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Ephaptic transmission is the origin of the abnormal muscle response seen in hemifacial spasm

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HIGHLIGHTS

- Abnormal muscle responses result from antidromic motor impulses rather than trigeminal sensory input.
- Slow conducting motor fibers traveling at 33 m/s give rise to lateral spread, inducing orthodromic impulses.
- Ephaptic transmission takes place at the site of vascular compression rather than the facial nerve nucleus.

ABSTRACT

Objective: In patients with hemifacial spasm, stimulation of a branch of the affected facial nerve elicits an abnormal response in the muscles innervated by another branch. We tested the hypothesis that this anomaly results from lateral spread of impulses from one motor axon to another at the site of the nerve compression by the offending artery.
Methods: In a preoperative study of 21 patients, we delivered a series of stimuli, in short increments, successively distally along the temporal branch of the facial nerve to record abnormal muscle responses from the orbicularis oculi and mentalis muscles. In intraoperative monitoring of 10 patients during microvascular decompression, we monitored propagating nerve action potentials with a handheld electrode placed on the facial nerve 3 mm distal to the vascular compression site.
Results: With incremental shifts of stimulating points distally, the latency of abnormal muscle responses increased by 0.3 ± 0.1 ms/cm. This finding implicates the antidromic motor impulse as the trigger for lateral spread. The nerve action potentials recorded during surgery comprised the initial antidromic signal followed by one or more additional peaks. The latter immediately abated, together with abnormal muscle responses, after microvascular decompression. Thus, the secondary peaks must represent the orthodromic impulses generated by ephaptic transmission. An average inter-peak interval of 1.1 ms between the first and secondary peaks is consistent with the estimated conduction time from the stimulation point to the site of vascular compression but not to the facial nucleus and return.
Conclusion: An abnormal muscle response results from lateral spread of impulses between motor axons at the site of vascular compression rather than at the facial nucleus.
Significance: This study establishes the mechanism of lateral spread responsible for abnormal muscle responses and contributes to the understanding of pathophysiology underlying hemifacial spasm.

1. Introduction

Hemifacial spasm, caused by intracranial vascular compression of the facial nerve, abates promptly after microvascular decompression, as a pivotal surgical strategy (Cook and Jannetta, 1984; Jannetta, 1997). Electrophysiological studies explored the

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complicated circuitry of brainstem network with the facial and trigeminal nerves, considering blink reflex, axono-axonal lateral spread, and F waves or recurrent discharge at the facial nucleus. Although there is a general belief that the hyperexcitability responsible for hemifacial spasm involves the facial nerve or the nucleus (Møller and Jannetta, 1985; Møller, 1987; Ishikawa et al., 1996), currently available data still lack direct evidence to precisely locate the site of lateral spread that causes a widespread facial contraction.

In patients with hemifacial spasm, stimulation of the supraorbital nerve elicits a blink reflex not only in the orbicularis oculi but also in the other facial muscles and is generally accepted as electrophysiologic evidence of synkinesis (Kimura et al., 1975). This finding indicates that reflexive activation of the facial nucleus lead to a lateral spread either at the facial nucleus or more distally. The aberrant response, however, does not necessarily depend on a trigeminal sensory input, as an electrical stimulation of a branch of the facial nerve also gives rise to similar abnormal muscle responses in the facial muscles innervated by another branch.

Many electrophysiologic studies conducted over two decades attempted to elucidate the pathophysiologic mechanism of lateral spread. In one study, the use of subthreshold stimulation led to the conclusion that an impulse of trigeminal input rather than antidromic activation of the facial nerve gave rise to abnormal muscle responses (Misawa et al., 2006). Conversely, supramaximal stimulation of facial nerve terminals showed a progressive shortening of latency with incremental displacement of the stimulation site away from the supraorbital nerve, implicating the antidromic motor impulse as the trigger to initiate the drive (Montero et al., 2007).

During intraoperative monitoring, microvascular decompression quickly abolishes the abnormal muscle responses that are considered an electrophysiologic correlate of synkinesis (Sekula et al., 2009; Kim et al., 2010; Thirumala et al., 2011). This finding led to two hypotheses for generation of abnormal muscle response, ephaptic transmission between motor axons of the facial nerve at the site of vascular compression (Nielsen, 1984a,b, 1985; Nielsen and Jannetta, 1984) or widespread recurrent discharge of the facial nerve motoneurons (Møller and Jannetta, 1985; Møller, 1987). Sanders (1989) reported that a low jitter value of abnormal muscle response assessed by single fiber recording suggested an ephaptic transmission at the site of compression. Nielsen (1984a,b, 1985) showed a delay of R1 of the blink reflex on the affected side and postulated that slow-conducting motor nerve fibers triggered ephaptic transmission at the compressed nerve segment. Conversely, Møller and Jannetta (1985), based on their intraoperative findings, indicated that the fastest-conducting axons participated in the generation of lateral spread at the facial nucleus. In the current study, we wished to resolve the controversies by direct recording of nerve action potentials responsible for lateral spread during intraoperative monitoring.

In the current experiment, we first conducted a preoperative study to determine whether abnormal muscle responses induced by facial nerve stimulation result from antidromic motor impulses or trigeminal sensory input. Subsequent intraoperative studies tested the hypothesis that antidromic impulses in one branch of the facial nerve cause ephaptic transmission in other branches, thereby giving rise to abnormal muscle responses. We also postulate that microvascular decompression should abolish the secondary orthodromic impulses concomitant with abnormal muscle responses, leaving the initial antidromic signal unaffected.

2. Patients and methods

All patients agreed in writing to participate in the study after reading an informed consent approved by the local Institutional Review Board of Nishi-Niigata Chuo National Hospital.

The study consisted of two parts: (1) preoperative electrophysiological study to show that the antidromic facial nerve impulse, rather than trigeminal sensory input, generates the abnormal muscle response. (2) Intraoperative study to localize the site of lateral spread by analyzing the initial antidromic impulse and secondary orthodromic impulses recorded from the facial nerve distal to the site of vascular compression.

2.1. Preoperative electrophysiological study

The study included a total of 21 patients (15 women) aged 32–78 years (mean, 53) referred from outside clinics for evaluation of intractable idiopathic hemifacial spasm of 0.5–13 year duration (mean, 6 years). They all underwent a successful microvascular decompression of the facial nerve.

All patients received oral administration of diazepam (10 mg) for preoperative studies, conducted by a Neuropack Sigma or MEB-9204 (Nihon Kohden, Tokyo, Japan), with a filter setting of 50 Hz to 10 kHz. A series of surface stimulations of the facial nerve along its temporal branch elicited direct muscle responses in the frontalis muscle and abnormal muscle responses in the orbicularis oculi and mentalis muscles (Fig. 1). We delivered four incremental electrical stimulations, one-cm apart, along the course of the nerve distally from (0) defined as the point just behind the external angular process of the orbit. Electrical stimulation consisted of a single 0.2 ms-square wave pulse, with intensity set at double the threshold, which just elicited an abnormal muscle response in the mentalis muscle. For comparison, stimulation of the trigeminal nerve at the supraorbital foramen elicited R1 of the blink reflex in the frontalis, orbicularis oculi and mentalis muscles. In five patients, we also tested the effect of electrical stimulation delivered to the mucosa of nasal septum, which activated sensory fibers selectively.

2.2. Intraoperative monitoring

Of the 21 patients, 10 underwent intraoperative monitoring during microvascular decompression surgery conducted under total intravenous anesthesia with propofol and remifentanil. Omission of any muscle relaxant after intubation under general anesthesia minimized the influence of anesthesia on monitoring results. We used Neuromaster MEE1216 (Nihon Kohden, Tokyo, Japan), with a filter setting at 50 Hz to 3 KH, for surface recording of the direct muscle response from frontalis, and abnormal muscle responses from the orbicularis oculi and mentalis muscles after delivering a single supramaximal 0.2-ms square wave pulse, by subcutaneous needle electrodes, with the cathode placed proximally at (0) of the temporal branch of the facial nerve (Fig. 2). Simultaneous recording of facial nerve action potentials with a handheld monopolar electrode placed 3 mm distal to the site of vascular compression and the reference electrode on the cervical skin allowed assessment of impulses propagating across the facial nerve before and after microvascular decompression.

3. Results

3.1. Preoperative electrophysiological study

With incremental shifts of the stimulus point from (0) along the temporal branch of the facial nerve distally, the latency of abnormal muscle response progressively increased by 0.3 ± 0.1 ms/cm (Fig. 1). In all 21 patients, stimulation of the supraorbital nerve at the supraorbital foramen elicited an aberrant blink reflex in mentalis muscles. Its R1 latency (12.6 ± 1.0 ms) consistently exceeded the latency of the abnormal muscle response evoked by stimulation of the facial nerve at (0) (10.7 ± 1.1 ms). The average