Sympathetic nerves bridge the cross-transmission in hemifacial spasm

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ABSTRACT

The pathophysiologic basis of hemifacial spasm is abnormal cross-transmission between facial nerve fibers. The author hypothesized that the demyelinated facial nerve fibers were connected with the sympathetic nerve fibers on the offending artery wall, and thus the latter function as a bridge in the cross-transmission circuit. This hypothesis was tested using a rat model of hemifacial spasm. A facial muscle response was recorded while the offending artery wall was electrically stimulated. The nerve fibers on the offending artery wall were blocked with lidocaine, or the superior cervical ganglion, which innervates the offending artery, was resected, and meanwhile the abnormal muscle response was monitored and analyzed. A waveform was recorded from the facial muscle when the offending artery wall was stimulated, named as "Z-L response". The latency of Z-L response was different from that of abnormal muscle response. When the nerve fibers on the offending artery wall were blocked by lidocaine, the abnormal muscle response disappeared gradually and recovered in 2 h. The abnormal muscle response disappeared permanently after the sympathetic ganglion was resected. Our findings indicate that cross-transmission between the facial nerve fibers is bridged by the nerve fibers on the offending artery wall, probably sympathetic nerve fibers.

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1. Introduction

Hemifacial spasm (HFS) is a neuromuscular disorder characterized by frequent, involuntary facial muscle contractions that cause physical discomfort and embarrassment, and impair the life quality. Although there are many different etiologies such as Bell's palsy, facial nerve injury, demyelinating lesions and hereditary [18], it's generally accepted that the major etiology of hemifacial spasm is vascular compression of the seventh cranial nerve (the facial nerve, Fig. 1A) at its root exit zone (REZ) [2,6]. The compression is caused by offending vessels, such as the anterior inferior cerebellar artery, posterior inferior cerebellar artery, and vertebral artery [2,6,9]. Up till now, the pathogenesis of HFS is unclear yet.

In patients with HFS, electrical stimulation of one branch of the facial nerve on the affected side can elicit a delayed response from the muscles supplied by other branches; this has been called an "abnormal muscle response" (AMR), also known as “lateral spread response” (LSR). The presence of an AMR has been documented only in patients with HFS, so an AMR serves as a “marker” of HFS and is useful for the diagnosis and intraoperative monitoring during microvascular decompression surgery [17]. An AMR suggests that abnormal cross-transmission takes place between facial nerve fibers, and this is believed to be the main pathogenic basis for HFS [13,17,19]. However, the location and style of cross-transmission are still controversial. Two hypotheses have prevailed. One supposes that ephaptic transmission occurs between individual facial nerve fibers at the site of neurovascular compression because compression injures the myelin [16] and brings bare axons close together [4,15]. The other hypothesis states that chronic injury to the facial nerve may make the facial motor nucleus hyperexcitable and cause the opening of dormant synapses, which could cause cross-transmission in the facial motor nucleus [7,8,13,14]. In this paper, the former is referred to as the “ephaptic transmission hypothesis” (Fig. 1B) and the latter as the “hyperexcitable nucleus hypothesis” (Fig. 1C). The advantages and shortcomings of these two hypotheses are discussed later.

Abbreviations: AMR, abnormal muscle response; ZLR, Z-L response; ECA, external carotid artery; EMG, electromyogram; HFS, hemifacial spasm; MVD, microvascular decompression; REZ, root exit zone.

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In our clinical practice, we have often found that once the offending vessel is detached from the facial nerve, the AMR disappears immediately, and such patients generally have immediate spasm relief after surgery. This observation is consistent with the literature [11,12,20]. However, neither the ephaptic transmission hypothesis nor the hyperexcitable nucleus hypothesis successfully explains this very common and important clinical phenomenon. It seems inconceivable that hyperexcitability of facial motor neurons would decrease immediately after detaching the offending vessel. Similarly, it is impossible that the histological changes at the sites of compression, such as demyelination, vacuolization of the myelin sheath, and partial degeneration of axons [16], will disappear immediately after decompression. Based on these two hypotheses, it might be expected that most cases of HFS would resolve gradually after MVD surgery. However, this is not the case. The abnormal cross-transmission seems dependent on the close contact between the facial nerve and the offending vessel. Thus, we hypothesized that the offending vessel itself may be part of the cross-transmission circuit, so the circuit is broken as soon as the offending vessel is detached from the facial nerve. Nerve impulses (action potentials) can only be conducted through nerve fibers, and there are abundant sympathetic nerve fibers on the artery wall [3]; thus, we further hypothesized that the sympathetic nerve fibers on the offending artery wall may connect to the demyelinated facial nerves and function as a "bridge" in the cross-transmission of HFS, named as "sympathetic bridge hypothesis" (Fig. 1D).

If the sympathetic bridge hypothesis is true, there follows three deductions: (1) If the sympathetic nerve fiber on the offending artery wall is electrically stimulated, the impulse will be conducted to the facial nerve, and then a facial muscle response can be recorded; (2) If the sympathetic nerve fiber on the offending artery wall is blocked with lidocaine, the cross-transmission circuit will be broken, and then AMR will be eliminated, but the facial nerve conduction remains intact; (3) If the sympathetic ganglion which innervates the offending artery is removed, the cross-transmission circuit will be broken permanently. Following these deductions, the hypothesis was tested in animal experiments.

2. Methods

2.1. Animal model of HFS

Experiments with animals were performed in accordance with the legal requirements of Xinhua Hospital. Rat models of HFS were produced under anesthesia with pentobarbital (40 mg/kg, intraperitoneally), following the methods reported by Kuroki and Møller [8]. At the first stage, the extracranial portion of the facial nerve was exposed under a Møller–Wedel surgical microscope; and then the main trunk of the facial nerve was dissected. Afterwards a chromic gut ligature was placed in the gap between the facial nerve and the temporal artery, which runs just beneath the facial nerve at a right angle. At the second stage (2 weeks later), the chromic gut ligature was removed, and then the temporal artery was transposed with a teflon felt so that it came in close contact with the facial nerve (Fig. 2). Four weeks after the second stage, abnormal muscle response was recorded [8] from the mentalis muscle in response to electrical stimulation of the ipsilateral temporal branch of the facial nerve (S1 and R1, Fig. 2), using an evoked potential system (Medtronic Keypoint 4, Dantec, Denmark) with the stimulation intensity of 3–10 mA × 0.1 ms. Only those AMR-positive rats were kept for further study. Those failed to induce AMR were rejected.

2.2. Test the first deduction

Two groups of rats were included in this experiment. The HFS group (n = 10) underwent 2 stages of operation as mentioned above, and were confirmed AMR-positive. The control group of rats

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**Fig. 1.** Models of three hypotheses regarding the cross-transmission of hemifacial spasm. (A) The normal status of facial nerve. The blue line represents a facial nerve fiber in the marginal mandibular branch. (B) Ephaptic transmission hypothesis supposes that ephaptic transmission occurs between individual facial nerve fibers just at the site of neurovascular compression. (C) Hyperexcitable nucleus hypothesis claims that chronic injury to the facial nerve may cause the opening of dormant synapses that would cause cross-transmission in the facial motor nucleus. (D) Sympathetic bridge hypothesis assumes that at the site of neurovascular compression, cross-transmission between the facial nerve fibers is bridged by the sympathetic nerve fibers (the green lines) on the offending artery wall. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

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**Fig. 2.** Schematic diagram of the animal experiment, using a rat model of hemifacial spasm established by Møller et al. To record abnormal muscle response (AMR): stimulating the temporal branch of the facial nerve (S1) and recording from the mentalis muscle (R1). To record electromyogram (EMG): stimulating the main trunk of the facial nerve at the stylomastoid foramen (S2) and recording from the mentalis muscle (R2). To record Z-L response (ZLR): stimulating the temporal artery wall (S3) and recording from the mentalis muscle (R3). **The beginning of the external carotid artery (ECA; upstream of the temporal artery) was exposed, and 1 mg/50 μL. lidocaine was injected around the external carotid artery to block the nerve fibers on the artery wall.** The superior cervical ganglion was resected.
(n = 10) underwent only the second stage of operation, i.e., the facial nerve was compressed by temporal artery, but not demyelinated in advance. Four weeks after the surgery, a novel waveform was recorded. Briefly, the needle reference electrodes were inserted into the back, and the needle recording electrodes into the mentalis muscle. The needle stimulating electrodes were placed on the temporal artery wall under surgical microscope (S3 and R3, Fig. 2). The stimulation intensity was 1 mA × 0.1 ms, and then a waveform was recorded with the evoked potential system using the "F-Responses" mode.

2.3. Test the second deduction

This experiment included 10 rats of HFS. While the AMR was monitored, the beginning of the external carotid artery (ECA; upstream of the temporal artery) was exposed, and 1 mg/50 μL lidocaine was injected around the ECA to block the nerve fibers on the artery wall (Fig. 2). Then, AMR was recorded every 5 min (S1 & R1, Fig. 2). Meanwhile, an electromyogram (EMG) was recorded while the facial nerve was stimulated at the stylomastoid foramen (S2 and R2, Fig. 2) to exclude the possibility that the facial nerve was affected by lidocaine.

2.4. Test the third deduction

This part included 10 rats of HFS. We resected the ipsilateral superior cervical ganglion that supplies sympathetic innervation to the temporal artery while AMR monitoring to further confirm that sympathetic nerve fibers take a role in the abnormal cross-transmission circuit.

3. Results

All animals in the HFS group were AMR-positive (Fig. 3A), and all in the control group were AMR-negative (Fig. 3B). The latency of AMR was 6.6 ± 0.9 ms. When the offending artery was electrically stimulated, a facial muscle response was recorded in all rats of the HFS group. This novel waveform was named as “Z-L response”, abbreviated as “ZLR” (Fig. 3C). The latency of ZLR was 5.1 ± 0.7 ms, shorter than that of AMR (P < 0.05, Student’s t-test). However, ZLR cannot be induced in any animal of the control group (Fig. 3D), although the temporal artery was in close contact with the facial nerve as well. It implied that direct contact of artery and facial nerve was not sufficient for generation of ZLR.

While the AMR was monitored dynamically, the nerve fibers on the ECA wall were blocked with lidocaine (Fig. 4). The AMR remained unchanged at the time of lidocaine injection, but the waveform amplitude decreased significantly 5 min later. The AMR turned into a very small wave 10 min later. Then, about 15 min later, the AMR disappeared completely. The incision was then rinsed three times with physiologic saline, and AMR monitoring continued. The AMR did not reappear until 95 min, and then it recovered gradually. The AMR became a normal shape at 110 min. When the AMR disappeared, the EMG remained normal (Fig. 4) while the facial nerve was stimulated at the stylomastoid foramen (medial to the vascular compression site of the rat model), indicating that the conduction of facial nerve was not affected by lidocaine.

The superior cervical ganglion on the affected side was resected while AMR monitoring. Two minutes later, the AMR disappeared completely and did not reappear thereafter (1 day, 1 week, and 2 weeks; Fig. 5).

4. Discussion

The ephaptic transmission hypothesis [15] claims that cross-transmission occurs among individual facial nerve fibers injured by neurovascular conflict. It is supported by a pathologic study that found histologic changes on facial nerves at the site of compression, such as demyelination, vacuolization of the myelin sheath, and partial degeneration of axons [16]. However, Møller and colleagues [10,13,14] found a difference of 2 ms between the AMR latency and the sum of the conduction times in the portions of the facial nerve that would have been involved if the cross-transmission had occurred at the site of neurovascular conflict. Thus, the ephaptic

![Image](image-url)
transmission hypothesis failed to pass electrophysiologic verification.

Based on their electrophysiologic findings, Moller and Jannetta proposed the hyperexcitable nucleus hypothesis [13] assuming that cross-transmission occurs in the facial motor nucleus. The facial motor nucleus is not compressed by vessels; however, vascular irritation of the facial nerve generates abnormal neural activity, which makes the facial motor nucleus hyperexcitable and gradually causes opening of dormant synapses that would cause cross-transmission in the facial motor nucleus. Yamashita et al. [20] studied the AMRs elicited by double stimulation in 12 patients with HFS. They found that the second response (R2) appeared after a fixed refractory period without facilitation or depression in a latency and amplitude recovery curve. Their findings convincingly suggested that the AMR does not arise from facial motor neurons. Therefore, the hyperexcitable nucleus hypothesis failed to pass electrophysiologic verification, too.

In this paper, we proposed the sympathetic bridge hypothesis. We succeeded in recording a facial muscle response while stimulating the offending artery wall, which verified the first deduction of our hypothesis. One may argue that the electrical stimulation on the offending artery may directly spread to the facial nerve as physical current flow. We found that Z-L response was induced only in the HFS group, but not in the control, thus it is very likely that the slight impulse (1 mA × 0.1 ms) delivered to the temporal artery wall conducted to the facial nerve through nerve conduction rather than as physical current flow, because in both groups the temporal artery was in close contact with the facial nerve. It follows that there should be a neural connection between the offending artery wall and the facial nerve.

When the nerve fibers on the offending artery wall were blocked with lidocaine, AMR was eliminated; meanwhile the facial nerve conduction was not affected. This finding indicates that nerve fibers on offending artery wall are part of cross-transmission circuit in hemifacial spasm. Resection of the sympathetic ganglion that innervates the offending artery eliminated AMR completely. Therefore, the second and the third deductions were verified. Taken together, we believe that the sympathetic nerve fibers on the offending artery wall are the indispensable component of the abnormal cross-transmission circuit in hemifacial spasm.

Anatomic studies [1,3] found that many sympathetic fibers are distributed on the surface of the arteries, beneath the tunica adventitia vasorum. We assume that the continuous irritation of arterial pulse (in human beings) or the chronic gut ligature (in animal model) damages the tunica adventitia vasorum and the epineurium. Thus, the nude sympathetic nerve fibers come in close contact with the demyelinated facial nerve fibers, and action potentials is possible to spread from one facial nerve fiber to others via the “bridge” of sympathetic fibers. We assume this might be the electrophysiologic basis of HFS.

The sympathetic bridge hypothesis considers Moller and Jannetta’s “2-ms difference” [13] because sympathetic nerve fibers are grade C nerve fibers, with conduction velocities much slower than facial nerve fibers (grade A). This hypothesis is also in agreement with the findings of Yamashita et al. [20] because it does not involve the facial nucleus.

Our hypothesis indicates that treatment of HFS may target the sympathetic nerves as well. Patients who have a failed MVD surgery might get benefit from stellate ganglion block or selective resection of vertebral plexus sympathetic nerves. Sympathetic nerve targeted therapy may result in such complications as Horner’s syndrome, seizures, locked-in syndrome and pneumatothorax [5], but it is not as complex as a posterior cranial fossa operation and may be performed under local anesthesia. Thus it may serve as an alternative treatment for those patients who failed a MVD surgery, and those who are unwilling or unable to endure a posterior cranial fossa operation.

Conflict of interest statement

All the authors declared no conflict of interest.

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