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Facial Nerve Demyelination and Vascular Compression are Both Needed to Induce Facial Hyperactivity: a Study in Rats*

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Summary

It is generally assumed that hemifacial spasm (HFS) is caused by vascular compression of the facial nerve at the root exit zone (REZ), but the mechanism for the development of HFS is not known. Evidence has been previously presented that the signs of HFS are caused by hyperactivity of the facial motonucleus that is caused by the irritation to the facial nerve from the vascular contact. This assumption has been supported by the finding that daily electrical stimulation of the facial nerve in the rat facilitates the development of an abnormal muscle response that is a characteristic sign of HFS in man and is an indication of an abnormal cross-transmission that makes it possible to elicit a contraction of muscles innervated by one branch of the facial nerve by electrically stimulating another branch of the facial nerve.

In the present study we show that close contact between a peripheral branch of the facial nerve and an artery also facilitates the development of an abnormal muscle response, but only if the facial nerve has previously been slightly injured (by a chromic suture) at the location of the arterial contact. We also show that blocking neural conduction in the facial nerve proximal to the artificial vascular compression abolishes the abnormal muscle contraction, which supports the assumption that the anatomical location of cross-transmission that is causing the abnormal muscle response is central to the vascular compression, most likely in the facial motonucleus. These findings may explain why the facial nerve is only susceptible to vascular compression near its REZ, where an injury to its myelin is more likely to occur than where the nerve is covered with schwann cell myelin.

Keywords: Hemifacial spasm; vascular compression; hyperactivity of facial nucleus; demyelination.

Introduction

Microvascular decompression (MVD) of the facial nerve offers a high success rate (85–95%) for cure of hemifacial spasm (HFS)[1, 11] (for a recent review see Møller[18]). It is assumed that vascular contact with the facial nerve where it exits the brainstem (root exit zone, REZ) is necessary for HFS to become manifest[10].

Despite the high cure rate of HFS using MVD, the pathophysiology of this disorder is still unclear. Two hypotheses have been presented regarding how the signs of HFS are generated: one assumes that the cause is ephaptic transmission at the site of compression[4, 5], and the other assumes that it is hyperactivity of the facial nucleus due to continuous irritation at the site of compression[3].

A specific facial electromyographical (EMG) response that seems to be specific for HFS has been used as a tool in diagnostic studies of the pathophysiology of HFS as well as in intraoperative monitoring during MVD procedures to treat HFS[6, 26]. This "lateral spread response" or "abnormal muscle response"[2, 9, 10, 21–23, 28] can be elicited by electrical stimulation of one branch of the facial nerve while recording from facial muscles that are innervated by another branch of the facial nerve. This response can only be elicited on the affected side and it disappears instantaneously when the offending vessel is moved off the facial nerve[23]. The abnormal muscle response represents a cross-transmission of neural activity from one branch of the facial nerve to another. The anatomical location of this cross-transmission is assumed to be the location of the physiological abnormality that causes the signs and symptoms of HFS.

Results obtained from neurophysiological recordings during MVD operations for HFS[21–25, 31] have supported the hypothesis that the signs and symptoms of

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HFS are caused by a hyperactive motonucleus[3], and it has been hypothesized that the vascular irritation of the facial nerve generates an abnormal neural activity that makes the facial motonucleus hyperactive[17, 19–21, 24, 25].

Histological examinations of the nerve that had been compressed by a vessel in cases of HFS revealed anatomical changes at the site of compression such as demyelination, vacuolization of the myelin sheath, partial degeneration of axons, etc.[12, 29]. Such histological changes, together with the fact that only vascular compression that occurs at or central to the Obersteiner-Redlich zone (or REZ)[10] seems to cause symptoms, are considered to be important factors to the generation of HFS.

Previous animal studies[27, 30, 32] have shown that electrical stimulation of the facial nerve may cause the development of the abnormal muscle response. This was taken to support the hypothesis that abnormal neural activity in the facial nerve may make the facial motonucleus hyperactive and cause the opening of dormant synapses that would cause cross-transmission in the facial motonucleus, which is a prerequisite for the abnormal muscle response.

In the present study we show in experiments in rats that a close contact between a blood vessel and a partly demyelinated section of a branch of the peripheral facial nerve may also cause the development of an abnormal muscle response. The demyelination was accomplished by placing a chromic suture around the nerve, which was shown by Sunderland[33] and Lehman and Ule[14] to cause a partial demyelination of a nerve following the development of an absorption granuloma, and which is known to render the nerve sensitive to mechanical irritation[7]. We made use of the finding that a demyelinated peripheral nerve is sensitive to mechanical irritation when developing our model of HFS by using vascular irritation of a peripheral branch of the facial nerve. Lehman and Ule[14] found histological changes 21 days after placing a chronic suture on a nerve in a rabbit. Also, the increase in response to mechanical manipulations of roots and nerves with lesions[7] occurred 6 days or more after the lesion was made. On the basis of these findings we chose to transpose the artery between 14 and 21 days after placing a chronic suture on the facial nerve.

In the present study we also provide evidence that these signs of HFS are not caused by cross-transmission in the peripheral nerve at the site of the vascular compression but rather that the cross-transmission occurs at a location central to the vascular compression and more likely in the facial motonucleus.

Methods

Twenty-three female adult Wistar rats, each originally weighing 250 to 300 grams, were used in this experiment. Four rats underwent

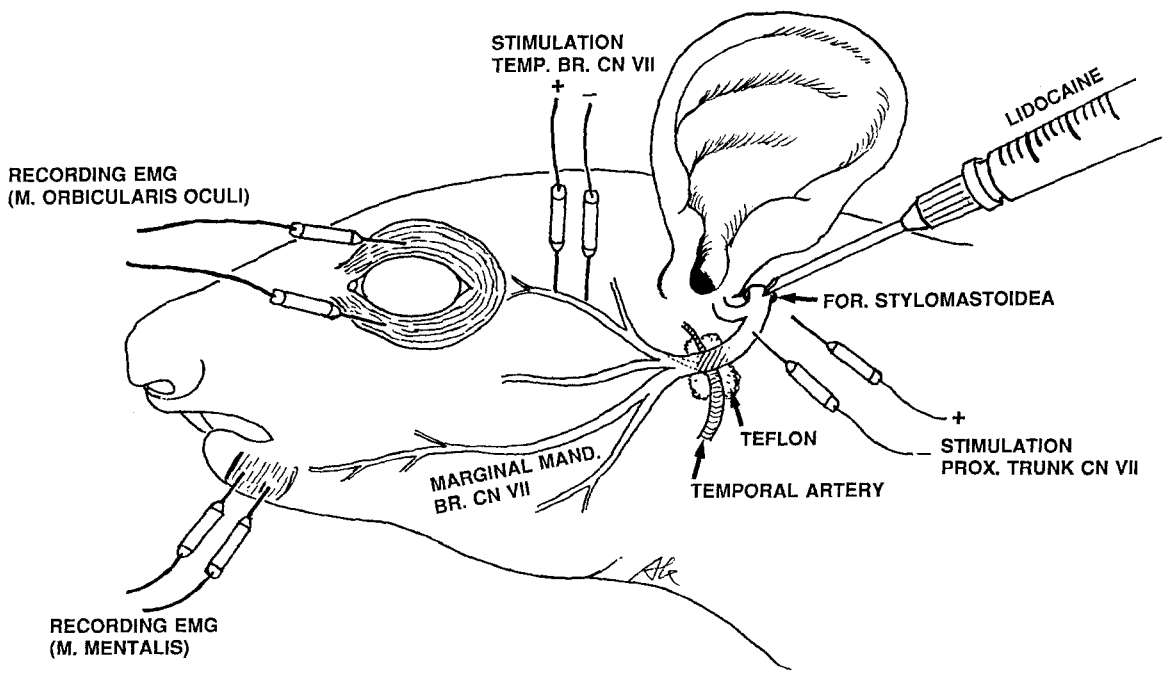


Fig. 1. Schematic drawing to show the location of the demyelination and arterial contact and the stimulation and recording electrodes

only artificial demyelination of the facial nerve, accomplished by placing a chromic gut suture around the nerve. Fifteen rats underwent both artificial demyelination and arterial compression. An additional 4 rats underwent only arterial compression. Facial electromyograms (EMG) were recorded from the mentalis/orbicularis oris muscles as well as from the orbicularis oculi muscles (Fig. 1). In each rat EMG responses evoked by electrical stimulation of the temporal branch of the facial nerve were recorded several times before and after the application of the chromic suture and transposition of the artery to the facial nerve.

The rats were anesthetized with a combination of ketamine and acepromazine (160 mg and 1.6 mg/kg bodyweight, respectively, i.m.). With the aid of a Zeiss operating microscope, the extracranial portion of the facial nerve was exposed through a retro- and infra-auricular incision, and the main trunk of the facial nerve just distal to the branching of auricular nerve was carefully dissected and a chromic gut ligature gently placed around it. The skin was closed.

The rats were housed in individual cages until the second stage of the operation for arterial compression. Between 14 and 21 days after the first operation, the rats were again anesthetized in the same way as for the first operation and the facial nerve was then re-exposed to transpose an artery to make the arterial compression at the site where the chromic gut ligature had been placed. The temporal artery (a branch of the external carotid artery that usually runs just beneath the facial nerve) was transplanted so that it came in contact with the facial nerve. This was done by dissecting the temporal artery from surrounding connective tissue for a length of about 10 mm and gently pulling the vessel by a sling made from 4–0 Ethicon suture so that it came in firm contact with the facial nerve. A small piece of shredded Teflon was inserted underneath the artery to make it permanently touch the facial nerve. The skin was closed after making sure that the artery was in close contact with the facial nerve and that the facial nerve was moving synchronously with the pulsations of the artery. The rats were again placed in individual cages and the recordings of EMG responses were repeated at least once every other week.

The presence of the abnormal muscle response was tested by recording EMG responses from the orbicularis oculi muscles and from the mentalis/orbicularis oris muscles in response to electrical stimulation of the ipsilateral temporal branch of the facial nerve (Fig. 1). Evoked EMG from these two muscle groups were also recorded in response to electrical stimulation of the ipsilateral ophthalmic division of the trigeminal nerve to test facial nerve function after the operation[30]. Platinum needle electrodes (Type E2, Grass Instrument Co., Box 516, 101 Old Colony Ave., Quincy, Massachusetts 02169) were used both for stimulating the facial nerve and for recording EMG. To stimulate the temporal branch of the facial nerve, two needle electrodes were inserted percutaneously, with a distance of 3 mm at their mid-points between the external ear canal and the corner of the eye (Fig. 1). The stimuli were rectangular impulses of 100 μs duration, delivered by a stimulator (Type SD9, Grass Instrument Co.). To record EMG, two needle electrodes were inserted percutaneously into the orbicularis oculi muscle 5 mm apart, while two other needle electrodes were inserted in the mentalis/orbicularis oris muscles (Fig. 1). The recorded potentials were amplified and filtered (3–3000 Hz) (Type P511K, Grass Instrument Co.). Single responses as well as averaged responses to several stimuli (presented at a rate of 5.1 pps) were collected, stored, and analyzed using an Apollo DM 3500 workstation equipped with a 12-bit analog-to-digital converter.

The presence of the abnormal muscle response was tested repeatedly, in the same way as mentioned above, in the rats in which only a chromic gut ligature was placed around the facial nerve but no arterial compression as well as in the rats in which only an arterial compression was made without first placing a chromic gut ligature. The conduction velocity of the facial nerve was measured by electrically stimulating the main trunk of the exposed facial nerve after the first stage of operation, and the average conduction velocity was found to be 44.0 m/s (range 30.6–66.7 mm/s; n = 8). When the presence of the abnormal muscle response was tested, the distance between the recording site and the stimulating site was at least 30 mm. An axonal reflex response would therefore occur with a latency of no longer than 1 ms. On the basis of this, we concluded that responses from the mentalis muscle that have latencies longer than 4–5 ms must be an indication of an abnormal muscle contraction. If a muscle response with a 4 ms latency is a direct response, the conduction velocity in the facial nerve should be 7.5 m/s or lower.

In order to determine the location of the cross-transmission that caused the abnormal muscle response in rats in which the abnormal muscle response had developed, neural conduction in the facial nerve proximal to the site of vascular compression was blocked by injecting

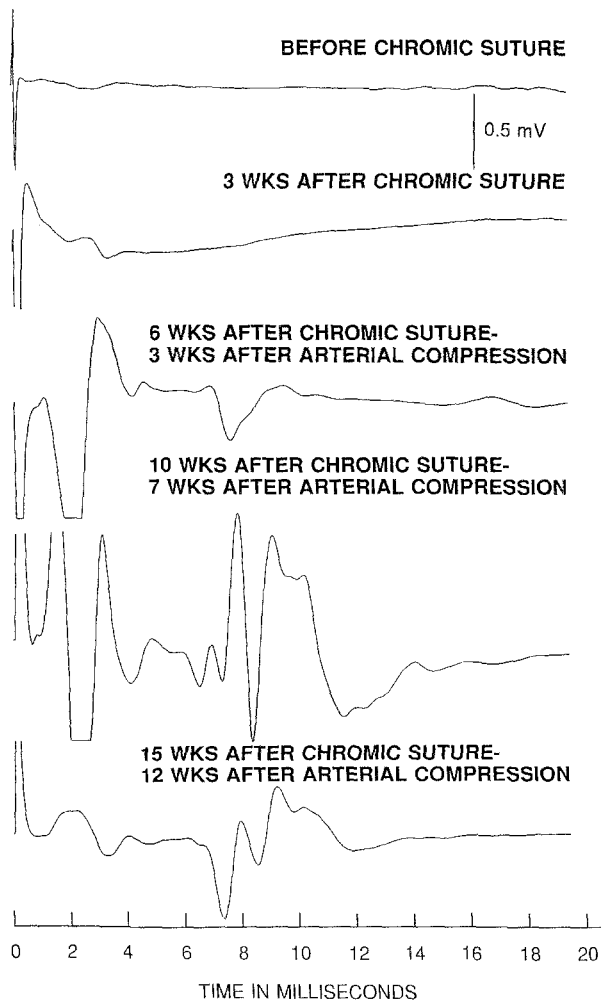


Fig. 2. Development of the abnormal muscle response after transposition of an artery to contact the facial nerve. Chromic suture was placed 3 weeks before this transposition

lidocaine (0.5% with 1:200,000 epinephrine) around the stylomastoid foramen (Fig. 1). After this, the temporal branch of the facial nerve was again stimulated electrically to elicit the muscle response, and neural conduction in the facial nerve – including the portion that was compressed – was tested by electrically stimulating the nerve proximal to the site of compression and recording the response from the mentalis muscle (Fig. 1).

Throughout the operations and the electrophysiological recordings rectal temperature was maintained at around 38 °C with the use of a heating pad.

The experiments described in this paper were approved by the Animal Care and Use Committee of the University of Pittsburgh School of Medicine.

Results

A clear abnormal muscle response developed gradually in 11 of 13 rats in which both a chromic gut ligature had been placed and an arterial compression had been made (Fig. 2). (EMG activity that occurred at latencies longer than 5 ms was regarded to be a sign of the abnormal muscle response). No abnormal muscle response was observed over a period of 3 weeks after placement of the chromic suture nor were there any detectable abnormal responses immediately after the artery was made to permanently touch the facial nerve where the chromic gut ligature had been placed about 3 weeks earlier. The development of the abnormal muscle response took at least 4 weeks after the arterial compression was made. The fully developed abnormal muscle response varied in waveform and latency among the different rats. Figure 3 shows typical examples obtained in 3 different rats. As seen, the abnormal muscle response occurred with an onset latency of 5–7 ms. The properties of the abnormal muscle response were similar to those seen in patients with HFS[21–25]. Thus the response did not diminish or disappear in response to high-frequency stimulation – such as 25.1 pps – of the temporal branch of the facial nerve. The amplitude of the abnormal muscle response increased just after high-frequency stimulation, which is similar to the abnormal muscle response seen in patients with HFS[24].

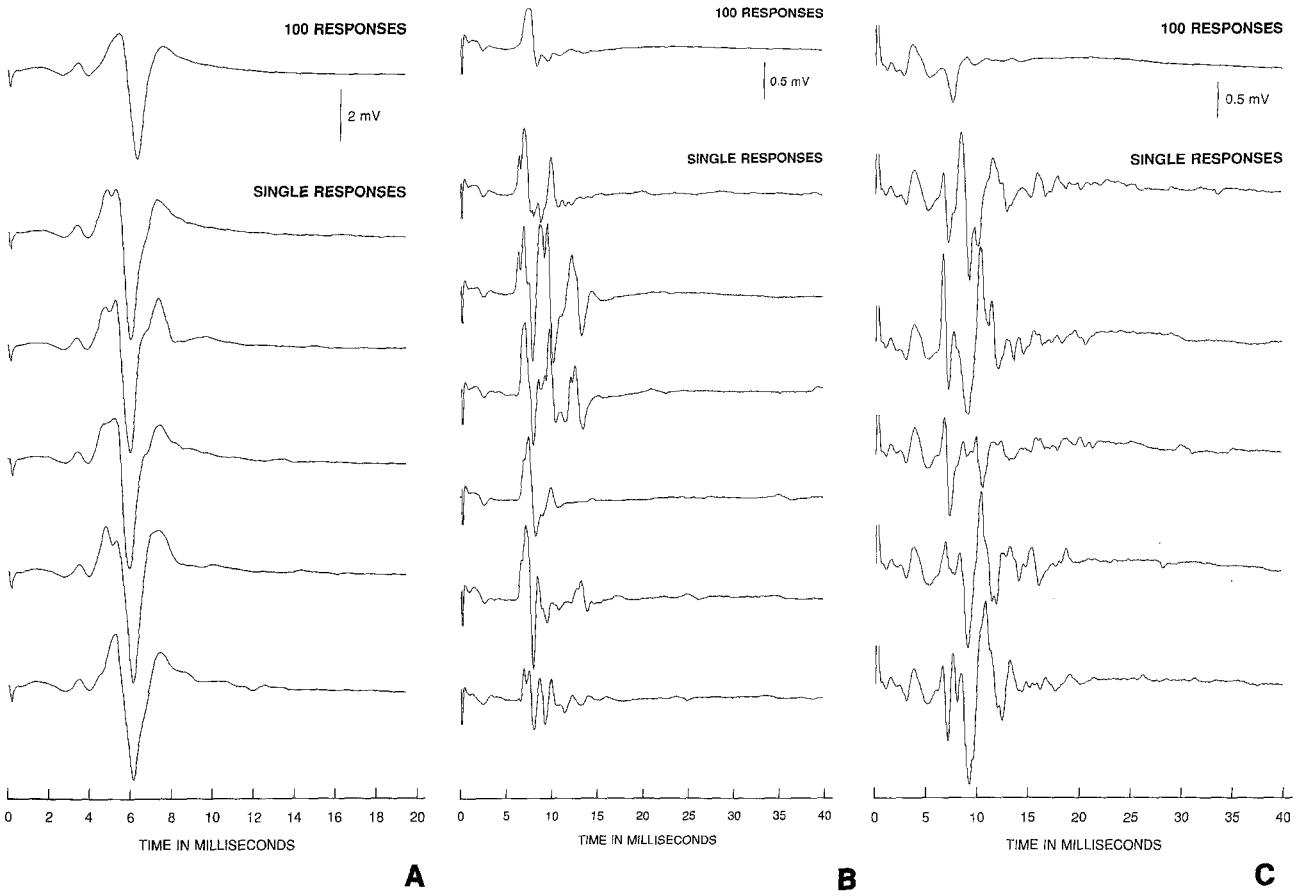


Fig. 3. Typical illustration of the fully developed abnormal muscle response (single responses and averaged responses) in 3 rats (A, B, and C) obtained 13, 20, and 6 weeks, respectively, after vascular compression was produced. The chromic suture was placed 3 weeks before the vascular compression was made in all 3 rats

In order to find out if the cross-transmission of the facial nerve activity that caused the abnormal muscle contraction occurred at the site of the vascular compression or more proximal to it (e.g., in the facial motonucleus), we injected lidocaine (0.5% with 1 : 200,000 epinephrine) around the stylomastoid foramen. After a 0.1 ml injection, the abnormal muscle response gradually decreased in amplitude, was usually completely absent within about 20 minutes, and then slowly returned to the same amplitude as before the injection (Fig. 4 A).

We ascertained that the lidocaine had not caused a block of the facial nerve at the site of vascular compression by testing neural conduction in the part of the facial nerve where the vascular compression was made by recording the response from the mentalis/orbicularis oris muscle to electrical stimulation of the main trunk of the facial nerve at the point between the stylomastoid foramen and the compressed lesion site (Fig. 1). Electrical stimulation of the facial nerve elicited a response from the orbicularis oculi and the mentalis/orbicularis oris muscles that was little affected by the lidocaine injection that abolished the abnormal muscle response from the mentalis muscle (Fig. 4 B). We considered this an indication that the effect on the abnormal muscle response from blocking the facial nerve was not on the segment of the nerve that was compressed but rather that the block occurred central to this site. These results thus indicate that the anatomical location of the cross-transmission that causes the abnormal muscle response is proximal to the location of vascular compression.

In 8 normal rats no abnormal muscle response could be obtained from the mentalis/orbicularis oris muscle when supramaximal stimulus intensity was used to elicit the response from the orbicularis oculi muscle. Small and unstable EMG responses, however, could occasionally be observed within the range of latencies of the abnormal muscle response in normal rats when the stimulus strength was increased to more than 30 V, which is 2–3 times the stimulus strength used to elicit the abnormal muscle response in the rats with vascular compression (Fig. 5).

No abnormal muscle response was noted in 3 out of 4 rats with a chromic gut ligature alone (with no

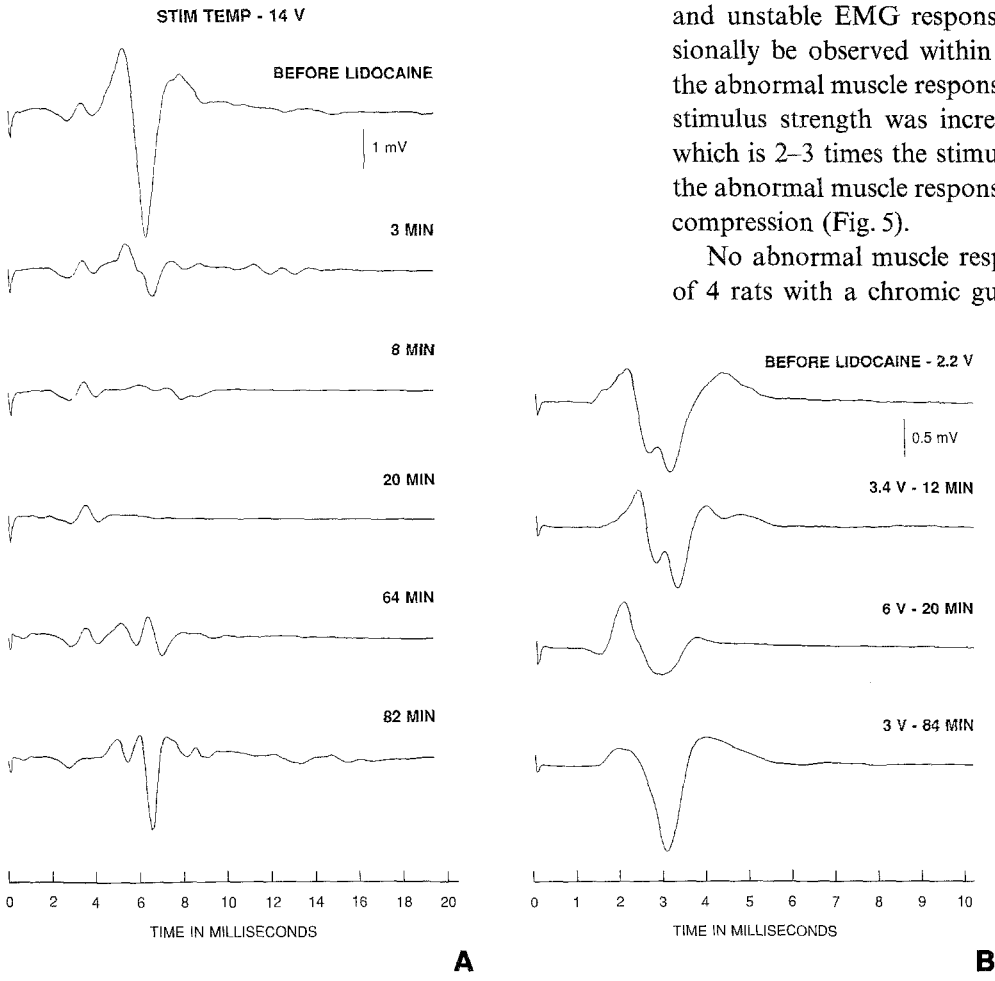


Fig. 4. (A) Effect on the abnormal muscle response of blocking the facial nerve central to the site of vascular compression. The time refers to the injection of lidocaine. (B) Nearly simultaneous testing of the neural conduction in the facial nerve at the site of vascular compression obtained by electrical stimulation of the facial nerve between the stylomastoid foramen and the site of vascular compression. The response was recorded from the mentalis/orbicularis oris muscle

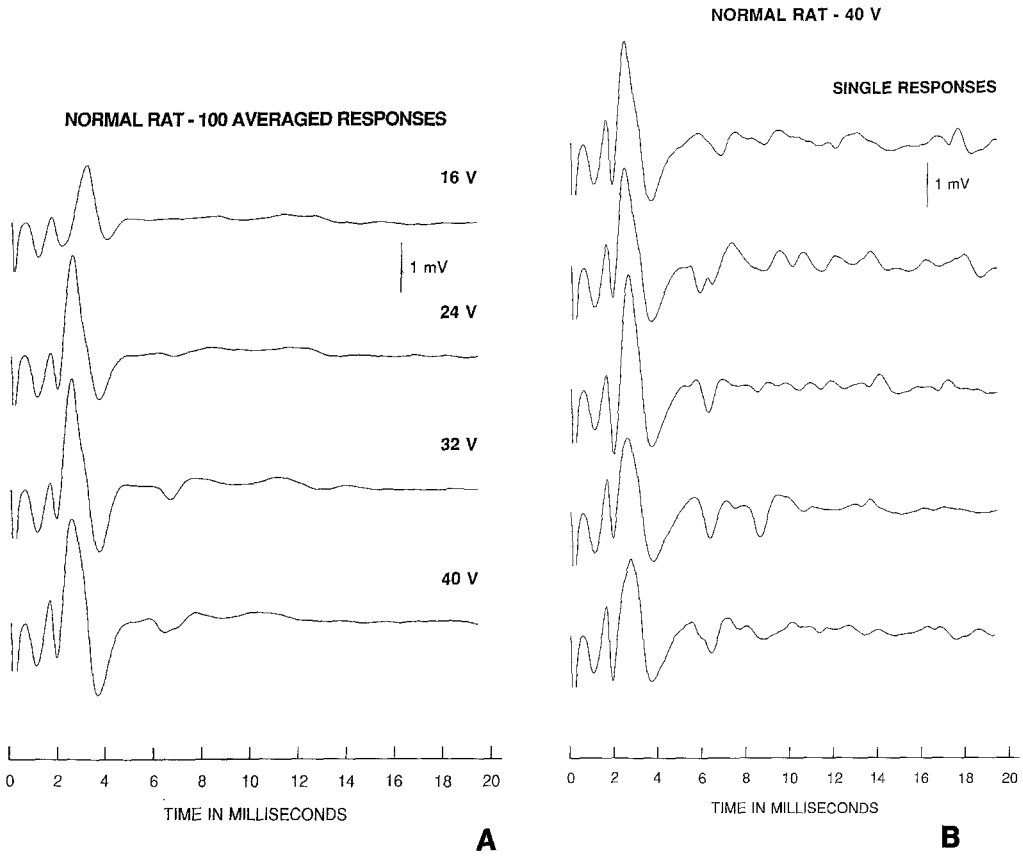
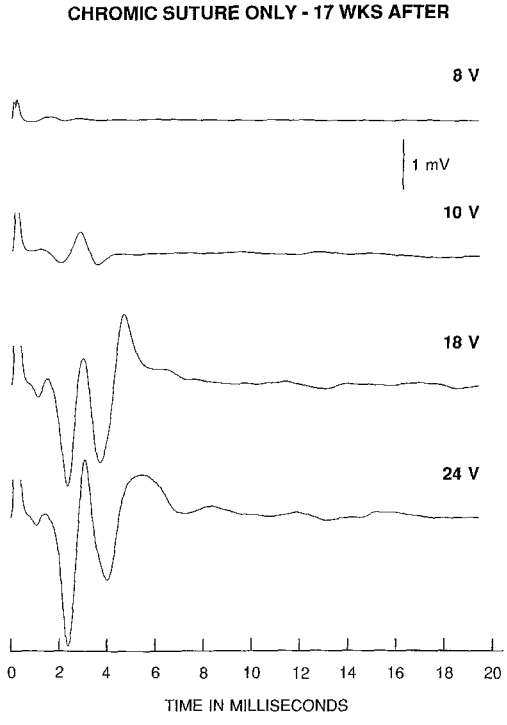


Fig. 5. Recordings similar to those in Fig. 2, but obtained in a normal rat. (A) Averaged response to stimuli, the intensity of which was about the same as used to elicit the abnormal muscle response in rats with vascular compression 16 V and 24, 32, and 40 V. (B) Response similar to that in (A), but to single stimuli at 40 V



arterial compression) throughout a 6-month period of repeated recordings of EMG activity following the application of the chromic suture (Fig. 6).

EMG recordings made in the same way in 4 rats with arterial compression only (without chromic gut ligature) and made from the time the arterial compression was done to more than 3 months after failed to show any abnormal muscle response in any of the 4 rats (Fig. 7) unless stimulated at more than 30 V.

Three rats (2 with a chromic gut suture and arterial compression, and 1 with a chromic gut suture alone) were excluded from the study because of injury to the facial nerve as a result of surgical manipulation, so indicated by marked changes in the amplitude and latency of the blink reflex response recorded from the orbicularis oculi muscle after dissecting the facial nerve

Fig. 6. Results similar to those in Fig. 5, but obtained in a rat with only a chromic gut suture. The records were obtained 17 weeks after placement of the chromic suture

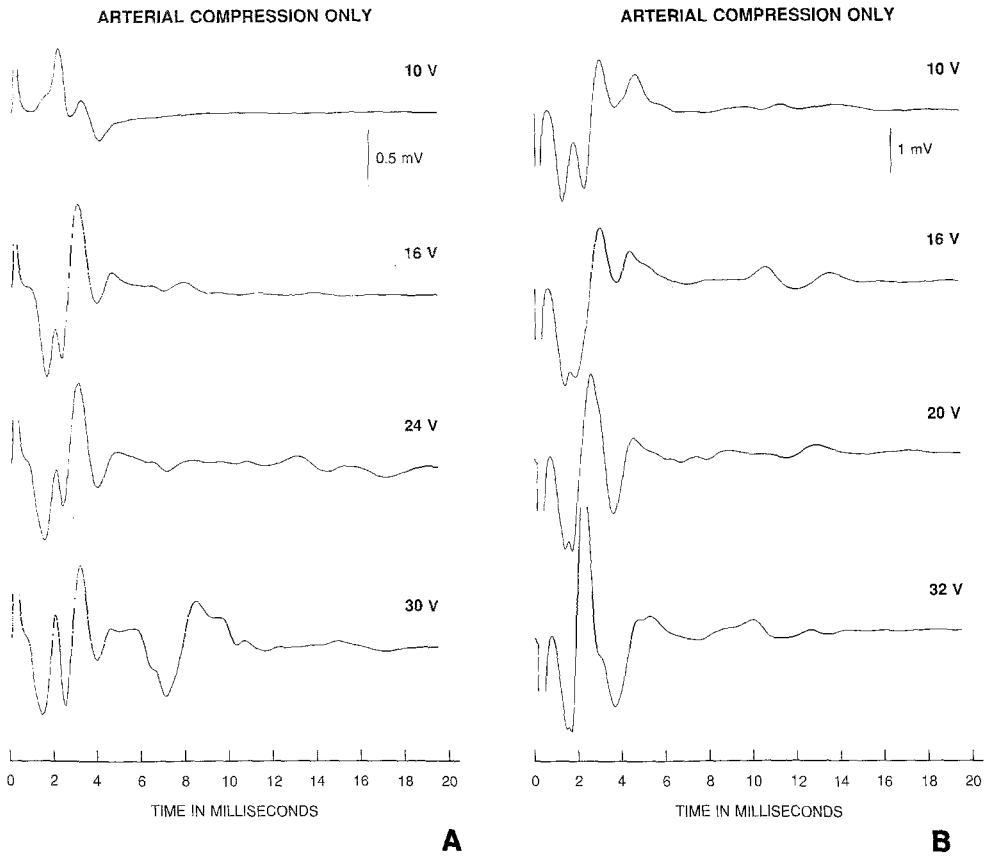


Fig. 7. Results similar to those in Fig. 5, but obtained in 2 rats (A and B) having only vascular compression

for placement of chromic gut ligature and/or for arterial compression.

Discussion

The results of the present study in rats show that both demyelination and arterial compression are required to cause the development of the abnormal muscle response. Thus neither demyelination alone nor arterial compression alone causes the development of the abnormal muscle response. The finding that blocking neural conduction in the facial nerve by lidocaine injection central (proximal) to the site of the demyelination and vascular compression abolished the abnormal muscle response without abolishing the facial EMG response to direct stimulation of the peripheral facial nerve was taken as an indication that the cross-transmission that caused the abnormal muscle response in these experimental rats did not occur at the site of the compression but rather more centrally, probably in the facial motonucleus. Thus these results support the assumption that the facial motonucleus may become hyperactive after long-term irritation of a demyelinated portion of the facial nerve from an artery.

It had been assumed earlier that it is only that portion of the facial nerve (REZ) having central myelin that is susceptible to vascular compression[10]. The results of the present study thus indicate that slight injury to the myelin sheath of the peripheral portion of the facial nerve can make the nerve susceptible to microvascular compression. The injury we induced (demyelination) is supposed to give rise to ectopic nerve activity and make the nerve susceptible to mechanical irritation[7], and we assume that this activity travelling antidromically in the facial nerve would stimulate the facial nucleus and over time make it hyperactive. The portion of peripheral facial nerve that was demyelinated by the chromic suture was assumed to have properties similar to those of the central portion of the facial nerve at the REZ.

It is interesting to note that 4 case reports of HFS due to peripheral injury of the facial nerve have been reported by Martinelli *et al.*[15,16], who also showed signs of changes in central neural structures from injury to

the peripheral portion of the facial nerve. We used a chromic gut ligature in our study to make a demyelination of the peripheral facial nerve, since this material has been proven to produce a resorption granuloma with focal demyelination over a length of several mm of a nerve[14, 33]. Demyelination produced by a chromic gut ligature was considered by Howe *et al.*[7] to make the peripheral nerve sensitive to mechanical irritation, and these investigators showed that acute mechanical compression of a chronically injured nerve can induce prolonged repetitive firing of the nerve.

While we know that the close contact between a blood vessel and a cranial nerve may cause the development of specific symptoms and signs, we do not know what effect close contact between a blood vessel and a nerve has on the function of the respective nerve. On the basis of the present results we hypothesize that chronic irritation of a blood vessel on a chronically injured nerve may induce focal neural activity that reaches the facial motonucleus and, over a period of time, makes the nucleus hyperactive, as has been suggested on the basis of intraoperative recordings from patients undergoing operations for HFS[17, 18, 21, 24, 25]. This hypothesis was also supported by the finding that chronic electrical stimulation of the facial nerve causes the development of an abnormal muscle contraction[32] and signs of hyperexcitability of the facial motonucleus[27].

The present study as well as many earlier studies on the pathophysiology of HFS has made use of the abnormal muscle response to indicate hyperactivity of the facial motonucleus. The abnormal muscle response is not a direct measure of hyperactivity but rather an indication of an abnormal cross-transmission that may be a sign of synkinesis, which is also a typical sign of HFS. That hyperactivity of the facial motonucleus would facilitate such an establishment of abnormal routes of neural transmission is not immediately obvious, but we believe that an opening of dormant synapses, which could facilitate such cross-transmission, is associated with hyperactivity of the facial motonucleus. Thus Kugelberg[13] noted that synkinesis of the blink reflex in normal individuals could occasionally be induced by strong electrical stimulation of the supraorbital nerve. This is similar to what we have observed in normal rats, namely that an abnormal muscle response can occasionally be elicited in response to strong electrical stimulation of the temporal branch of the facial nerve.

The results of the present study support the hypothesis that the signs of HFS are a result of hyperactivity of the facial motonucleus and that the hyperactivity may be the result of abnormal neural activity in the facial nerve that is generated by close contact between the facial nerve and a blood vessel.

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