A Novel Hypothesis on the Mechanism of Hemifacial Spasm

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Abstract

Regardless neurovascular conflict has been believed to be the cause of hemifacial spasm, the mechanism of the disorder remains unclear to date. Current theories, merely focusing on the facial nerve, failed to explain the clinical phenomenon of immediate relief following a successful microvascular decompression (MVD) surgery. With experience of thousands MVDs and preliminary investigations, we have learnt that the offending artery may play a more important role rather than the effect of mechanical compression in the pathogenesis of the disease. Due to the mutual friction of nerve and artery with pulsation, the surfaces in contact are abraded. Neurotransmitters released from the sympathetic nervous endings in the adventitia may spillover from the artery wall and spread to the demyelinated nerve fibers in close contact. As these neurotransmitters bind with the transmembrane receptor proteins, ectopic action potentials are triggered from those nerve fibers with lower excitability threshold caused by vascular compression. When those messy impulses expand to the neuromuscular junctions, involuntary contractions of facial muscles occur. In this chapter, this "sympathetic hypothesis" was evaluated with logical and theoretical evidences as well as our experimental data.

Keywords

Hemifacial spasm • Mechanism • Offending artery • Sympathetic nerves • Ectopic action potentials • Transmembrane receptor proteins • Neurotransmitters

4.1 Introduction

Hemifacial spasm (HFS) is a common disorder of intracranial nerve hyperexcitability, which is caused by vascular compression of the seventh nerve root (Campbell and Keedy 1947; Gardner

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S.-T. Li et al. (eds.), *Microvascular Decompression Surgery*, DOI 10.1007/978-94-017-7366-9_4

1953; Wartenberg 1950; Iwai et al. 2001; Marneffe et al. 2003; Miller and Miller 2012; Chung et al. 2001). Although the neurovascular conflict theory has been verified by successful microvascular decompression (MVD) surgery (Jannetta 1970, 1980, 1981; Jannetta et al. 1977), the underlying pathogenesis of HFS has been debated extensively for more than a century since Gowers first described (Valls-Solé 2007; Gowers 1892). Until now, many scholars have contributed their researches on the mechanism of the disease, and there are two main hypotheses so far, which were referred as the peripheral and the central.

4.1.1 The Peripheral Hypothesis

In 1962, Gardner (1962) postulated the symptom of HFS was an unstable and reversible pathophysiologic state caused by a mild compression of the nerve root which permitted transaxonal excitation while not interfering with axonal conduction. This local irritation of the nerve 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. Several experiments observed some histological changes at the site of compression, such as demyelination, vacuolization of the myelin sheath, and partial degeneration of axons (Nielsen 1984a, b; Nielsen and Jannetta 1984; Sanders 1989). However, researches have not involved the detail concerning the ectopic excitability emersion from the facial nerve fibers yet.

4.1.2 The Central Hypothesis

With development of electrophysiology, a characteristic wave of HFS has been recorded (Moller and Jannetta 1987). It was called abnormal muscle response (AMR). The wave could only be monitored in HFS patients by stimulating one branch of the facial nerve while recording from the muscle innervated by the other branch within approximately 10 msec (Kuroki and Moller 1994; Moller and Jannetta 1986). If the peripheral hypothesis was correct, the latency for AMR should theoretically equal the latency of a stimulus delivered to the facial nerve branch and recorded at the site of vascular compression plus the latency of a direct facial root stimulation at the compressed site. However, it was found that the sum of these latencies consistently fall short of the actual latency (Moller and Jannetta 1984). This extra time was then assumed to be consumed in the facial motor nucleus. Whereas this central hypothesis did not explain how a vascular compression results in central changes.

Whatever, the above hypotheses failed to explain the clinical phenomenon of immediate relief following a successful MVD operation. Nevertheless, it is hard to answer the question: why vascular compression of the facial nerve root results in neural hyperactivity (spasm) rather than hypoactivity (palsy)?

4.2 A New Hypothesis

With experience of thousands MVDs (Zhong et al. 2012, 2014), we have learnt that the offending artery may play a more important role other than the effect of mechanical compression in the pathogenesis of the disease. Eventually, a novel hypothesis was then proposed.

When the facial root is compressed by an artery, the neurovascular interfaces could be abraded with pulsation. As the adventitia is worn out, neurotransmitters that released from sympathetic endings in the offending artery wall may spillover and spread to the contact facial nerve. Meanwhile, the excitability threshold of the compressed nerve drops down due to transmembrane proteins (iron channels and receptors) occurs in the damaged axons. With the neurotransmitter-receptor interaction, G-protein-coupled Na^+ channels are activated, which induces ectopic action potentials on the facial nerve fibers. As these irregular impulses expand to the neuron-muscle junctions, involuntary contractions of facial muscles occur.

4.3 Evidences

4.3.1 Logics

During the MVD processes (Nielsen 1984b; Zhong et al. 2015; Xia et al. 2015; Ying et al. 2011, 2013; Zhou et al. 2012a), it was observed that once the offending artery was removed away from the nerve, the AMR wave was diminished immediately and the symptom of spasm ceased postoperatively in most of the cases (Gowers 1892; Ying et al. 2011, 2013; Zhou et al. 2012a; Martin et al. 1980; Habibi et al. 2011; Zheng et al. 2012a, b; Wang et al. 2014). This could not be explained by the peripheral or central hypotheses, for neither the histological changes at the conflict sites nor the hyperexcitability of facial motor neurons was able to repair at once after decompression (Zhong et al. 2010, 2011a, b, 2012; Kim et al. 2008; Kurokawa et al. 2004). Moreover, it was noticed that the episode of HFS is likely to occur when the patient is excited. Based on the fact that the symptom occurs with emotions and disappears with transposition of the offending artery, we guessed that the attack may relate to sympathetic nerves and the offending artery seemed to be the hinge (Dou et al. 2015). Given that the neurovascular conflict has been widely accepted as the etiology of the disease, it does not make sense to put emphasis on the nerve and to ignore the artery for investigation of the pathogenesis.

4.3.2 Animal Model

Møller's classical HFS mode in SD rats was adapted (Kuroki and Moller 1994; Zhou et al. 2012b). With a post-auricular skin, the main trunk of the facial nerve distal to stylomastoid foramen and the ipsilateral superficial temporal artery were exposed, which were then put in close contact. A 2/0 thread of chromic suture was squeezed in between them in order to induce lesions at the interfaces (Fig. 4.1). Two weeks later, the chromic suture was withdrawn and the artery and nerve were still kept in tighten contact. Another 2 weeks later, the animal was ready for electrophysiology. Finally, a stable AMR wave was monitored in 60 % of the experimental animals (Fig. 4.2). The result implied that HFS could be developed from vascular compression of the facial nerve root, but this neurovascular contact may not always lead to HFS.

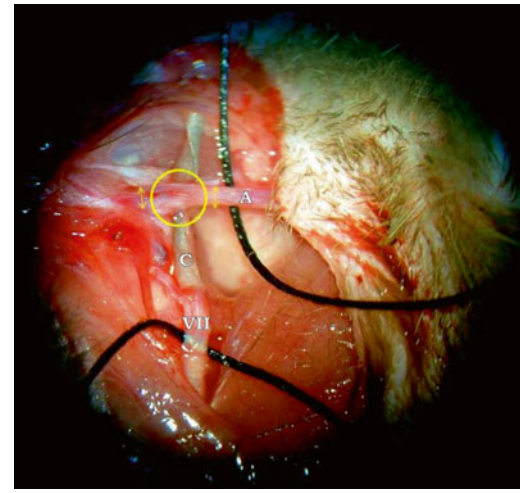

Fig. 4.1 A microscopic view of the HFS animal model. The SD rat was adopted in the animal model of hemifacial spasm. Under microscope, the superficial temporal artery (*A*) and extracranial facial nerve (*VII*) were dissected and put together in tight contact (*circle*). A chromic thread (*C*) was squeezed in between the nerve and the artery in order to induce lesions. To evaluate the effect of offending artery, a segment of the offending artery was cut off (*double arrows*) at both sides of the nerve, which yet was still in close contact with the facial nerve

4.3.3 Pathology

4.3.3.1 Attrition of the Neurovascular Interface Is the Precordium of HFS

The pathology demonstrated lesions of epineuria and/or adventitia at the neurovascular interfaces. However, only those with both lesions of the epineuria and the adventitia were monitored a stable AMR wave. As a result, we concluded that the precondition of HFS is the abrasion of neurovascular interfaces much than the vascular compression of

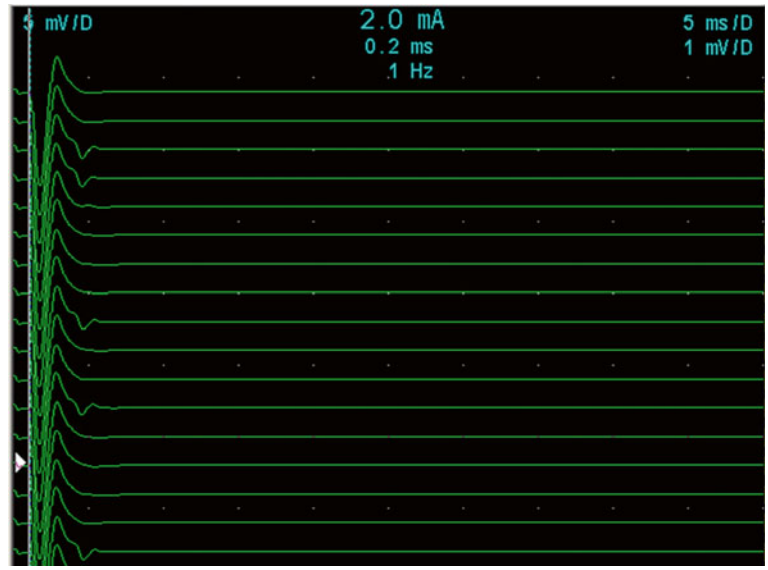

Fig. 4.2 A stable AMR wave

facial nerve root. This conclusion can explain why so many neurovascular contact cases were found in cadavers who had no history of HFS (Martin et al. 1980; Habibi et al. 2011).

4.3.4 Effect of Offending Artery

4.3.4.1 The Offending Artery May Play a Role More than Mechanical Compressions

HFS-mode rats were used to evaluate the effect of offending artery. After coagulation, a segment of the offending artery crossing the facial nerve was cut off at both sides of the nerve (Fig. 4.1). For the sham surgery group, the animal underwent the same operation except for cutting of the offending artery. Thirty HFS rats with positive AMR were randomly grouped, 20 for treatment and 10 for sham operation. Postoperatively, the AMR disappeared in 14 from the offending artery excluded group, while in three from the sham surgery group (p <0.05) (Zhou et al. 2012a). This experiment implied that the vascular connection rather than the vessel per se has some effect on the facial nerve root to trigger an attack of HFS.

4.3.4.2 The Sympathetic Nerve in the Artery Wall Might Be Involved in Generation of HFS

Anatomically, arteries are coated by adventitia which contains sympathetic nerve endings as well as vasa vasorum. Normally, the sympathetic 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). Accordingly, we made a denervation of the offending artery to assess the sympathetic effect in the HFS rats. With microscopy, the supper cervical ganglion was identified, and the ganglionectomy was completed. Twenty-four HFS rats were used in this series, 16 for treatment and eight for sham surgery. Postoperatively, the AMR disappeared in 12 of the treatment group, while in two of the sham surgery group (p <0.05) (Zhou et al. 2012b). For the fact that sympathetic denervation of the artery resulted in AMR vanish, we presumed that the sympathetic nerves may be involved for the pathogenesis of HFS. This explains why the attack often occurs when the patient is nervous.

4.3.5 Electrophysiology

4.3.5.1 Biological Connection between the Artery and the Nerve

In order to investigate how the sympathetic endings act upon the damaged nerve and induce an impulse, we conducted a clinical study. During the MVD for patients with HFS, we monitored a typical AMR wave with a latency of 10.7±0.5 ms (Zhong et al. 2012; Zheng et al. 2012a, b; Ying et al. 2011). When we directly stimulated the facial nerve root, we recorded a waveform with a latency of 7.3±0.8 ms, which disappeared when the offending was moved away from the nerve (Zheng et al. 2012a, b). Based on the latency difference, we deduced that something must have happened before an action potential emerged from the compressed nerve, as a physical current spread in light velocity with little time consumed in conduction.

4.3.5.2 An Irregular Impulse Could Be Induced by Neurotransmitters

As norepinephrine is the predominant neurotransmitter released from the sympathetic endings in the adventitia, we dripped norepinephrine onto the neurovascular conflict site in the animal experiment. Twelve HFS rats following exclusion of the offending artery were randomized into two groups according to drip with norepinephrine or normal saline. Postoperatively, the AMR reappeared in 4/6 animals of the norepinephrine group, while 0/6 in the normal saline group (p <0.05). The result demonstrated that the sympathetic effect may be executed through neurotransmitters (Zhou et al. 2012b).

4.4 Analysis

4.4.1 A Low Excitation Threshold in a Traumatic Nerve Fiber

Basically, functional proteins that synthesized intracellularly would accurately migrate to proper sites of the cell membrane (Wang et al. 2011). When the nerve fibers are injured, this protein synthesis and migration process could be out of control, and ectopic proteins may occur in the cell membranes. With sialylated extracellular domains of the injured neuron, negative charges are present surrounding the damaged neuron. This makes the resting transmembrane potential moves toward the polarization direction. As extracellular positive charges tend to neutralize these negative charges, the membrane potential is fluctuating. This phenomenon is called subthreshold membrane potential oscillation (SMPO) (Xing et al. 2001) (Fig. 4.3). It means the excitability threshold decreases in a traumatic nerve.

4.4.2 Ectopic Excitabilities

The amplitude and frequency of SMPO depends on voltage, which can be affected by a variety of factors, especially the opening and closing of the Na^+ channel. When this potential fluctuation reaches the threshold level, an action potential emerges (Xing et al. 2001, 2003; Xie et al. 2011). Recently, some transmembrane proteins have been found, such as α-adrenergic (Taylor and Ribeiro-da-Silva 2011), cholinergic (Moalem et al. 2005), and ATP (Coddou et al. 2011) receptors. It was reported in a chronic dorsal root ganglion crush injury experiment, stimulation of ATP receptors could increase the excitability (Xiang et al. 2008). While in a peripheral nerve injury study, the excitability reduced with the α_2-adrenergic receptor being blocked (Tulleuda et al. 2011). Our recent study showed that AMR could be recorded with a drip of norepinephrine (Zhou et al. 2012a). This implied that the relevant ligand may exist on the demyelinated facial nerve fibers. With a combination of norepinephrine and its receptor, the electrical voltage across the membrane decreases, and the membrane potential shifts from −90 mV toward 0 level, which allows the G-protein-coupled sodium channels ($Na_v1.8$) to open and induces occurrence of a propagable action potential (Xia et al. 2014) (Fig. 4.3).

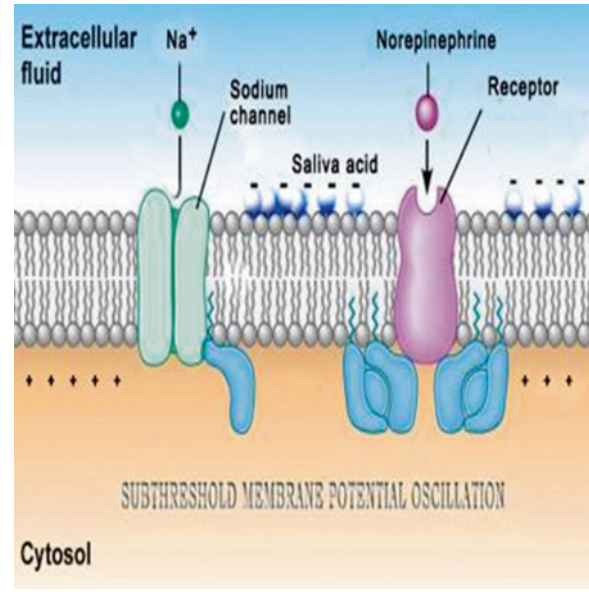

Fig. 4.3 An illustration of ectopic action potential emerged in a traumatic nerve. While the nerve fibers are damaged, the process of protein synthesis and migration can be out of control and ectopic proteins may emerge in the cell membranes, which make the extracellular domains of the injured neuron sialylated. Because of negative charges carried by sialic acids, the resting transmembrane potential moves toward the polarization direction. With combination of norepinephrine and its receptor, the electrical voltage across the membrane decreases further, which allows the G-protein-coupled sodium channels to open and finally induces a propagable action potential

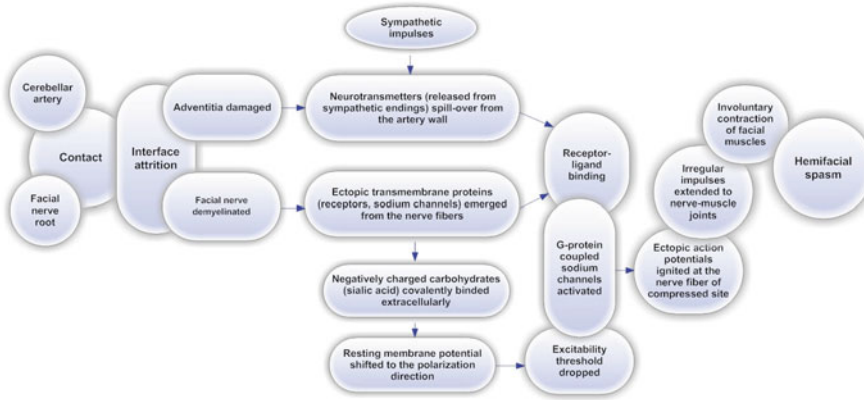

Fig. 4.4 An illustrative summary of the sympathetic hypothesis. Due to mutual friction with pulsation, the neurovascular interfaces are abraded. When the adventitia is worn out, neurotransmitters that released from sympathetic endings in the offending artery wall may spillover and transmit to the demyelinated facial nerve in close contact. Meanwhile, the excitability threshold of the nerve drops due to transmembrane proteins (iron channels and receptors) occurs in the abraded axons. With neurotransmitter-receptor interaction, G-protein-coupled Na+channels are activated, which induces ectopic action potentials on the facial nerve fibers. When those irregular impulses expand to the neuromuscular junctions, involuntary contractions of facial muscles occur

4.5 Summary

Eventually, we regard the essence of HFS attack as ectopic excitabilities that generated from the nerve fibers of facial root at the site where the artery compressed rather than from the central nucleus. While these irregular impulses propagate to the never-muscle junction, involuntary contractions of facial muscles happen. The pathological basis of the disease is the lesions of both epineurium and adventitia at the nerve-artery interface caused by mutual abrasion with pulsation in the posterior fossa. Since it has been found that the resting transmembrane potential in an injured nerve fiber may arise from transmembrane proteins (including receptors and channels), it make sense that neurotransmitters could

trigger an ectopic action potential on the compressed facial nerve fibers via receptor-ligand interaction (Fig. 4.4). However, we still need evidences to prove the factor that norepinephrine can spill over from an arterial wall in case of adventitia attrition.

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