Review

Electrophysiological Features of Neurons in the Mesencephalic Trigeminal Nuclei

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Key Words

Mesencephalic trigeminal nuclei · Excitability classification · Transition · Subthreshold membrane potential oscillation · Resonance

Abstract

Mesencephalic trigeminal nucleus (Mes V) neurons represent an uncommon class of primary sensory neurons. Besides receiving somatosensory information, Mes V neurons are also involved in regulating multisensory information. The present review first describes the passive features as well as three important currents, followed by a distinct excitability classification and a description of the excitability transition of Mes V neurons. Furthermore, their resonance property, the existence of membrane oscillation and electrical coupling which may promote strong synchronization, as well as their function in controlling stretch reflex activity, are discussed.

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Introduction

Mesencephalic trigeminal nucleus (Mes V) neurons are traditionally regarded as sensory neurons correlated to the stretch reflex. In amphibians, other than receiving somatosensory information, Mes V neurons can also be driven synaptically through visual connection and thus may play an integrative role in regulating multisensory information [1]. The Mes V has other roles including transferring information of vibrissa movements to other central nervous system (CNS) areas [2] as well as regulating feeding and exploratory behavior [3]. According to the morphological characteristics and terminating patterns, three types of neurons could be classified in Mes V: (1) jaw muscle spindle afferent Mes V neurons, (2) periodontal ligament mechanoreceptor afferent Mes V neurons and (3) interneurons [4, 5]. However, some investigators think that the small multipolar interneurons are not necessarily Mes V neurons.

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Rather, they might be other types of neurons from the surrounding areas [4]. As multipolar Mes V neurons may exhibit different properties from pseudounipolar ones, the electrophysiological features reviewed in this paper are mainly referring to common Mes V neurons which receive projections from muscle spindles in the jaw-closing muscles and periodontal mechanoreceptors [6]. Mes V neurons were identified on the basis of their morphological characteristics: a spherical or oval cell body, a large nucleus, a prominent single nucleolus and a pseudounipolar process [5]. The electrophysiological features, reflecting the input-output relation of a single cell, are important for exploring the basic function of a cell within a circuit. As unique primary sensory neurons in the CNS, the majority of Mes V neurons may have passive properties similar to those of other peripheral sensory neurons such as dorsal root ganglion (DRG) and trigeminal ganglion (TG) neurons.

Neurons are excitable, though cells with identical inputs may respond differently. It was Hodgkin who was the first to study crustacean nerve axons to distinguish neuronal excitability into three classes according to responses of the cell to applied stimuli [7]. Correspondingly, alterations in certain parameters, such as the dynamic characteristics of a current, can be crucial, since these change the neuron's firing behavior from one type to another [8–12].

Resonance is an inherent property that some neurons have to respond selectively to input signals at a proper frequency [13, 14]. It occurs when there are complex interactions among different passive membrane properties which are time and voltage dependent [13]. Coherent network oscillations are correlated with different behavioral states in the brain and are determined by intrinsic resonance properties [13]. As parts of the intrinsic neuronal properties, resonance and membrane oscillation have been found both in the CNS [15–22] and in peripheral sensory neurons including Mes V, TG and DRG neurons [23, 24].

In this paper, we review findings primarily from passive electrophysiological features, following three important currents which play crucial roles in the neuronal behavioral variety of Mes V neurons. Subsequently, studies on the distinct excitability classification and excitability transition of Mes V neurons, combined with analyses of underlying ionic currents including the persistent sodium current (I_{NaP}) and the noninactivating 4-aminopyridine (4-AP)-sensitive potassium current (I_{4-AP}), are introduced. Furthermore, we will discuss their resonance property, the existence of membrane oscillation and electrical coupling which may promote strong synchronization as well as their function in controlling stretch reflex activity.

The Membrane Properties of Mes V Neurons

Most of the passive characteristics of adult Mes V neurons reported are similar, with a resting membrane potential (RMP) of -56.4 ± 6.5 mV and an input resistance (R_{in}) of 143.6 ± 52.9 M Ω , no matter whether they come from whole-cell current-clamp recording of dissociated cells [4] or from brain slices [25]. Development has little effect on the RMP but a prominent effect on R_{in} , which is supported by work from Chandler and coworkers [26]. In their investigation, based on Sprague Dawley (SD) rats aged postnatal day (P)2–12 and using in vitro whole-cell patch-clamp recording, they found that the R_{in} decreased gradually from 225.8 ± 166.8 to 106.2 ± 64.4 M Ω , with the cell body having increased between P2 and P12. Correspondingly, the whole-cell capacitance gradually increased from 35.7 ± 8.8 to 62.8 ± 12.4 pF. Similar results have been found by Yang et al. [27], who utilized 140 Mes V neurons from SD rats aged P9–14. Compared to the above data, there are some exceptional studies in which mean R_{in} ranges from 13.4 to 24 M Ω are reported [28, 29].

The neurons in Mes V seldom fire in the resting state; in fact, they respond by only one spike to a depolarizing step of short duration (0.06 ms) [4]. In the study by Yoshida and Oka [4], the amplitude of the action potential (AP) was 92.5 ± 11.9 mV and the spike duration was 0.94 ms. Repetitive discharges could be evoked if the depolarizing current pulse was extended to above 350 ms. The authors reported that the great majority of Mes V neurons responded to the stimuli with the maximum spike number, usually less than 3, acting as a rapidly adapting neuron, while other neurons belonged to slowly adapting neurons which produced increasing spikes when the current intensity was increased.

In later investigations, rhythmical burst discharges became a remarkable subject. In this condition, cells discharge high-frequency trains of spikes in response to a depolarizing current [26, 30]. The following properties of rhythmical burst discharges could be observed: the mean threshold for initiating rhythmical burst was -51 ± 4 mV (-44 to -60), the range of mean cycle periods (0.4–19.0 s) and the burst durations (0.04–5.1 s) were quite different between neurons, and the mean intraburst firing frequency was 99 ± 19 Hz (69–156) when measured at the threshold for rhythmical bursts [26]. Further study suggested that the subthreshold oscillation frequency determined the intraburst spike frequency and the high rate of discharge produced on Mes V neurons were actually caused by the underlying high-frequency subthreshold oscillation, a relation which will be introduced in more detail in the following section. Compared to the TG neurons which mediate the nociceptive sensation of the masseter muscle, Mes V neurons only have brief AP of a limited duration of 1 ms [31]. An interesting phenomenon is that there are two kinds of soma spikes in Mes V neurons, one initiating directly from the soma, the other caused by invasion of an axonal spike. This is true in immature animals – though in mature animals, it is difficult to record an antidromic discharge in Mes V somata by stimulating a jaw muscle nerve. Some researchers think that the impulses from the peripheral sensor (spindle or mechanoreceptor) run through the peripheral process directly across to the central axon at their joint point, so as not to collide away within the unipolar trunk.

Three Important Currents in Mes V Neurons

For Mes V neurons of the rapidly adapting type, the depolarization-induced AP was reversibly inhibited by tetrodotoxin (TTX) or by eliminating Na^+ from the bathing medium, suggesting a TTX-sensitive Na^+ channel foundation [29]. However, in conditions of various stimuli, many ion channels participate in the electrophysiological activity of MesV neurons, of which $I_{4\text{-AP}}$, I_{NaP} and the hyperpolarization-activated cationic currents (I_h) are especially important.

4-AP-Sensitive Potassium Current

$I_{4\text{-AP}}$ widely occurs in mammalian CNS [32–34], sensory neurons and trigeminal motor nuclei, among other locations [35, 36]. It is now ascertained that there are two distinct 4-AP-sensitive outward currents: one is transient ($I_{\text{TOC-S}}$; I_{Aslow} , slow inactivating component of the A type K^+ current), and the other is sustained (noninactivating-component $I_{4\text{-AP}}$) [30]. $I_{4\text{-AP}}$ (which is blocked by 30–100 μM 4-AP) is more sensitive than $I_{\text{TOC-S}}$ (blocked at 1–5 mM 4-AP). In Mes V neurons, under the application of 100 μM 4-AP, $I_{4\text{-AP}}$ was recorded [30]. Thus, in Mes V neurons, the 4-AP-sensitive current components of $I_{\text{TOC-S}}$ and $I_{4\text{-AP}}$ determine the sustained period of spike trains. In these, the noninactivating $I_{4\text{-AP}}$ plays a critical role in determining whether cells exhibit accommodation or sustained repetitive discharge. Moreover, it is now accepted that Mes V neurons, especially those from P12–18 immature neurons, have two kinds of soma spikes: one initiated directly from the soma, the other caused by invasion of an axonal spike. $I_{4\text{-AP}}$ has been reported to have different effects on these two original

spikes: facilitating axonal spike invasion and suppressing soma initiation [37]. Consistent with this, $K_v1.1$ and $K_v1.6$, which belong to the 4-AP-sensitive potassium family, were detected in the soma but not in the stem axon of Mes V neurons [37].

Persistent Sodium Current

I_{NaP} , which is a voltage-dependent and noninactivating inward current when given a depolarized stimulus, has been extensively found in mammalian neurons located in striated (cardiac) muscles, skeletal muscles and the CNS [38–42]. By applying depolarizing voltage ramps from -90 to 10 mV within 3 s, Wu et al. [43] isolated I_{NaP} in Mes V neurons in neonatal SD rats. I_{NaP} was activated around -76 mV, which is 20 mV more negative than the value for the transient sodium current, and peaked at -48 mV. This is similar to the properties in other neurons reported previously [44–46]. The peak amplitude of I_{NaP} in Mes V varies widely from cell to cell (ranging from -133.7 to -918.7 pA), though the current density is between 4.6 and 6.9 pA/pF. The inactivation of I_{NaP} is also time and voltage dependent, and the recovery after inactivation needs a few seconds ($\tau_{onset} = 2.04$ s, $\tau_{recovery} = 2.21$ s). Compared to TTX, a relatively special blocker for I_{NaP} was proposed to be riluzole. In Mes V neurons, riluzole reduced the peak I_{NaP} by 53% at 2 μ M and by 81% at 5 μ M. Thus, a concentration of riluzole <5 μ M could be considered a relatively special blocker compared to TTX in Mes V neurons [26].

As regards function, I_{NaP} is crucial for determining excitability behavior. Some evidence shows that I_{NaP} is the amplification factor of subthreshold membrane potential oscillation (SMPO) in many different neurons, and blockade of I_{NaP} could decrease SMPO or even abolish the burst discharge [15, 47–50]. Apart from this, I_{NaP} is also the amplifier of many membrane resonance currents [51, 52] and exerts an amplified action on the subthreshold excitatory postsynaptic potential [53–55]. By dual recording at the soma and the axon hillock of Mes V neurons, Kang et al. [56] believe to have shown that I_{NaP} may be involved in spike initiation at the axon hillock, though I_{NaP} detected on the soma of Mes V neurons was considered to underlie the bursting behavior. In support of this, sodium currents (transient, resurgent and persistent) can be recorded in Mes V neurons, where I_{NaP} is considered to be the current flowing during the interspike interval of high-frequency firing, which, along with the transient sodium current flowing during the upstroke of AP and the resurgent sodium current flowing at the peak of afterhyperpolarization, contributes to Mes V electrogenesis [57]. The $Na_v1.6$ isoform is partly responsible for the I_{NaP} composition; thus, in $Na_v1.6^{-/-}$ mice, a reduced impedance-frequency relationship and attenuated SMPO can be observed in Mes V neurons compared to wild-type littermates [58]. Moreover, in Mes V neurons, the generation of SMPO and resonance are related to both I_{NaP} and I_{4-AP} . I_{NaP} could be reversely regulated by 5-HT through a cAMP/PKA pathway [59].

Hyperpolarization-Activated Cationic Currents

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are intermembrane proteins that serve as nonselective ligand-gated cation channels in a variety of cells. HCN channels are encoded by four genes (HCN1, 2, 3 and 4) and are widely expressed throughout the heart and the CNS [60, 61]. The current mediated by HCN (hyperpolarization-activated cationic inward current, I_h), along with I_{KIR} , is a typical anomalous inward rectification current which is slowly activated by hyperpolarization to generate an inward current. I_h is permeable to both Na^+ and K^+ and can be activated by -60 - to -90 -mV hyperpolarizing square-wave stimulation [62, 63]. It can be blocked by extracellular Cs^+ at a low concentration, though ZD7288 is the specific inhibitor for I_h [25, 64].

In 1998, Khakh and Henderson [65] first recorded I_h in Mes V neurons and found that membrane hyperpolarization (from -62 to -132 mV) can activate I_h with a half-maximal activation potential ($V_{1/2}$) of -93 mV, maximal currents (I_{max}) of around 1 nA and a reversal potential

of -57 mV. Using a hyperpolarization step protocol of 2–5 s, Tanaka et al. [25] detected the characteristics of the activation and deactivation dynamics of I_h in Mes V neurons, indicating that they could be described by two time constants. I_h has been found to be involved in a number of neuronal functions, participating in pacemaker activity in both the heart and the brain [66], setting an RMP which is self-limiting and stabilizing [67, 68], controlling membrane resistance and dendritic integration and regulating synaptic transmission [64]. Most of the abovementioned functions have been proved to exist in Mes V neurons, since blockade of I_h produces membrane hyperpolarization, extends the duration of afterhyperpolarization and decreases the firing frequency in the majority of Mes V neurons [25]. The function of mediating the low-frequency membrane resonance of I_h has also been explored in Mes V neurons. There are studies reporting that I_h could be regulated by a subset of G protein-coupled receptors such as P2Y₁ receptor [69]. In addition, activation of the P2X receptor has been shown to have inhibiting effects on I_h [65]. I_{NaP} can be modulated not only by neurotransmitters but also by other ionic currents. For instance, activation of I_h results in the generation of an Na-K pump current, which, in reverse, can facilitate the activation of slow I_h [70]. Mes V neurons are covered by numerous microvilli, which express both h-channels and Na-K pumps. An Na⁺ microdomain, which can be formed in such microvilli, underlies this bidirectional interaction [70].

Neuronal Excitability Classification and Excitability Transition in Mes V Neurons

Fundamentally, neuronal excitability, which can be divided into three classes according to responses of the cell to applied stimuli, was first put forward by Hodgkin [7]. Interneurons within the Mes V area have been reported to be categorized into three subtypes: tonic-firing (type I), bursting-firing (type II) and spike-adaptive (type III) neurons [71]. On account of this, after a series of studies, Yang et al. [27] showed that Mes V neurons in rats can be classified into three types. As shown in figure 1A, class 1 neurons are sensitive to the strength of the stimuli applied (fig. 1A1). Dissimilarly, those of class 2 show a relatively stable firing frequency responding to the injected current (fig. 1A2). For class 3 excitability, usually a single AP is generated in response to current steps with different intensities, with 3–5 spikes generated even with extreme current stimuli (fig. 1A3). Of these three types of neurons, class 2 neurons, which are similar to the rhythmical burst neurons mentioned above, have received excessive attention [26, 28, 30]. With the help of nonlinear dynamics theory, these three classifications are described to have different dynamic bifurcation mechanisms [72].

Fig. 1. Excitability classification and transition in Mes V neurons. **A1** Class 1 neurons respond to intracellular current steps with repetitive AP firing (left), which is current intensity dependent. This is shown in either the ramp stimulation-evoked response (middle) or in the F-I curve (right), which is approximately linear with respect to the current intensities. **A2** Class 2 neurons respond to current stimuli with a constant spike frequency (left) which is current intensity independent, as shown in either the ramp stimulation-evoked response (middle) or in the F-I curve (right). **Inset** There are SMPO along with the ramp current-evoked rhythmical bursting. **A3** Class 3 neurons have a higher current intensity, which is required to evoke spikes, and the cell does not fire more than 3 spikes at the highest stimulus intensity (1,000 pA, left). A strong current ramp (1.5 nA) failed to evoke any response (right). **B1** Excitability transition between class 2 and class 1. The application of 4-AP transformed class 2 (left) to class 1 firing (middle); the addition of riluzole reversed the spike firing pattern back to class 2 firing, though at a lower frequency (right). **B2** Excitability transition between class 2 and class 3. The application of riluzole transformed class 2 (left) to class 3 firing (middle); the addition of 4-AP reversed the spike firing pattern back to class 2 firing, though at a lower frequency (right). Reproduced from Yang et al. [27] with permission. ACSF = Artificial cerebrospinal fluid.

(For figure see next page.)

Ample evidence indicates that the discharge pattern of one type of neuron can be changed into another type under physiological conditions or an experimentally applied approach [8], which means that the input-output relation changes thereafter. In an interesting study on the chronic compression of rat sciatic nerves, it was shown that at a bifurcation point of critical sensitivity, patterns of bursting in an experimental pacemaker can be altered when the extracellular calcium concentration is changed [12, 73, 74]. For Mes V neurons, a theoretical study using mathematical models has demonstrated that small changes in the parameters related to ionic currents could lead to transitions between different classes of membrane excitability [72]. Different dynamic properties of ionic currents which were detected in different types of Mes V neurons provide experimental support for this possibility. Using a method similar to that of Del Negro and Chandler [30], Yang et al. [27] found that in class 2 Mes V neurons, I_{4-AP} was activated at a relatively depolarizing potential (-57.5 ± 5.9 mV), and $V_{1/2}$ was -48.0 mV. In class 3 neurons, the value was significantly different: the activation threshold of I_{4-AP} was about -63.6 ± 3.7 mV, and $V_{1/2}$ was -54.2 mV. As to I_{NaP} , the authors found that it was activated at about -70 mV in both class 2 and 3 neurons, with $V_{1/2}$ at -51.0 mV ($k = -5.4$) for class 2 and -49.9 mV ($k = -5.7$) for class 3. Moreover, it was also found that the application of ZD7288 could increase the firing threshold of class 2 neurons, but the excitability of this cell type was unchanged [27].

A corresponding experiment has also been conducted to determine this excitability transition. It was found that reducing I_{4-AP} transformed class 3 to class 2 and finally to class 1 neurons, while suppressing I_{NaP} transformed class 2 to class 3 neurons [27]. More importantly, the application of 4-AP reversed the firing patterns that were abolished by riluzole (fig. 1B2), and, in turn, riluzole could reverse the excitation effect of 4-AP (fig. 1B1). These results suggest that electrophysiological behaviors (including neuronal excitability) are determined not only by the absolute magnitudes and inherent features of the critical currents (in this study, the critical currents were I_{4-AP} and I_{NaP}) but also by the balance between these currents, which has been confirmed in another report [75]. In agreement with this standpoint, within a short period during the process of drug application, the neuronal behavior displays the mixed characteristics of both class 1 and class 2. This strongly supports the abovementioned opinion that during the process of transformation, the relative proportion of I_{4-AP} and I_{NaP} keeps changing, which induces Mes V neurons to exhibit different excitability behaviors until a new balance is established.

The SMPO of Mes V Neurons

In the CNS, SMPO (i.e. membrane potential alternative fluctuation, usually expressed in millivolts) [76] is a common and important rhythmic activity. For a long time, there have been two opinions regarding the production of this rhythmicity. One opinion presumes that the synchronized rhythm stems from the neuronal network and that the neurons do not exert individual oscillation behaviors. The other presumes that the network rhythm comes from the intrinsic oscillation of each neuron within this area. More and more evidence for the existence of SMPO with different properties has been found in many encephalic regions of the CNS [77–81]. For example, theta wave frequencies (2–7 Hz) in hippocampal CA1 pyramidal neurons were generated by the subthreshold activity of three noninactivating currents [21, 79], SMPO in guinea pig cortical neurons is related to the potassium current and I_h [15, 82], and SMPO in the nucleus olivaris inferior is calcium dependent [83]. In addition, SMPO at a high frequency can be observed in DRG, as in Mes V [84], which belongs to the primary afferent sensory neurons [85, 86].

In Mes V neurons, the work by Pedroarena et al. [28] was focused on a specific electrophysiological property, i.e. the ability to exhibit robust and sustained SMPO activity on

membrane depolarization. They found that 52.6% of neurons generate periodic fluctuation with an amplitude of 2–4.3 mV and a frequency of 108.9 ± 15.5 Hz when the membrane potential is positive to -53 ± 2.3 mV. The following study by Wu et al. [26] investigated the change of SMPO during development. The oscillation amplitude and frequency had increased before P6 and further increased to a plateau level after P7–12. They also found that the amplitude of SMPO increased with further membrane depolarization, and AP were generated when the amplitude of SMPO reached the threshold. Along with the membrane potential depolarization, the peak frequency of SMPO switched to higher values until a maximum peak was reached, after which a decline occurred with further depolarization. The dominant frequency could be found after analyzing the power spectrum, which indicates that Mes V neurons have the tendency to respond selectively to a proper input frequency. Yang et al. [27] also found that about 39.3% of Mes V neurons from P9–14 SD rats have an SMPO similar to that mentioned above – although it is even more interesting that the neurons which have an SMPO usually are classified as class 2 neurons, in which SMPO and, as a result, a constant firing frequency are observed. Otherwise, a persistent depolarizing stimulus could not evoke continued discharge from neurons in which SMPO does not occur. Thus, it is clear that even though SMPO is a phenomenon of low amplitude, it has a critical role in determining the neurons' input and output characteristics and may decide the final output state [26, 87]. On the other hand, this oscillatory activity of Mes V neurons may play a very important role in jaw movement control, as originally postulated [28].

The Resonance Phenomenon of Mes V Neurons

SMPO could be considered the consequence of neural resonance. Resonance generally exists in nature; it has originally been regarded as a physical term defined as the tendency of a system to oscillate with greater amplitude at some frequencies than at others. Resonant frequencies are known as those frequencies at which the response amplitude is a relative maximum. In the nervous system, resonance indicates that it can distinguish input signals from their receiving frequency, so that the largest responses may be evoked by oscillatory inputs near the resonant frequency. Many neurons have this frequency selectivity (frequency preference), and they show the best response to an input stimulus in a very narrow frequency spectrum [21, 26, 82]. Exciting investigations show that resonance plays a key role in learning and memory as well as in synaptic plasticity when the brain neural network is in a coordinated condition [21, 25, 26, 78]. Neurons possess resonance properties because of the interaction between their passive and active characteristics. The passive characteristics include two aspects: the membrane resistance formed by membrane permeability and the membrane capacitance formed by the membrane lipid bilayer, which form the low-pass filter in physical circuits and have the function of weakening the high-frequency components from the input signal. However, the membrane resistance-capacitance circuit is not necessarily the low-pass filter. As we know that, the TASK1/3 channel, which belongs to the two-pore domain channel family, has been widely accepted to be underlying the cell membrane potential and R_{in} . Various agents including volatile anesthetics and neurotransmitters can modulate the function of the TASK channel and thus can modulate the low-pass filter. The active elements of neurons are composed of voltage-gated ion channels [13] and have the function of inductors in the band-pass filter circuit, which permits passage of the high-frequency component of an input signal [15, 82]. Only in this way, neurons can make a strong response to an input signal which has a close relationship to their own resonant frequency.

Based on rats aged P2–12, Wu et al. [26] found that when holding the membrane potential at -57 mV, Mes V neurons showed a voltage-dependent high-frequency resonance (110 Hz) in response to injection of a computer-generated impedance amplitude profile (swept-sine wave) input current of changing frequencies between 0 and 250 Hz into neurons. It was also clarified that the resonant current was I_{4-AP} , and I_{NaP} could amplify this resonance. In a further investigation into class 2 neurons and part of class 3 neurons, we found another low-frequency resonance (<10 Hz) when holding the membrane potential at the hyperpolarization level (about -70 mV; data to be published). $50 \mu\text{M}$ of 4-AP could abolish the high-frequency resonant peak but caused little or no change to the low-frequency resonant peak, while $10 \mu\text{M}$ ZD7288 could abolish the low-frequency resonant peak but caused little or no change to the high-frequency resonant peak.

Neurons live in an environment which is full of noise, such as from stochastic opening and closure of the membrane ion channels and stochastic release of the neurotransmitters at synapses. It has recently been shown that neurons could take advantage of noise in detecting weak signals through stochastic resonance or autonomous stochastic resonance [88–91]. In our work, through observing and comparing effects of noise on the three classes of excitability, we found that only in class 2 neurons could a certain intensity noise reduce the membrane potential level at which SMPO is produced. The degree of such a reduction increases with the increment in noise intensity. This effect, along with the reduction of the spike threshold, contributes to increasing the excitability of class 2 neurons (data not shown). Indeed, the ion channel mechanism underlying this phenomenon still needs further investigation.

Electrical Coupling Promotes Strong Synchronization

The Mes V nucleus, formed by the somatic primary afferents initiating from jaw-closing muscles, is one of the first proofs supporting the existence of electrical synapses in the mammalian CNS. Four decades ago, classic experiments were carried out to interpret the ‘short-latency depolarization’ happening in Mes V, which suggested ‘electrotonic coupling’ as the mechanism for that phenomenon [92]. Lately, some proof that Mes V neurons form coupled networks via electrical and excitatory connections was reported by virtue of transmission electron microscopy [93] and horseradish peroxidase injection into masseter and temporalis muscles [93, 94]. However, this direct approach for the detailed analyses of the features of these electrical contacts has not been further pursued until recently. Curti et al. [95] found that electrical coupling is restricted to small clusters of Mes V neurons. They also indicated that connexin-36-containing gap junctions mediated electrical transmission between Mes V neurons [96]. A kind of developmentally regulated brain protein, drebrin, was found to be located at axosomatic synapses and neuronal gap junctions; thus, it is an ideal marker of Mes V neurons [97]. Interestingly, the development of a coupling increase is responsible for the repetitive firing in these neurons, which parallels the development of inherent membrane properties. For instance, bursting is initiated after P6 and is largely determined by the oscillation frequency, which again emerges from the resonant properties of Mes V neurons [26]. Therefore, certain membrane properties may collaboratively interact with electric coupling to promote synchronization between Mes V neurons [95], but how these features contribute to their function, e.g. regulation of the stretch reflex, still needs further investigation. Moreover, since there are only few reports, more modeling work for the reproduction of electrophysiological behavior (such as excitability, resonance and SMPO as well as coupling activities) is needed, which could be a guide for introducing the functional state of MesV neurons [98].

Conclusion

The variety in excitatory responses of Mes V neurons does not only depend on the dynamic state of RMP such as SMPO and the frequency range of resonance, but it also rests on the classification of excitability and the underlying ionic currents. Whether the classification of excitability and its transition are also important for the variety in excitatory responses in other neurons is still unclear and will form an interesting topic for future research.

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