The mechanism of hemifacial spasm: a new understanding of the offending artery

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Although neurovascular confliction was believed to be the cause of hemifacial spasm (HFS), the mechanism of the disorder remains unclear to date. Current theories, merely focusing on the facial nerve, have failed to explain the clinical phenomenon of immediate relief following a successful microvascular decompression surgery (MVD). With the experience of thousands of microvascular decompression surgeries and preliminary investigations, we have learned that the offending artery may play a more important role than the effect of merely mechanical compression in the pathogenesis of the disease. We believe that the attrition of neurovascular interface is the essence of the etiology, and the substance of the disease is emersion of ectopic action potentials from the demyelinated facial nerve fibers, which were triggered by the sympathetic endings from the offending artery wall. In this paper, we put forward evidence to support this hypothesis, both logically and theoretically.

Keywords: Hemifacial spasm, Microvascular decompression, Pathogenesis, Sympathetic endings, Ectopic excitability

Introduction

Hemifacial spasm (HFS) is defined as unilateral, involuntary, irregular clonic, or tonic contractions of the facial muscles innervated by the ipsilateral seventh cranial nerve. It affects the periorbital muscles at early stage and gradually leads to the ipsilateral facial muscles. With a prevalence of approximately 10 per 100,000, the onset is usually in middle or old age, but young adults and children can also be affected. Since Dandy first proposed that cranial nerves compressed by ectatic vessels could cause clinical syndromes in 1934, an increasing volume of evidence has been presented to support the fact that neurovascular confliction is the etiology of HFS. In the 1970s, Jannetta published a series of papers regarding successful treatment of HFS with microvascular decompression surgery (MVD), i.e., transposition of the offending artery from the facial nerve root. However, why does vascular compression of the facial nerve root result in neural hyperactivity rather than hypoactivity? As early as 1962, Gardner postulated that the local irritation of the nerve caused by vascular compression may facilitate the initiation of impulses in active fibers by impulses traveling over adjacent fibers or, in other words, ectopic excitation and ephaptic impulse transmission. This hypothesis had been widely accepted until the finding of abnormal muscle response (AMR). Since 1987, Møller and Jannetta electrophysiologically monitored a characteristic wave in patients with HFS. This wave with a latency of approximately 10 milliseconds, is called AMR, which could only be registered in HFS patients by electrically stimulating one branch of the facial nerve, while recording from the muscle that is innervated by the other branch of the facial nerve. When one facial branch is stimulated, the stimulus pulse transmits along the axon in both directions, orthodromically and antidromically. If the former hypothesis is completely correct, theoretically, the latency of the AMR should equal the latency of a stimulus delivered to the facial nerve branch and recorded at the site of vascular compression plus the latency from direct facial root stimulation at the site of vascular compression and the resulting muscle depolarization. However, it was found that the sum of these latencies consistently falls short of the actual latency by approximately 2 milliseconds, which could not be explained by the peripheral hypothesis. The additional time was then assumed to be consumed in the central projections and processing within the facial motor nucleus. But the central hypothesis could not explain the reverse trans-synaptic transfer and what role vascular compression...
plays in the disease and how it results in central changes.

After completion of thousands of MVDs, we found that once the offending artery was intraoperatively removed from the nerve, the AMR wave diminished immediately and the symptom disappeared as soon as the patient woke up from anesthesia in most of the cases, which was also proven by other medical centers. This result could not be explained by peripheral or central hypothesis, since neither the histological changes at the sites of compression nor the hyperexcitability of facial motor neurons were able to repair at once after decompression. Meanwhile, we have noticed that the episode is likely to occur when the patient is emotional, e.g., while she or he is going to speak at a formal occasion. Based on the fact that the symptom is gone with transposition of the offending artery and has come with emotions, we presumed that the episode may relate to a sympathetic nervous system and the offending artery seems to be the hinge between the sympathetic endings and the facial nerve. Whatever, HFS could actually come down to an ectopic excitation that emerges from the VII cranial nerve root and the initiation may locate at the site compressed by the offending artery. By reviewing relevant studies in the literature, we found the previous researchers focused on the facial nerve, except Kuroki and Møller, who found that facial nerve demyelination and vascular compression were both necessary to induce facial hyperactivity. Given that the neurovascular confliction has been widely accepted as the cause for the disease, it does not make sense to emphasize the nerve and to ignore the artery while investigating the pathogenesis. Therefore, we put forward a new hypothesis and have listed numerous evidences to analyze logically and theoretically.

**A Sympathetic Hypothesis**

Due to a mutual friction with pulsation, the neurovascular interface is abraded. When the adventitia is worn out, neurotransmitters released from autonomic nerves in the adventitia may spill-over and spread to the demyelinated nerve fibers and interact with transmembrane receptor proteins, which trigger ectopic action potentials in those nerve fibers under the status of SMPO. When those irregular impulses extend to the neuromuscular junctions, involuntary contractions of facial muscles occur (Fig. 1).

**Evidence and Discussion**

In order to verify our conjecture, we adapted Møller’s classical HFS mode in SD rats with AMR monitoring and developed a series of experiments. The attrition of neurovascular interface is the essence of the etiology. A 20-mm long skin incision was made post-auricularly, and the main trunk of the facial nerve just distal to stylomastoid foramen was carefully dissected under a surgical microscope. Meanwhile, the ipsilateral superficial temporal artery (a branch of the external carotid artery resided above the facial nerve) was exposed and pushed toward the nerve. A 2/0 thread of chromic suture (Kangldia Medical Products Co., Ltd, Heze, China) was tucked in between the nerve and the artery in order to raise lesions at the neurovascular interfaces. The nerve and the artery were kept in close contact with each other. Then, the incision was closed. Two weeks later, the animal was operated on again to withdraw the chromic suture, and the nerve and artery were still kept in tight contact. Post-operatively, the animal was sent back to
the same laboratory environment with free access to food and water for another 2 weeks. The appearance of a stable AMR wave was used as the criterion of a successful HFS model. Afterward, electron microscopy showed lesions of the epineuria (Fig. 2) and/or the adventitia (Fig. 3). Interestingly, AMR was only recorded in those with both the lesions. Accordingly, we hypothesized that the adventitia of the offending artery may play a role in the pathogenesis of HFS.

**The offending artery may play a more important role rather than a mechanical effect**

When we cut off a segment of the offending artery that crossed the facial nerve on both sides (the offending artery was not actually detached from the facial nerve, but disconnected at the segment in contact with the nerve), we observed the same effect as a MVD surgery – the AMR disappeared. This implied that the vascular connection rather than the vessel per se has effect on the VII cranial nerve to trigger an attack.

**The role that the sympathetic nerve plays in the mechanism of HFS**

Anatomically, arteries are coated by adventitia, which contains autonomic nerve endings as well as vasa vasorum. Normally, the autonomic nerve endings release neurotransmitters that act on the nerve–muscle junctions to control contraction and dilation of the vascular smooth muscles (to regulate the vascular diameter). In experiments, as we removed the ipsilateral cervical sympathetic ganglion, the AMR disappeared. Because the sympathetic denervation of the artery caused the AMR to vanish, we presumed that the sympathetic nerves may be involved in the pathogenesis of HFS.

**The sympathetic effect may be executed through neurotransmitters**

The next question is: how does the sympathetic nerve affect the VII cranial nerve? During the MVD surgery for the patient with HFS, we monitored a typical AMR wave with a latency of 10.7 ± 0.5 ms in most of our cases. When we directly stimulated the VII cranial nerve, we recorded a waveform analogous to AMR with a latency of 5.0 ± 0.1 ms. While we stimulated the offending artery, we monitored another wave with a latency of 7.3 ± 0.8 ms, which was labeled ‘Z-L response.’ When we did it again after the offending artery was moved away from the nerve, we recorded nothing. Based on the difference of latency, we deduced that the ‘Z-L response’ was a phenomenon of potential conduction rather than physical current. Because a physical current moves so quickly, as in light velocity, and almost no time is consumed in conduction, we believe that something other than a mechanical compression must have happened between the nerve and the artery. Due to the mutual friction of nerve and artery with pulsation in posterior fossa, the surfaces in contact are abraded. While the adventitia is wearing out, especially at the moment when a sympathetic impulse comes, neurotransmitters released from sympathetic endings may spill-over from the breakage and spread to the VII nerve fibers in close contact with the offending arteries. As norepinephrine (NE) is the predominant neurotransmitter released from the sympathetic endings, we dripped norepinephrine onto the neurovascular conflict site in those offending-artery-excluded and AMR-negative HFS rats, and the AMR reappeared. The results demonstrated that the sympathetic effect may be executed through neurotransmitters.

**Ectopic action potentials emerge from demyelinated nerve fibers**

The other question is: how do neurotransmitters interact with the VII cranial nerve? Normally, functional proteins that are synthesized intracellularly will migrate accurately to proper sites of the cell membrane. When the nerve fibers are damaged, the process of protein synthesis and migration could be out of control and ectopic proteins may emerge in the cell membranes. These transmembrane proteins were found to include some receptors, such as alpha-adrenergic, cholinergic, ATP receptors, and so on. For instance, it was observed in a chronic dorsal root ganglion crush injury model that stimulation of ATP receptors could directly increase the excitability of dorsal root ganglion. In a peripheral nerve injury...
experiment, the excitability of the damaged nerve reduced, while the $\alpha_2$-adrenergic receptor was blocked. In addition to the 'transmitter-receptor' effect, the binding of endogenous ligands to receptors can also influence cellular excitability. A research regarding trigeminal neuralgia demonstrated that the expression of $\text{Na}_\text{V}1.7$ or $\text{Na}_\text{V}1.8$ was significantly higher in the painful nerve than that in the non-painful nerve.

Although the VII cranial nerve is different from the V cranial nerve, which is mainly composed of motor fibers, it is reasonable to expect that the up-regulation of ion channels and receptor proteins occur in the damaged facial nerve fibers, because of the same etiology. With syntheses of some ion channels and other membrane proteins, the extracellular domains of the injured neuron are sialylated. Because sialic acids carry abundant negative charges, a ‘negative electrical halo’ surrounding the injured neuron develops. It causes the resting transmembrane potential to move toward the polarization direction. Meanwhile, extracellular positive charges tend to neutralize these negative charges, which make the membrane potential fluctuate in an unstable manner. This phenomenon is called sub-threshold membrane potential oscillation (SMPO). The amplitude and frequency of SMPO depend on voltage, which can be affected by a variety of factors, especially the opening and closing of the $\text{Na}^+$ channel. When this potential fluctuation reaches the threshold level, an action potential emerges.

**Conclusion**

Eventually, we believe that the offending artery may play a more important role in the pathogenesis of HFS, and that the ectopic action potential of the facial nerve is triggered by sympathetic nerves in the wall of the offending artery. Nevertheless, this ‘sympathetic hypothesis’ (Fig. 1) needs to be proven by more experimental data.

**Disclaimer Statements**

**Contributors**

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Conflicts of interest Authors have no conflicts of interest.

Ethics approval Our experiment has been approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine.

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**References**


**Figure 3** A scanning electron microscopy of the offending artery. A. The adventitia of the offending artery was observed damaged compared with the uncompressed side () (×1000). B. The outermost layer of the artery wall was worn out (×10 000).
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