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Impulse Trafficking in Neurons of the Mesencephalic Trigeminal Nucleus

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In the primary sensory neuron of the mesencephalic trigeminal nucleus (MTN), the peripheral axon supplies a large number of annulospiral endings surrounding intrafusal fibers encapsulated in single muscle spindles while the central axon sends only a few number of synapses onto single α-motoneurons (α-MNs). Therefore, the α-γ linkage is thought to be very crucial in the jaw-closing movement. Spike activity in a γ-motoneuron (γ-MN) would induce a large number of impulses in single peripheral axons by activating many intrafusal fibers simultaneously, subsequently causing an activation of α-MNs in spite of the small number of synapses. Thus, the activity of γ-MNs may be vital for modulation of jaw-closing movements. Independently of such a spindle activity modulated by γ-MNs, somatic depolarization in MTN neurons is known to trigger the oscillatory spike activity. Nevertheless, the trafficking of these spikes arising from the two distinct sources of MTN neurons is not well understood. In this short review, switching among multiple functional modes of MTN neurons is discussed. Subsequently, it will be discussed which mode can support the α-γ linkage. In our most recent study, simultaneous patch-clamp recordings from the soma and axon hillock revealed a spike-back-propagation from the spike-initiation site in the stem axon to the soma in response to a somatic current pulse. The persistent Na^+ current was found to be responsible for the spike-initiation in the stem axon, the activation threshold of which was lower than those of soma spikes. Somatic inputs or impulses arising from the sensory ending, whichever trigger spikes in the stem axon first, would be forwarded through the central axon to the target synapse. We also demonstrated that at hyperpolarized membrane potentials, 4-AP-sensitive K^+ current (IK_{+A}) exerts two opposing effects on spikes depending on their origins: the suppression of spike initiation by increasing the apparent electrotonic distance between the soma and the spike-initiation site, and the facilitation of axonal spike invasion at higher frequencies by decreasing the spike duration and the refractory period. Through this mechanism, the spindle activity caused by γ-MNs would be safely forwarded to α-MNs. Thus, soma spikes shaped differentially by this IK_{+A} depending on their origins would reflect which one of the two inputs was forwarded to the target synapses.

Key words: mastication, γ-motoneuron, H-reflex, α-γ linkage, mesencephalic trigeminal nucleus

Introduction

Hoffman reflex (H-reflex) is not easily induced by electrical stimulation in the masseter muscle at resting state (Fig. 1Aa) while it could be induced during clenching (Fig. 1Ab) (Fujii and Mitani 1973). This is in contrast to the H-reflex in the limb muscles (e.g. soleus muscle; Fig. 1Ac). Because of this observation, the pro-prioceptive control by muscle spindles in the jaw-closing movement has been considered to be very poor. However, the number of intrafusal fibers per spindle in the human masseter has been reported to be unusually high (Fig. 1Ba) (Eriksson *et al.* 1994). This report clearly shows the importance of H-reflex arc in jaw-closing movements in spite of the difficulty of eliciting H-reflex. The difficulty of eliciting H-reflex may be mainly due to the small impact or number of synaptic terminals arising from the central axon

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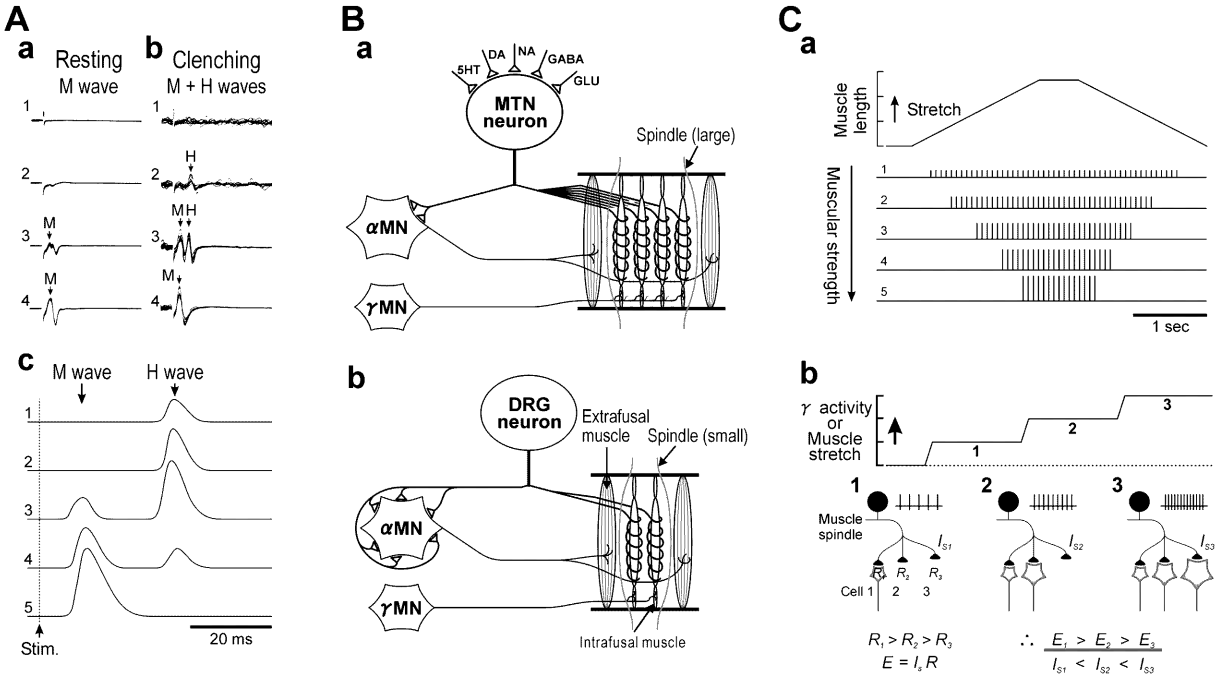

Fig. 1. A, H-reflex in masseter (a and b) and limb muscles (c). In masseter muscle, H-wave is seen only during clenching (b), but not at resting state (a). Stimulus intensity was increased along with trace number increase. B, H-reflex arc in masseter (a) and limb muscles (b). In masseter and limb muscles, numbers of intrafusal fibers per spindle were large (20-36) and small (2-10), respectively, while numbers of Ia-α-MN synapses were small (2-3) and large (5-10), respectively. Note the temporal summation of Ia EPSPs in masseter α-MNs and the spatial summation of Ia EPSPs in limb α-MNs. C, Rank order recruitment of motor units by reflex mechanism. Rank order recruitment of α-MNs seen during voluntary movement is reproduced by muscle stretch (a). A hypothetical model of rank order recruitment depending on the input resistance of α-MNs (b). Rank order recruitment occurs with an increase in impulse frequencies in spindle afferents, caused either by γ-MN activity or by muscle stretch.

of the mesencephalic trigeminal nucleus (MTN) onto α-MNs (Fig. 1Ba) as clarified by electrophysiological (Appenteng *et al.* 1978) as well as morphological data (Appenteng *et al.* 1985; Kishimoto *et al.* 1998). These features are in contrast to the H-reflex arc in limb move-ments (Fig. 1Bb).

In view of these structural specificities in both ends of the peripheral and central axons of MTN neurons (Fig. 1Ba), it is conceivable that spike activity in a γ-MN would induce a large number of impulses in single peripheral axons by activating many intrafusal fibers simultaneously. Then, a temporal summation of Ia EPSPs would occur to activate α-MNs, in spite of the small number of synapses. Therefore, the activity of γ-MNs may be vital for modulation of jaw-closing movements. In fact, EMG activity of masseter muscle during cortically-induced rhythmic mastication of test strips was facilitated in a manner dependent on the hardness of the strip, and this facilitation preceded the onset of the bite force increase during the second or subsequent masticatory cycles (Komuro *et al.* 2001). This was attributed to the enhanced activity of MTN neurons innervating muscle spindles (Hidaka *et al.* 1999; Komuro *et al.* 2001), presumably caused by the feedforward activity of γ-MNs.

Then, what functional roles can such feedforward activation of H-reflex arc play? What is the advantage for the control system to use the feedforward activation of H-reflex arc? It is well known that the rank order recruitment of motor unit is seen during voluntary isometric muscle contraction as well as during linear increases in muscle length (Fig. 1Ca) (Henneman and Mandel 1981). This indicate that activation of H-reflex arc may be involved in rank order recruitment of motor unit. If α-MNs with varying sizes receive the same amount of Ia synaptic current, activation of α-MNs will occur in a manner dependent on their input resistances when the firing frequency of Ia afferents was linearly increased either by stretch or by activation of γ-MNs (Fig. 1Cb). This may be one of the possible mechanisms underlying the rank order recruitment because the smaller the size of α-MNs is, the higher the input resistance is. However, it is not known if the control system use the H-reflex arc for rank order recruitment of motor units (Henneman 1981).

On the other hand, somatic depolarization in MTN neurons is known to trigger the oscillatory activity independently of such a spindle activity caused by γ-MNs (Pedroarena *et al.* 1999; Wu *et al.* 2005; Wu *et al.* 2001). Such depolarizations may be mediated by synaptic inputs (Hinrichsen and Larramendi 1970; Liem *et al.* 1992) onto various types of receptors in the soma of MTN neurons (Copray *et al.* 1990; Ishii and Kang 2002; Lazarov 2002). Therefore, MTN neurons would display two kinds of spikes, one resulting from invasion of the impulse generated in the sensory

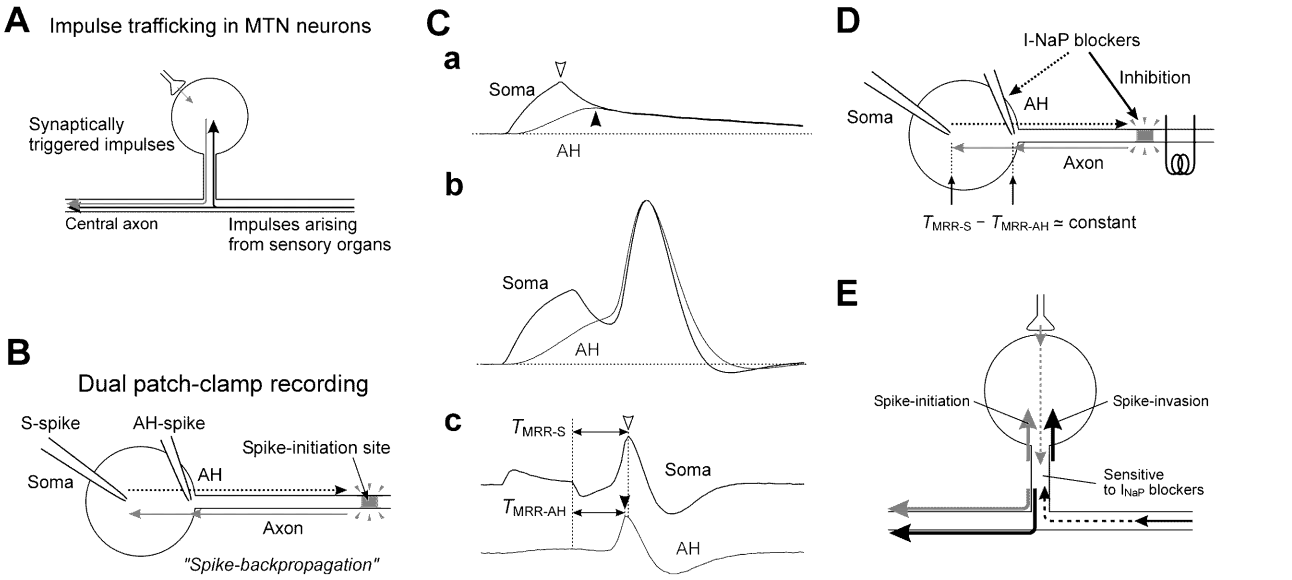

Fig. 2. Impulse trafficking in MTN neurons. A, Synaptically triggerd impulses versus impulses arising from sensory organs: (1) Which one of the two types of impulses is forwarded through the central axon? (2) Does the cell body reflect which one of the two types of impulses was forwarded through the central axon? B, "Spike-backpropagation" can be revealed by the dual patch-clamp recording. C, Delayed activation of S-spike in response to somatic depolarization (b) suggests the remote spike-initiation site from the soma, as revealed in the difference in the time-to-peak of the subthreshold depolarizations between the soma and AH (a). The AH-spike occurrence invariably preceded the S-spike occurrence (b). The time to the maximum rate of rise of spikes was measured from the time of current pulse offset as T_{MRR-S} and T_{MRR-AH} (c). D, I_{NaP} blockers prolonged the delay in activation of both S- and AH-spikes, leaving the time difference between T_{MRR-S} and T_{MRR-AH} unchanged. This suggests that I_{NaP} blockers decreased the excitability only in the stem axon, but not in the cell body. E, Involvement of I_{NaP} in spike-initiation and spike-invasion in the stem axon. Synaptic inputs or peripheral impulses, whichever triggers spike in the stem axon first, can be forwarded through the central axon to the target synapse.

ending and the other being triggered by somatic inputs (Fig. 2A). Nevertheless, the trafficking of these spikes arising from the two distinct sources of MTN neurons is not well understood. It is also not known if there are any differences between the two spikes recorded in the soma of MTN neurons. If there are, would such differences reflect which one of the two kinds of impulses is forwarded to target synapses through the central axon? Our recent study (Saito *et al.* 2006) addressed these questions in MTN neurons by using single and dual patch-clamp recording methods together with an immunohistochemical technique (Fig. 2B).

Spike-initiation in the stem axon mediates spike-backpropagation and spike-invasion

Using a dual patch-clamp recording from the soma and the axon hillock of single MTN neurons, it was demonstrated recently that MTN neurons display spike-backpropagation from the spike-initiation site somewhere in the stem axon to the soma in response to injection of current pulses into the soma (Saito *et al.* 2006), similar to those seen in cortical pyramidal neurons (Stuart *et al.* 1997). A potential role of the persistent Na^+ current (I_{NaP}) in spike-initiation in the stem axon of MTN neurons has also been demonstrated (Kang *et al.* 2004).

In response to injection of short current pulses into the soma, MTN neurons displayed soma spikes (S-spikes) with a delay after the offset the current pulse, and the axon hillock spike (AH-spike) occurrence invariably preceded the S-spike occurrence (Fig. 2Ca and Cb). Bath application of I_{NaP} blockers increased the delay in activation of S-spikes in response to the same depolarization, without marked changes in spike itself. Simultaneous patch-clamp recordings obtained from the soma and AH revealed the parallel increase in the delays in the activation of S- and AH-spikes during the perfusion of 50 nM TTX, indicating that there is no increase in the delay in the backpropagation from AH to the soma, and consequently suggesting that the increase in the delay occurred at the stem axon (Fig. 2Cc and D). This is consistent with increases in the latency of the spikes following stimulation of the stem axon, which resulted in a failure of axonal spikes. The three different I_{NaP} blockers, TTX, riluzole and QX-314, similarly caused activation delay. Therefore, I_{NaP} expressed in the stem axon is likely to be involved in spike-initiation as well as in spike-invasion. (Fig. 2E)

Through-conduction vs. trigger-zone-mediated conduction

A simulation study (Amir and Devor 2003) argued that neither the excitability in the stem axon nor in the soma affects the through-conduction from the peripheral to the central axon (Fig. 3Aa and Ab). Nevertheless, whenever an impulse arising from the peripheral axon failed to invade the stem axon, it also failed to invade the central axon, as demonstrated in frog dorsal root ganglion (DRG) neurons (Stoney 1990) (Fig. 3Ac). Taken together with the findings

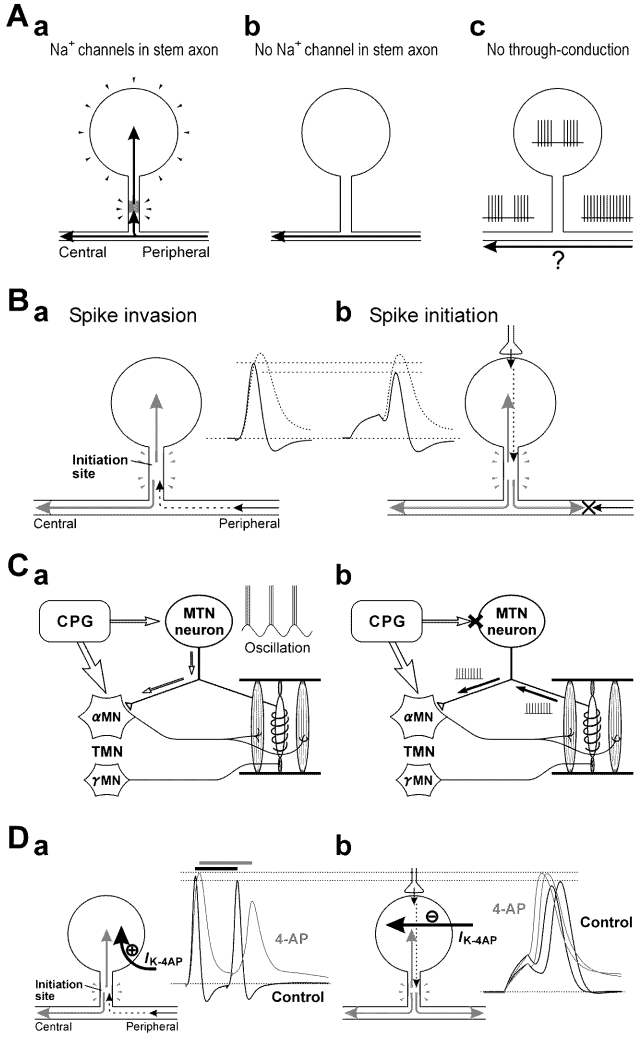

Fig. 3. A, Models for through-conduction. Regardless of the presence (a) or absence (b) of Na^+ channels in the stem axon, through-conduction occurs. No through conduction (c). B, Spike initiation vs. spike invasion. Spikes either caused by invasion of axonal impulse (a) or triggered by soma depolarization (b). Solid and dotted traces were obtained before and after 4-AP application, respectively. C, Two functional modes of MTN neurons that can be switched voltage-dependently. (a) Acting as interneuron by generating oscillatory activity at depolarized membrane potentials. (b) Acting as primary sensory neuron by relaying high-frequency impulses originated from peripheral receptor endings at hyperpolarized membrane potentials. D, Two opposing roles of 4-AP-sensitive K^+ current. (a) $I_{K\text{-}4AP}$ shortens the refractory period of spikes arising from invasion of peripheral impulses, facilitating the spike invasion at higher frequencies. (b) $I_{K\text{-}4AP}$ increases threshold for initiated spikes, pausing a delay in spike activation.

on the spike initiation mechanism in the stem axon (Saito *et al.* 2006), it is likely that impulses arising from the peripheral axon trigger impulses in the stem axon before they reach the three-way junction, and then invade into the soma as well as the central axon (Fig. 3Ba). If this is the case, the Na^+ channel density of the axonal membrane around the three-way junction should be relatively low. Then, without triggering impulse in the stem axon, there would be no conduction from the peripheral to the central axon. Indeed as reported previously, the central axon of MTN neurons displayed a pause of impulse activity whenever soma spiking was inhibited during jaw-opening phase (Fig. 3Ac) (Kolta *et al.* 1995; Westberg *et al.* 2000). It is most likely that no impulses would be seen in the central axon whenever impulses arising from the muscle spindles fail to invade the stem axon and/or soma, as originally suggested in a series of previous studies (Kolta *et al.* 1995; Westberg *et al.* 2000). On the other hand, when a spike was initiated in the stem axon in response to synaptic action, it would invade the central axon, and also propagate backward into the soma (Fig. 3Bb). Thus, provided that there is no through-conduction, either somatic inputs or impulses arising from the sensory ending whichever trigger spikes in the stem axon first could be forwarded through the central axon to the target synapse (Fig. 3B).

Differential involvement of 4-AP-sensitive K^+ current between spike initiation and spike invasion in MTN neurons

In our recent study, the amplitude of the invaded soma spike was found to be significantly larger than that of the initiated soma spike, when compared in the same MTN neuron (solid traces, Fig. 3B) (Saito *et al.* 2006). Since such a spike amplitude difference was abolished by 4-AP application (dotted traces, Fig. 3B), it was strongly suggested that 4-AP-sensitive K^+ channels were involved in differentially shaping the soma spikes, in a manner dependent on whether the spike was initiated (backpropagated) or generated by the invasion of axonal spikes (Saito *et al.* 2006).

Since the activation of Na^+ current is much faster than that of 4-AP-sensitive K^+ currents ($IK_{4\text{-}AP}$) (Patlak 1991; Rudy 1988) the involvement of the presumed $IK_{4\text{-}AP}$ would be smaller when soma spike is evoked by the rapid invasion of an axonal spike than when soma spike is activated with a delay during the decay phase of the depolarizing response to injection of current pulses into the soma. This delay was due to the unusual electrotonic separation of the soma from the spike-initiation site, which was revealed by dual whole-cell recordings (Saito *et al.* 2006). Such an delayed activation may allow time for backpropagated spikes to be shaped by the presumed $IK_{4\text{-}AP}$. Due to the differential involvement of the presumed $IK_{4\text{-}AP}$, there were distinct differences in the amplitude and duration between spikes being initiated and arising from invasion of axonal impulses. These observations strongly suggest the differential distribution of 4-AP-sensitive K^+ channels in the soma and stem axon. In agreement with these electrophysiological suggestions, strong immunoreactivities for Kv1.1 and Kv1.6, among 4-AP-sensitive and low-voltage-activated Kv1 family examined, were detected in the soma but not in the stem axon of MTN neurons, whereas immunoreactivity for Kv2.1 were seen both in the somata and in the stem axons (Saito *et al.* 2006). Therefore, S-spikes shaped differentially by $IK_{4\text{-}AP}$ would reflect which

one of the two inputs, arising from the soma or sensory ending, is forwarded to the target synapses (Fig. 3B).

Voltage-dependent switching between two functional modes presumed in MTN neurons

Masticatory movement has been considered to be mediated by the central pattern generator (CPG), from which MTN neurons receive synaptic inputs and thereby act not only as PSNs but also as interneurons independent of the activities of the peripheral receptors (Fig. 3C). In addition, it is well established that the central axon of MTN neurons can act independently of the activities of somata through the mechanism of GABA-mediated primary afferent depolarization (Kolta *et al.* 1995; Verdier *et al.* 2003; Westberg *et al.* 2000). Thus, MTN neurons can display multiple functional modes.

At depolarized membrane potentials in the somata (Fig. 3Ca) where 4-AP-sensitive K currents might be largely inactivated, MTN neurons display oscillatory firing activity either spontaneously (Pedroarena *et al.* 1999; Wu *et al.* 2005; Wu *et al.* 2001) or triggered synaptically (Verdier *et al.* 2004; Yamuy *et al.* 2000). In contrast, at hyperpolarized membrane potentials in the soma of MTN neurons (Fig. 3Cb) where the inactivation of 4-AP-sensitive K currents is largely removed, 4-AP-sensitive K currents would facilitate spike invasion arising from sensory endings (Fig. 3Da), but prevent MTN neurons from initiating spikes in response to fast synaptic inputs (Fig. 3Db). However, as suggested by the previous studies (Kolta *et al.* 1995), a further hyperpolarization in the soma might prevent the spike-initiation site from being activated by impulses arising from the peripheral axon, provided that the safety factor for the saltatory conduction from the peripheral axon to the spike-initiation site in the stem axon is relatively low due to the low Na channel density around the three-way junction. This possibility of Na channel distribution may be very important for preventing through-conduction.

Thus, MTN neurons can act either as PSNs or as interneurons depending on the membrane potential levels (Fig. 3C and D), although the slow modulatory actions underlying the membrane depolarization and hyperpolarization have not been clarified yet. Serotonin and dopamine receptors which are expressed in MTN neurons (5-HT_{1-5}, Kolta *et al.* 1993; Lazarov 2002) and D_{2} (Lazarov 2002; Lazarov *et al.* 1998), may be strong candidates for inducing the slow membrane depolarization (Beique *et al.* 2004; Zhang 2003) and hyperpolarization.(Einhorn *et al.* 1991; Lacey *et al.* 1987) respectively.

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