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Anatomical organization of descending cortical projections orchestrating the patterns of cortically induced rhythmical jaw muscle activity in guinea pigs

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ABSTRACT

Repetitive electrical microstimulation to the cortical masticatory area (CMA) evokes distinct patterns of rhythmical jaw muscle activities (RJMAs) in animals. This study aimed to investigate the characteristics of the descending projections from the CMA, associated with distinct patterns of RJMAs, to the thalamus, midbrain, pons and medulla in guinea pigs. RJMAs with continuous masseter and digastric bursts (CB-RJMAs) and stimulus-locked digastric sub-bursts (SLB-RJMAs) were induced from the anterior and posterior areas of the rostral region of the lateral agranular cortex, and chewing-like RJMAs from the rostral region of the granular cortex. Anterograde tracer, biotinylated dextran amine, was injected into the three cortical areas. The cortical area inducing CB-RJMAs had strong ipsilateral projections to the motor thalamus, red nucleus, midbrain reticular formation, superior colliculus, parabrachial nucleus, and supratrigeminal region, and contralateral projections mainly to the lateral reticular formation around the trigeminal motor nucleus (Vmo). The cortical area inducing SLB-RJMAs had moderate projections to the motor thalamus and lateral reticular formation around the Vmo, but few projections to the midbrain nuclei. The cortical area inducing chewing-like RJMAs had strong projections to the ipsilateral sensory thalamus and contralateral trigeminal sensory nuclei, and moderate projections to the lateral reticular formation. The three cortical areas consistently had few projections to the ventromedial reticular formation. The present study demonstrates that multiple direct and indirect descending projections from the CMA onto the premotor systems connecting the trigeminal motoneurons represent the neuroanatomical repertoires for generating RJMAs during the distinct phases of natural ingestive behavior.

Abbreviations: 3V, third ventricle; 7N, facial nerve; ABC, avidin–biotin–peroxidase complex; Ag, agranular cortex; BDA, biotinylated dextran amine; CB-RJMA, RJMA with continuous masseter and digastric bursts; cc, corpus callosum; Cl, claustrum; CL, central lateral nucleus of the thalamus; CM, central medial nucleus of the thalamus; CMA, cortical masticatory area; cp, cerebral peduncle; Cu, cuneate nucleus; DR, dorsal raphe nucleus; EMG, electromyographic; Gr, granular cortex; IC, inferior colliculus; III, oculomotor nucleus; IO, inferior olive; Ins, insular cortex; Jc, jaw-closing nucleus of the Vmo; Jo, jaw-opening nucleus of the Vmo; MD, mediodorsal nucleus of the thalamus; ml, medial lemniscus; mRt, midbrain reticular formation; mt, mammillothalamic tract; PAG, periaqueductal gray; Pb, parabrachial nucleus; PB, phosphate buffer; PBS, phosphate-buffered saline; PC, paracentral nucleus of the thalamus; Po, posterior nucleus of the thalamus; py, pyramidal tract; pyx, pyramidal decussation; Re, reuniens nucleus of the thalamus; Rh, rhomboid nucleus of the thalamus; RJMA(s), rhythmical jaw muscle activity (-ies); RmJo, reticular region medial to the Jo; RN, red nucleus; Rt, reticular nucleus of the thalamus; SC, superior colliculus; SCD, deep gray layer of the SC; SCI, intermediate gray layer of the SC; SCS, superficial gray layer of the SC; scp, superior cerebellar peduncle; SLB-RJMA, RJMA with stimulus-locked digastric sub-bursts; Sm, submedial nucleus of the thalamus; SN, substantia nigra; SO, superior olive; Sol, nucleus of the solitary tract; Vc, trigeminal caudal subnucleus; Vi, trigeminal interpolar subnucleus; VII, facial nucleus; Vint, intertrigeminal region; Vjuxt, juxtatrigeminal region; VL, ventral lateral nucleus of the thalamus; VM, ventromedial nucleus of the thalamus; Vmes, trigeminal mesencephalic nucleus; Vmo, trigeminal motor nucleus; Vo, trigeminal oral subnucleus; Vp, trigeminal principal nucleus; VPL, ventral posterolateral nucleus of the thalamus; VPM, ventral posteromedial nucleus of the thalamus; Vsup, supratrigeminal region; Vtr, trigeminal spinal tract; XII, hypoglossal nucleus; X, vagal nucleus; ZI, zona incerta.

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1. Introduction

The cortical masticatory area (CMA) is named for the area covering the sensorimotor cortex in which repetitive electrical microstimulation induces rhythmical jaw muscle activities (RJMAs) in rats (Sasamoto et al., 1990; Satoh et al., 2007; Tsujimura et al., 2012), rabbits (Liu et al., 1993; Lund et al., 1984), cats (Iwata et al., 1990; Morimoto and Kawamura, 1973), and monkeys (Hatanaka et al., 2005; Huang et al., 1989). Several studies have shown that different areas of the CMA induce different rhythmical patterns of mandibular movement and jaw muscle electromyographic (EMG) activity (Hatanaka et al., 2005; Huang et al., 1989; Liu et al., 1993; Masuda et al., 2005). In addition, cortically induced RJMAs mimic the pattern of EMG activity of the jaw muscles and jaw movement trajectories during natural feeding behaviors (Iriki et al., 1988; Isogai et al., 2012; Liu et al., 1993; Lund et al., 1984; Masuda et al., 2002). RJMAs can also be induced by stimulating the CMA in guinea pigs. The cortically induced RJMAs associated with vertical open-close jaw movements are sub-classified into two types according to the characteristics of the digastric muscle bursts; these rhythmical bursts are characterized either by continuous muscular discharge, or by clusters of sub-bursts time-locked to each stimulus pulse (Chandler et al., 1990; Enomoto et al., 1995; Goldberg et al., 1982). A more recent study has shown that a third type of RJMA is induced with digastric and masseter muscle activation similar to natural chewing (Isogai et al., 2012). The three types of cortically induced RJMAs are represented in separate areas of the sensorimotor cortex in guinea pigs (Enomoto et al., 1995; Iriki et al., 1988; Isogai et al., 2012).

The distinct rhythmical patterns of cortically induced RJMAs reflect the characteristics of the net facilitatory inputs to the trigeminal motoneurons, formed by varying combinations of activity among premotor neural subpopulations (Westberg et al., 1998). Therefore, electrical stimulation of the CMA can generate a distinct descending influence directly to the subpopulations of trigeminal premotoneurons. Nonetheless, previous anatomical studies showed descending projections from the cortical sensory and motor areas associated with orofacial functions, to brainstem structures such as the thalamus (Haque et al., 2010; Hatanaka et al., 2005; Isogai et al., 2012; Reichova and Sherman, 2004) and midbrain (Enomoto et al., 1995), as well as to pontomedullary reticular formations and the trigeminal sensory nuclear complex where trigeminal premotoneurons are located (Chang et al., 2009; Kolta et al., 2000; Li et al., 1995; Turman and Chandler, 1994a, 1994b). These studies suggested the possibility that the areas of the CMA inducing RJMAs have unique descending pathways direct to the trigeminal premotoneurons as well as to other brainstem structures. However, the descending projections from the CMA to the brainstem structures have been rarely characterized in comparison to the recordings of cortically induced RJMAs. Therefore, the aim of the present study was to clarify the organization of the descending projections from the CMA where the distinct types of RJMAs were induced, by a combination of repetitive electrical microstimulation and anterograde neuronal tract-tracing techniques.

2. Materials and methods

2.1. Animal preparation

Experiments were conducted on 13 male Hartley guinea pigs weighing 600–700 g. All experimental procedures were approved by the intramural Animal Care and Use Committee of Osaka University Graduate School of Dentistry, and all efforts were made to minimize the number of animals used.

Surgery was performed under premedication of atropine sulfate (0.04 mg/kg, i.p.) and anesthesia with sodium pentobarbital (50 mg/kg, i.p.). Additional anesthesia (sodium pentobarbital: 5 mg/kg, i.p.) was applied if it was necessary to maintain a level of anesthesia at which neither apparent corneal reflex nor spontaneous eye movements were present. Rectal temperature was maintained at 37–38 °C by a controlled heating pad. To record EMG activities, pairs of urethane-coated stainless steel wires (0.12 mm diameter, 1.5 mm of the tip was bare) were inserted into the masseter muscles and the anterior belly of the digastric muscles on the left side contralateral to the cortical stimulation site. The other ends of the wire electrodes were tunneled subcutaneously and attached to a connector on the skull. For an atraumatic fixation of the animal's head during training and recording, a nut and cylindrical aluminum tube were cemented to the parietal skull using dental acrylic resin. The animal's head was secured in a stereotaxic frame by screwing the nut to the frame and attaching both ends of the aluminum tube to the bars of the frame (Isogai et al., 2012; Kanayama et al., 2010; Kato et al., 2013). For intracortical microstimulation, a part of the right skull was removed to expose the cortical surface between 2 mm posterior and 6 mm anterior to the bregma and between 1 and 8 mm lateral to the midline. The dura was covered with liquid paraffin filled in a chamber, and a removable lid was placed over the top of the chamber. After surgery, the animals were allowed to recover from the anesthesia in their cage. Antibiotic (oxytetracycline, 10 mg/kg, i.p.) and an analgesic (flurbiprofen axetil, Ropion®, 0.8 mg/kg, Kaken Seiyaku Co. Ltd., Tokyo, Japan) were administered for three days postoperatively. The animals were allowed to familiarize themselves with the head fixation apparatus under unanesthetized conditions after training for eight to ten days before the experiment.

2.2. Recording of natural chewing and cortically induced RJMAs

The experiments were performed using animals placed in the stereotaxic apparatus under unanesthetized conditions. To record the cortically induced RJMAs, repetitive stimulation with square pulses (30 Hz, duration 200 μs, <100 μA, 6 s) was applied to the right cortex in 13 animals, through glass-coated metal electrodes with a tip diameter of 40–50 μm (impedance: 1–2 MΩ at 1 kHz) (Isogai et al., 2012). Three cortical sites were chosen according to previous studies (Enomoto et al., 1995; Isogai et al., 2012); the stereotaxic coordinates of these areas were (a) 5 mm anterior (A5.0) and 3–4 mm lateral (L3.0 to L4.0), (b) 1–3 mm anterior (A1.0 to A3.0) and 3 mm lateral (L3.0), and (c) 0–1 mm anterior (A0 to A1.0) and 5–7 mm lateral (L5.0 to L7.0) to the bregma. In eight animals, natural chewing was induced by inserting a small food pellet into the mouth (Isogai et al., 2012; Kanayama et al., 2010). The recorded electrical signals representing EMG activity was stored on a personal computer (sampling rate for EMG activity: 2000 Hz) using the Spike2 software (Cambridge Electronic Design, Cambridge, UK).

2.3. Injection of tracer

After determination of the cortical sites that induced RJMs, the metal electrode was replaced by a glass micropipette with a tip diameter of 40–50 μm, and inserted into the appropriate site. The glass micropipette was filled with an anterograde tracer, 4% biotinylated dextran amine (BDA, 10,000 MW, Molecular Probes, Eugene, OR) in 0.1 M phosphate buffer (PB). A single injection of BDA solution (in all 13 guinea pigs) was administered iontophoretically (positive pulses, 4 μA, 300 ms, 2 Hz, 90 min) in 11 guinea pigs or by using an oil pressure injector (0.8 μl) in two guinea pigs. After tracer injection, all bone defects were sealed with dental cement and acrylic resin, and the animals were allowed to recover in their cages. Antibiotic and analgesic were administered for three days post-experimentally. The animals were kept alive for 10–14 days in accordance with the procedures of our preliminary experiments.