka, 2007, 2009). Accordingly, the LHb has been implicated in broad functions and pathologic conditions related to stress, pain and depressive disorder (for reviews, see Hikosaka (2010), Hikosaka et al. (2008), Lecourtier and Kelly (2007) and Shelton et al. (2012)), suggesting the possibility that the LHb also exerts some influences on body movements. However, little is known about the neuronal mechanisms of the LHb especially in motor control of jaw movements.

In this study, therefore, we sought to test whether there exists direct projection from the LHb, a center of negative emotions, to the Vmes by means of retrograde and anterograde neuronal tract-tracing techniques in the rat.

2. Results

2.1. *Retrograde labeling after FG injections into Vmes*

The rat Vmes nucleus formed a rostrocaudally long, mediolaterally narrow band of neurons that extended from the middle level of the superior colliculus (rostral end) to the caudal border of the Vmo caudally (caudal end) (e.g., Fig. 1 A and B). The Vmes was identified by recording single negative potentials, the latency of which was about 0.85 ms, after the electrical stimulation of the masseter nerve (Fig. 1C). A small amount of retrograde tracer Fluorogold (FG) was iontophoretically injected into the caudal level of Vmes in 11 rats (e.g., Fig. 1D) and into the rostral level of Vmes in five rats (e.g., Fig. 1E) (Table 1). Among the 11 cases of caudal injections, we analyzed the data obtained from six cases in which the injection sites successfully covered the caudal Vmes. In three (R706, R707, R807) out of the six cases, the injection sites slightly extended into the neighboring regions including the medial part of parabrachial nucleus, reticular formation ventral to the Vmes, rostral part of the LC, and lateral margin