

Chapter 2

Membrane Mechanisms of Tremor

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Keywords Membrane • Neurons • Oscillations • Loops • Spikes • Coupling • Synchronization • Thalamus • Inferior olive • Cerebellum

2.1 Background

A number of neurological and psychogenic disorders present with tremor. In some, there is a known structural abnormality, while in others the pathophysiology is unknown. For example, the scarcity of a neurotransmitter from presynaptic neuronal degeneration causes tremor in degenerative cerebellar or basal ganglia disorders (Jankovic and Tolosa 2007). Instability of the brainstem neural integrators may cause tremor of the eyes (pendular nystagmus) in patients with demyelinating disorders (Das et al. 2000). However, the anatomical and pathophysiological correlates of some tremor disorders, for example essential tremor, are unsettled. Regardless of the primary etiology (structural deficit or idiopathic) contemporary literature suggests that oscillations can arise at the level of neuronal membranes. More recently, it was proposed that membrane hyperexcitability could cause essential tremor (Shaikh et al. 2008). In support of this hypothesis, commonly used drugs (e.g., primidone, propranolol, gabapentin, topiramate) also have membrane stabilization effects (O’Suilleabhain and Dewey 2002; Zesiewicz et al. 2005).

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2.2 Outline

In this chapter we will focus on membrane electrophysiology and its relationship to tremor. We will review literature on membrane electrophysiology of the central neurons that are known to cause tremor. We will discuss how intrinsic membrane properties of these neurons can generate oscillations, and how isolated cellular oscillations are synchronized to generate tremor. We will also address computational studies that propose specific hypotheses for the membrane mechanisms of tremor. Finally we will discuss the pharmacotherapy of tremor that supports the membrane contribution to tremor generation. In this chapter we emphasize the role of membrane properties in the generation of tremor, but we do not exclude the role of anatomical and physiological abnormalities that also serve as a substrate for tremor. We only suggest that abnormalities in *both* anatomical circuits and the properties of membranes of their constituent neurons are important for a complete understanding of the genesis of tremor.

2.3 Membrane Mechanisms of Essential Tremor

Figure 2.1 shows a simplified diagram of the primate motor system and indicates possible sources of tremor. The mass and biophysical property of the part of the body to be moved is a key determinant of the frequency of any tremor (Elble and Koller 1990). Of course, neurological disorders producing tremor, such as essential tremor, clearly have a central origin (Timmermann et al. 2003; Volkmann et al. 1996). A strong coherence between the tremor and thalamic oscillations (Hua and Lenz 2004; Hua et al. 1998) and an influence of thalamic lesions on the tremor (Koller et al. 2000; Pahwa et al. 2000) support the role of a thalamocortical pathway in the pathophysiology of essential tremor (blue pathway in Fig. 2.1). Synchronized activity in a circuit comprised of cerebellar Purkinje neurons, the deep cerebellar nuclei, and the inferior olive plays a key role in motor learning and motor timing (Apps and Garwicz 2005; Wolpert et al. 1998). Increased synchronization of the inferior olive neurons by harmaline is a common way to generate an animal model of tremor (Lamarre et al. 1971; Lamarre and Mercier 1971; de Montigny and Lamarre 1973; Llinás and Volkind 1973). Increased activity in the olivocerebellar pathway has been reported in patients with essential tremor (Louis et al. 2004; Deuschl and Elble 2000; Jenkins and Frackowiak 1993). The olivocerebellar pathway is illustrated in a green color in Fig. 2.1.

Here we address two fundamental questions: Why do thalamocortical and olivocerebellar networks oscillate? Which factors predispose them to generate tremor? It is known that the intrinsic membrane properties of thalamic and inferior olive neurons facilitate spontaneous rhythmic firing (Jahnsen and Llinás 1984; Park et al. 2010; Llinás and Yarom 1986). These isolated cellular oscillations may become synchronized to generate sufficient drive causing actual tremor.

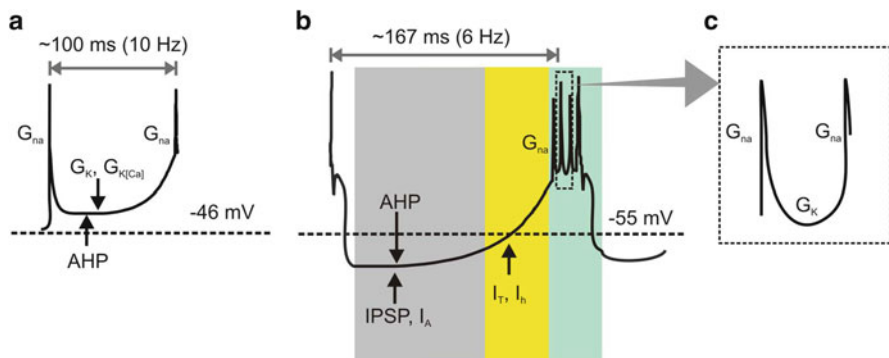


Fig. 2.2 This caricature illustrates the underlying ion currents responsible to two oscillatory attributes of the thalamic neurons. **(a)** Action potential spike is generated by fast acting sodium currents (G_{Na}). The spike is voltage-sensitive potassium current and calcium-dependent potassium currents, causing after-hyperpolarization. After hyperpolarization (AHP) typically brings membrane to threshold for fast spike, but not further negative than -55 mV. The threshold is sufficient for subsequent, spike in approximately 100 ms, causing 10 Hz spikes. **(b)** Strong hyperpolarization simulating inhibitory postsynaptic potential (IPSP) brings membrane potential further negative than -55 mV, de-inactivating 4-aminopyridine sensitive potassium current (I_A) to further prolong the duration of the hyperpolarized state. Latter then de-inactivates low-threshold calcium current (I_T) and hyperpolarization-activated mixed cation current (I_h) triggering a rebound spike of action potential (post-inhibitory rebound)

met isolated thalamic neurons generate spontaneous action potentials. Thalamic neurons have two key properties related to the generation of tremor: (1) partial depolarization of the membrane potential triggers a “burst” of low-threshold spikes; and (2) a further depolarized state results in sustained firing (“tonic discharge”) (Jahnsen and Llinás 1984; McCormick and Pape 1990).

The resting membrane potential of the thalamic neuron determines the frequency of cellular oscillations. A high frequency (9–11 Hz) oscillatory pattern emerges when the thalamic neuron is depolarized to around -46 mV (Jahnsen and Llinás 1984; Fig. 2.2a). Such a depolarized state activates a slow sodium conductance followed by fast sodium current to generate an action potential and subsequent after-hyperpolarization (Jahnsen and Llinás 1984). The after-hyperpolarization, caused by the voltage- and calcium-dependent potassium current (Hotson and Prince 1980; Llinás and Sugimori 1980; Llinás and Yarom 1981), brings the membrane potential to a subthreshold state lasting for about 100 ms. The duration of the subthreshold, “refractory,” state determines the frequency (9–11 Hz) of the oscillatory behavior. Figure 2.2a depicts a schema of the temporal sequence of ion conductances responsible for 9–11 Hz oscillations. The strength of hyperpolarization that follows the isolated action potential spike is generally not sufficient to de-inactivate I_T and I_h low-threshold spikes.

In the thalamus approximately 6 Hz oscillations emerge as the membrane is hyperpolarized beyond -55 mV. This strong hyperpolarization triggers a prolonged after-hyperpolarized state due to inhibitory postsynaptic potentials (IPSP)

and relatively prolonged inactivation state of I_A (gray zone in Fig. 2.2b). The hyperpolarized state triggers pacemaker currents (such as I_h and I_T currents) (Jahnsen and Llinás 1984; Pape and McCormick 1989; McCormick and Pape 1990; see yellow zone in Fig. 2.2b). The cell membrane is then depolarized, resulting in the burst of action potentials (post-inhibitory rebound, PIR; see light blue zone in Fig. 2.2b). Each action potential (within the burst) is followed by a voltage-dependent potassium current and then a successive spike of action potential (dashed black box in Fig. 2.2b, c). The rate of depolarization of the membrane that follows hyperpolarization after each single action potential is determined by the extracellular concentration of potassium ions. A reduced extracellular potassium concentration favors a rapid rate of membrane depolarization to reach the threshold for successive action potential, hence, an increased number of action potentials within the burst (i.e., the “strong” burst). A number of factors, including levels of I_h and I_T , determine the extracellular levels of potassium, the number of action potentials within the burst, and hence, the strength of PIR. Each burst typically lasts 20–30 ms and is followed by a refractory period (Jahnsen and Llinás 1984). The hyperpolarization, more negative to -55 mV, which follows each burst, again de-inactivates low-threshold currents and causes a subsequent PIR. In the presence of a periodic inhibitory stimulus, sustained, 6 Hz bursts of PIR appear. The relatively low frequency of the bursts of PIR is attributed to the longer inactivation time of the I_T current (Jahnsen and Llinás 1984).

2.3.2 Membrane Oscillations in the Inferior Olive Neurons

Neurons within the inferior olive show three types of oscillatory behavior; two are similar to thalamic neurons. Approximately 9–10 Hz oscillations are seen during the burst of spontaneous discharge (Llinás and Yarom 1986). These oscillations are comprised of a sequence of action potentials each of which typically is followed by a relatively short after-hyperpolarization. However, when the membrane is strongly hyperpolarized a relatively sustained after-hyperpolarization de-inactivates I_h and I_T currents and results in PIR (Llinás and Yarom 1986). In addition, subthreshold, 3–6 Hz sinusoidal oscillations of the resting membrane potential is a unique property of inferior olive neurons (Llinás and Yarom 1986). The amplitude and frequency of these subthreshold sinusoidal oscillations are independent of the amplitude of the transmembrane voltage during the resting state (Llinás and Yarom 1986). Attenuation of the fast sodium current has no effect on the subthreshold oscillations; however, antagonists of I_T abolish them. Generally, the depolarizing shift in the resting membrane potential during subthreshold sinusoidal oscillation does not cause action potentials. However, when the membrane is hyperpolarized, subthreshold oscillations frequently result in low-threshold currents, (such as I_T) that are often followed by a burst of action potentials (Llinás and Yarom 1986). In other words, in the hyperpolarized state, subthreshold sinusoidal oscillations increase the propensity to rhythmically generate action potential bursts.

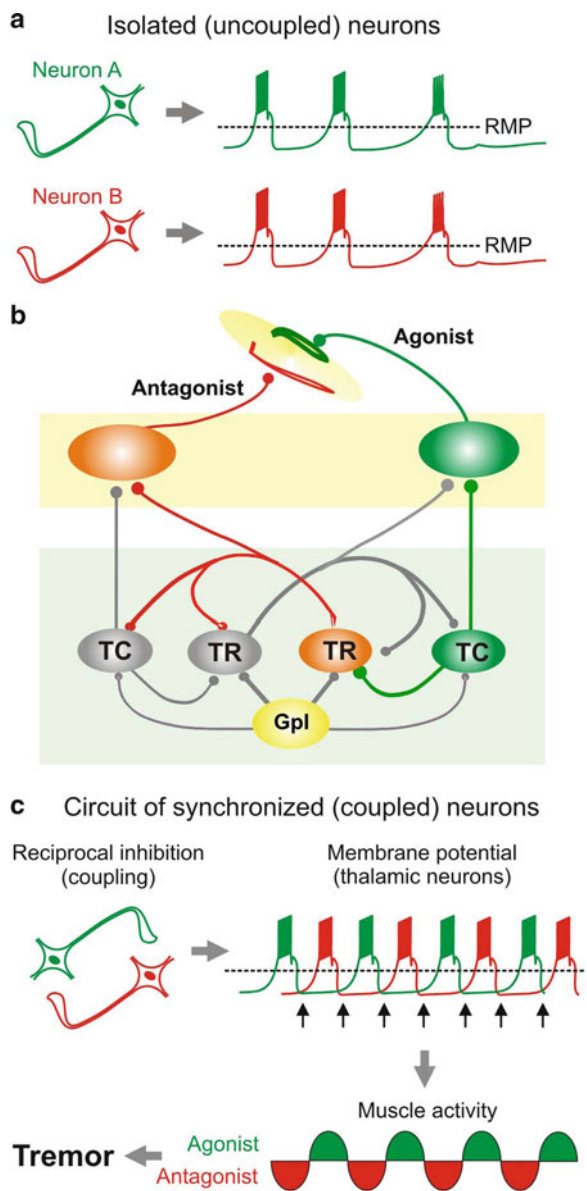


Fig. 2.3 (a) Caricatures of repetitive bursts from two thalamic neurons are illustrated. Due to membrane ion channel profile, the action potential in the given neuron is followed by after-hyperpolarization. When the strength of after-hyperpolarization is sufficient to bring the membrane potential more negative than -55 mV, there is de-inactivation of 4-aminopyridine sensitive potassium current, low threshold calcium current (I_T), and hyperpolarization-activated cation current (I_h). As a result there is rebound burst, post-inhibitory rebound. As illustrated in this panel, in absence of consistent, repetitive burst of inhibition, the bursting oscillatory behavior of these neurons dissipates. Furthermore, resultant spikes from an isolated neuron are not sufficient to generate

2.3.3 *Thalamic and Inferior Olive Oscillation and Relation to Harmaline Model of Tremor*

The mechanisms underlying spontaneous oscillations in the thalamus and inferior olive relate to the pathophysiology of harmaline-induced tremor, the popular experimental animal model of essential tremor (Lamarre et al. 1971; Lamarre and Mercier 1971; de Montigny and Lamarre 1973; Llinás and Volkind 1973). Local application of harmaline could enhance the de-inactivation of I_T and I_h , and increases the membrane excitability to cause occasional 3–6 Hz spike trains of action potentials (Llinás and Yarom 1986). Harmaline also accentuates the subthreshold sinusoidal oscillations and further increases the propensity to produce action potential in otherwise “silent” neurons (Llinás and Yarom 1986).

2.3.4 *Synchronization of Isolated Neuronal Oscillations*

Now that we have described underlying mechanisms for oscillations in isolated thalamic and inferior olive neurons, we must emphasize that when isolated, these neurons are unable to sustain their oscillations (Fig. 2.3a). Repetition of an inhibitory stimulus, generating inhibitory postsynaptic potentials, and subsequent PIR is required to maintain the oscillatory behavior. Furthermore, an ensemble discharge from a group of neurons is necessary to generate adequate drive to move a body part. In physiological system, the groups of neurons are coupled or synchronized to generate a sufficient motor drive and sustain their oscillations causing tremor. The sections below describe mechanisms of synchronization in thalamic and inferior olive neurons.

Fig. 2.3 (continued) adequate force generating tremor. These spikes would dissipate over time in absence of repetitive external impulse. **(b)** This panel illustrates the circuit of reciprocally innervating neurons controlling movements. As illustrated thalamocortical neurons (TC) and thalamic reticular neurons (TR) makes a circuit of reciprocally innervating neurons. Unless inhibited or hyperexcited the reciprocally innervating circuit can oscillate. The oscillations are normally inhibited by the globus pallidus internus (GpI) neurons. This panel is modified from Shaikh et al. (2008). **(c)** The thalamic reticular and thalamocortical neurons form reciprocally inhibitory circuit and thus couple with each other forming multiple synchronized patches. Here, in example of two inhibitory neurons A and B, due to reciprocal inhibition, a burst in neuron A is followed by a burst in neuron B (due to inhibition from neuron A). The burst in neuron B then result in burst in neuron A, hence, train of bursts in two mutually inhibitory neurons start. When these neurons are designated to innervate agonist and antagonist muscles, respectively, alternating firing of agonist and antagonist muscle pairs cause tremor

2.3.4.1 Coupling of Neurons in Thalamus

Reciprocal inhibition of agonist and antagonist neurons is necessary to generate sustained oscillations in the thalamic circuit (Sherrington 1908). This principle is schematized in Fig. 2.3b. Thalamo-cortical relay (TC) neurons send glutamatergic excitatory projections to thalamic reticular (TR) neurons, while TR neurons send GABA-mediated inhibitory projections to TC neurons (Pinault 2004; Guillery and Harting 2003). In addition, TR neurons mutually inhibit each other via inhibitory collaterals (Pinault 2004; Guillery and Harting 2003). This interaction amongst TC and TR neurons makes reciprocal loops, negative feedback from TR to TC, and mutually inhibitory TR neurons. This organization, reciprocal innervations of neurons that can generate PIR, could provide adequate drive to generate prompt and high-speed ballistic movements. However, such reciprocally innervating circuits are inherently unstable and are prone to generate oscillations (Shaikh et al. 2007, 2008; Ramat et al. 2005; Fig. 2.3b). Figure 2.3c illustrates a schematic of two reciprocally inhibitory thalamic neurons with a membrane profile suitable to generate PIR (neurons A and B). When a small pulse of neural signal, either spontaneous neural firing or a small voluntary movement, activates neuron A, it in turn would inhibit neuron B. The latter, having PIR, would have the burst of action potentials at the end of the inhibitory pulse from neuron A. Furthermore, neuron B would also inhibit neuron A (reciprocal inhibition), causing it to have PIR at the end of the pulse from neuron B. As consequence a sustained train of PIR, alternating between agonist and antagonist neurons (neurons A and B), would emerge and the reciprocally innervated neural circuit would begin to oscillate (Fig. 2.3c). The coupling between multiple neurons allows synchronization of oscillations in groups of neurons, allowing sufficient electrical drive to generate and sustain tremor.

2.3.4.2 Experimental and Computational Evidence of Thalamic Coupling as a Cause of Tremor

It was hypothesized that sufficient external inhibition is nature's solution to inherently unstable thalamic circuits (Shaikh et al. 2007, 2008). As schematized in Fig. 2.3b, inhibitory projections to TC and TR neurons from the globus pallidus internus (GPi) provide a substrate for GABAergic external inhibition to potentially unstable thalamic circuits (Parent and Hazrati 1995; Takada and Hattori 1987). Abolishing GABAergic inhibition in GABA mutant mice caused tremor phenotype (Kralic et al. 2005). A recent 11C-flumazenil PET study showed an association between reduced GABA function and increased availability of GABA receptors in cerebellar and thalamic sites (Boecker et al. 2010). Boecker and colleagues (2010) interpreted these results in support of the "GABA hypothesis," which attributes the thalamic oscillations to the scarcity of GABA function. However, the "GABA hypothesis" remains controversial in the pathogenesis of human essential tremor. García-Martín et al. (2011) did not find differences in the

frequencies of allelic variants in the genotypes of GABA receptors from the essential tremor patients and healthy subjects (García-Martín et al. 2011). Thus, indirectly, this study found no apparent molecular evidence of impaired GABAergic inhibition in patients with essential tremor. A different study did not find any mutation in the GABA receptor genotype in humans with essential tremor (Deng et al. 2006).

We proposed a novel hypothesis for the pathophysiology of essential tremor (Shaikh et al. 2008). Our hypothesis was based on the idea that increased excitability of TC and TR neurons causes reverberations in the coupled circuits (Shaikh et al. 2008). It was proposed that the effect of (normal) inhibition is reduced by increased excitability within a circuit of reciprocally innervated neurons. It is possible that increased activation kinetics of I_h or I_T , due to the alterations in the intracellular levels of second messengers or other regulators, increase the neural excitability (McCormick and Pape 1990; Shaikh and Finlayson 2005; Wainger et al. 2001; Lüthi and McCormick 1999). Computational models of the thalamic neurons with physiologically realistic membrane properties and anatomically realistic neural connections are compatible with a role for neuronal hyperexcitability in the pathogenesis of essential tremor (Shaikh et al. 2008). Key features of our model were (1) increased neural excitability secondary to increase in I_h and/or I_T currents and (2) inherent circuit instability resulting from reciprocal innervation between the neurons with PIR. A proposed increase in I_h and/or I_T simulated limb oscillations resembling essential tremor (Shaikh et al. 2008). Indeed NNC55-0396, a potent blocker of I_T , reduced tremor in GABA_A receptor null and harmaline-treated animal models and provided experimental support for our hypothesis (Shaikh et al. 2008; Quesada et al. 2011).

2.3.4.3 Other Causes of Thalamic Neuronal Excitability in Essential Tremor

All patients with essential tremor would not be expected to have the same cause for their increased excitability. A loss of inhibition due to a structural abnormality in cerebellar Purkinje neurons has been proposed for the subgroup of essential tremor patients (Axelrad et al. 2008; Louis and Vonsattel 2008; Louis 2010). Hypothetically a structural lesion in Purkinje neurons could increase the excitability of thalamic neurons by reducing inhibition in the dentate–thalamic projection. The gly9 susceptibility variant of the DRD3 gene was reported in some essential tremor families (Jeanneteau et al. 2006; Lucotte et al. 2006; Sóvágó et al. 2005). Such a mutation can prolong the intracellular action of mitogen-activated protein kinase (MAPK), leading to increased intracellular levels of cyclic AMP (cAMP) via excessive inhibition of phosphodiesterase E4 (Hoffmann et al. 1999; Houslay and Milligan 1997; Houslay et al. 1998; Jeanneteau et al. 2006). It is known that increased intracellular cAMP increases I_h and subsequently increases the membrane excitability of central neurons (Shaikh and Finlayson 2005).

2.3.4.4 Coupling of Neurons in Inferior Olive

Isolated inferior olive neurons generate small amplitude, episodic, subthreshold oscillations, which are only sustained for a few seconds (Llinás and Yarom 1981, 1986; Leznik and Llinás 2005; Yarom 1991; Placantonakis et al. 2006). If sustained and synchronized, these oscillations can also cause tremor. Recent studies increasingly supported a role for connexin gap junctions to synchronize and sustain the subthreshold oscillations in the inferior olive (Yarom 1991; Bleasel and Pettigrew 1992; Manor et al. 1997; Condorelli et al. 1998; Long et al. 2002; De Zeeuw et al. 2003; Placantonakis et al. 2006). Each inferior olive neuron is coupled with variable number of neighboring neurons (Hoge et al. 2011). The patches of inferior olive neurons have variable coupling strength (Hoge et al. 2011). Uncoupling resulting from genetic disruption of connexin 36 or its blockade, *in vivo*, with local injection of carbenoxolone or 18-glycyrrhetinic acid degraded the ensemble rhythm of the inferior olive (Leznik and Llinás 2005; Blenkinsop and Lang 2006; Placantonakis et al. 2006). Hence, it is likely that electrotonic gap junctions comprised of connexin molecules between adjacent inferior olive neurons are key elements for facilitating synchronization in the inferior olive. In the harmaline model of tremor, the role of subthreshold oscillations and the influence of harmaline on connexin gap junction remain controversial. Harmaline induced robust oscillations in animal knockout models for connexin36, which are the same as oscillations in wild-type phenotypes (Placantonakis et al. 2006). Therefore, it has been suggested that there is another ionic mechanism that facilitated synchronization of harmaline-treated connexin36, knockout animals (Placantonakis et al. 2006).

2.3.4.5 Influence of Cerebellum and Conditional Learning on Synchronized Inferior Olive Discharge and Tremor

It is hypothesized that cerebellar conditional learning may alter the kinematic properties (amplitude and regularity) of the inferior olive discharge (Shaikh et al. 2010). Synchronized activity of the inferior olive is transmitted to the cerebellar Purkinje cells by two parallel pathways—through climbing fibers and through parallel fibers via deep cerebellar nuclei. As seen in a classical conditioning paradigm, here Purkinje cells would learn an irrelevant conjunction from an inferior olive input arriving directly on climbing fibers, and indirectly, with a delay, on parallel fibers. The Purkinje cell would therefore pause with each inferior olive pulse, increasing the output of the inferior olive and making it smoother and larger. In patients with oculopalatal tremor (OPT), this hypothesis was tested by simulating pendular eye oscillations with a computational model (Hong and Optican 2008; Shaikh et al. 2010). The model featured the interaction between the inferior olive and the cerebellum using (1) high-conductance soma-somatic gap junctions in adjacent inferior

olive neurons, (2) synchronized discharge of a population of inferior olive neurons, and (3) cerebellar motor learning (Hong and Optican 2008; Shaikh et al. 2010). The similar process may also alter the characteristics of essential tremor originating due to hyperactivity of olivocerebellar pathway (Louis et al. 2004; Deuschl and Elble 2000; Jenkins and Frackowiak 1993).

2.3.5 *Membrane Electrophysiology and Essential Tremor Frequency*

Many factors influence the frequency of essential tremor. The mass and physical property of the mechanical system is one, for example. Tremor of an organ with a smaller mass (e.g., the fingers) is typically of a higher frequency than one with a larger mass (e.g., wrist) (Elble and Koller 1990). However, the frequency of essential tremor of the same organ among different subjects is variable (Deuschl et al. 2001). The conductance-based model of essential tremor predicts that profile of expression of I_h and I_T channels determines inter-subject variability in the frequency of tremor (Shaikh et al. 2008). Increasing the value of I_h in the conductance-based model of thalamic neurons increases the tremor frequency but decreases the amplitude (Shaikh et al. 2008). In contrast, increasing the value of I_T (while keeping I_h constant) increases the tremor amplitude but decreases the frequency. Simulations of the conductance-based model of thalamic neurons correlate well with the data from essential tremor patients (Shaikh et al. 2008). Although speculative, these simulations speak for the plausibility of a role for ion channel expression profiles and intrinsic membrane properties in the genesis and variability of tremor in patients.

As described earlier, thalamic neurons have two oscillatory characteristics, one with a low frequency (approximately 6 Hz) and the other with a relatively high frequency (9–11 Hz) (Jahnsen and Llinás 1984). Only the 6 Hz component is reflected in the frequency of the essential tremor (Elble 2000). We hypothesize that it is due to a selective synchronization of low frequency oscillations. Patch-clamp and computational studies showed that the inhibition of the coupled neuron has to be strong enough to evoke an IPSP, subsequent low-threshold spike, and PIR (Jahnsen and Llinás 1984; Shaikh et al. 2008). Therefore only rebound firing of the inhibitory (presynaptic) neuron could generate an IPSP in the inhibited (postsynaptic) neuron. Therefore amongst the coupled neurons only the “low-frequency thalamic oscillations” comprised of low-threshold spikes and PIR are synchronized. In contrast, individual hyperpolarization (responsible for “high-frequency thalamic oscillations”) does not evoke a sufficiently inhibitory postsynaptic potential to synchronize with the coupled neuron. Therefore high frequency oscillations are typically not seen in the patients with essential tremor.

2.3.6 *Pharmacotherapy of Tremor Supports the Membrane Hypothesis for Essential Tremor*

2.3.6.1 **Beta-Blockers and Membrane Physiology of Tremor**

Beta-blockers, such as propranolol, are considered a first-line treatment for essential tremor (Zesiewicz et al. 2005). Atenolol is used when propranolol is contraindicated, e.g., in patients with asthma (Zesiewicz et al. 2005). Beta-blockers reduce intracellular levels of cyclic AMP, inhibit signaling through protein kinase C and extracellular signal-regulated kinase (Sozzani et al. 1992; Pascoli et al. 2005; Franzellitti et al. 2011). The intracellular level of cyclic AMP is one of the key determinants of the strength of I_h and I_T currents; reduction in the levels of cyclic AMP reduces I_h and I_T and subsequently the membrane excitability (Shaikh and Finlayson 2003, 2005; Alvarez et al. 1996; Pape and McCormick 1989; Yue and Huguenard 2001; Jahnsen and Llinás 1984). It is not surprising that reduction in membrane excitability reduces tremor amplitude and frequency (Shaikh et al. 2008).

2.3.6.2 **Antiepileptics and Membrane Physiology of Tremor**

Primidone, an antiepileptic, is also considered a standard treatment for essential tremor (Zesiewicz et al. 2005). Primidone is a desoxybarbiturate with two active metabolites—phenylethylmalonic acid and phenobarbitone (Baumel et al. 1972). One of the active metabolites, phenobarbitone has a dual action—it enhances post-synaptic GABA-mediated inhibition as well as reduces neural excitability (Polc and Haefely 1976). Reducing excitability and enhancing external (GABAergic) inhibition on a reciprocally inhibited, unstable, oscillating circuit of thalamic neurons would promote stabilization and reduce tremor (Shaikh et al. 2008).

Gabapentin is an antiepileptic that is also effective in essential tremor. It reduces calcium trafficking by blocking the alpha-2-delta subunit of the calcium channel (Thorpe and Offord 2010). Gabapentin can also block NMDA glutamate receptors (Kim et al. 2009). As a result gabapentin could reduce membrane excitability in thalamic neurons and attenuate tremor (Shaikh et al. 2008).

Zonisamide, an antiepileptic and an I_T blocker, also may be effective in essential tremor. This too supports the hypothetical role of increased neural excitability (secondary to an increase in I_h and/or I_T) and subsequently a release of oscillations in the thalamocortical circuit, in the pathophysiology of essential tremor (Morita et al. 2005; Song et al. 2008; Handforth et al. 2009).

2.3.6.3 **Membrane Physiology of Tremor and Alcohol**

At least three membrane mechanisms might account for a reduction of tremor with the acute consumption of alcohol. Ethanol induces sustained GABA_A-mediated

inhibition, decreasing neural excitability and firing rate (Jia et al. 2008). Reduced thalamic neural excitability can attenuate tremor (Shaikh et al. 2008). Abnormalities within the NMDA pathway are another proposed mechanisms of essential tremor (Manto and Laute 2008) and increased glutamatergic stimulation can increase membrane excitability of thalamic neurons causing tremor (Shaikh et al. 2008). Ethanol antagonizes this effect by decreasing the glutamate concentration and NMDA current, which in turn would reduce membrane excitability and diminish tremor (Manto and Laute 2008; Shaikh et al. 2008).

2.4 Membrane Physiology and Tremor of Parkinson's Disease

There is increasing evidence that parkinsonism is a complex network disorder secondary to abnormally increased excitability, oscillatory activity, and synchrony in the basal ganglia neurons affecting their thalamic and cortical connections (Obeso et al. 1997; Bergman et al. 1990, 1998; Herrero et al. 1996; Mitchell et al. 1989; Vila et al. 1996, 1997; Galvan and Wichmann 2008; Gittis et al. 2011). The scarcity of dopamine has a key role in increasing excitability and facilitating the synchronization of oscillatory behavior in the basal ganglia (Bergman et al. 1998; Gittis et al. 2011).

One piece of evidence for increased excitability in parkinsonism comes from intracellular recordings from single, dopamine-deprived striatal neurons. They showed spontaneous GABA-mediated, depolarizing, postsynaptic potentials (Calabresi et al. 1993). Lesion of SNPr, which is the source of dopaminergic terminals to the striatum, increases postsynaptic (striatal) sensitivity of D2 dopamine receptors. This, in turn, enhances the release of glutamate and reduces D1 dopamine receptor-induced inhibition. Such an increase in striatal excitability could alter the striatal output to other nuclei in the basal ganglia (Vila et al. 1996, 1997; Wichmann et al. 1999; Orioux et al. 2000; Galvan and Wichmann 2008). The net response of enhanced excitability and attenuated inhibition would result in oscillatory activity which could produce or accentuate tremor.

Neurons within the subthalamic nucleus of patients with Parkinson's disease show three patterns of activity—tonic, irregular, and oscillatory (Rodriguez-Oroz et al. 2001). Neurons with irregular and tonic firing are relatively common and are equally activated by movement. Rhythmically firing neurons within the subthalamic nucleus are of two subtypes: those with long-lasting low-frequency bursts and those with high-frequency bursts. The dominant oscillation frequency of those with the high-frequency bursts matches that of tremor. Microstimulation or lesion of these neurons promptly attenuates the tremor (Rodriguez-Oroz et al. 2001; Wichmann et al. 1994; Baunez et al. 1995; Guridi et al. 1996; Krack et al. 1997; Limousin et al. 1998). The oscillatory behavior in subthalamic circuit further propagates to thalamic and cortical neurons. The neuronal discharges recorded from the thalamus and globus pallidus are also phase locked with tremor (Albe-Fessard et al. 1962; Lenz et al. 1994; Guridi et al. 1999; Vitek et al. 1998). The discharge within two

distinct cerebral cortical networks, temporoparietal-brainstem and frontal, is coherent with subthalamic oscillations (Litvak et al. 2011). Hence, it is proposed that the subthalamic nucleus, globus pallidus, thalamus, and cerebral cortex are all part of a neural circuit generating tremor in Parkinson's disease (Alexander et al. 1986; DeLong 1990).

2.5 Membrane Physiology in Drug-Induced Tremor

2.5.1 Valproate-Induced Tremor

Valproate, an anticonvulsant and mood stabilizer, has several known mechanisms of action. It enhances the effects of GABA by reducing its transamination (Chapman et al. 1982) and it selectively inhibits I_T (Kelly et al. 1990). Given these, valproate should enhance GABAergic inhibition and decrease the propensity to cause tremor by reducing membrane excitability and neuronal threshold. In contrast, parkinsonism and postural tremor can be side effects of valproate (Zadikoff et al. 2007). Why is there an increased risk of developing tremor and parkinsonism in patients exposed to valproic acid? One idea is that enhancement of GABA reduces the dopamine turnover in the nigrostriatal system (Waldmeier and Maitre 1978). For example, the GABA_B-agonist, baclofen, reduces the release of dopamine in the striatum (Kabuto et al. 1995). Therefore reduced dopaminergic tone could cause tremor and extrapyramidal symptoms resembling parkinsonism in patients taking valproate. Valproate-induced cerebellar atrophy can be associated with tremor in some patients (Papazian et al. 1995).

2.5.2 Lithium-Induced Tremor

Tremor is a common side effect of lithium, a commonly used mood stabilizer (Varaflor et al. 1970). Lithium replaces the sodium ions, causing marked depolarization and alters the configuration of the action potential (Carmeliet 1964). Due to its similarity to sodium, lithium is transported inside of the cell. However, it cannot bind with Na-K-ATPase pump and accumulates intracellularly (Carmeliet 1964). According to the Goldman-Hodgkin-Katz equation, replacement of sodium by lithium results in a depolarization shift of the resting membrane potential (Thiruvengadam 2001). A reduced neuronal threshold due to the depolarized state of the resting membrane potential can increase neuronal excitability and a propensity to develop tremor (Shaikh et al. 2008). In support of this idea, a beta-blocker, propranolol, improves lithium-induced tremor (Kellett et al. 1975). Propranolol non-selectively reduces I_h and I_T and consequently reduces neuronal excitability (Pape and McCormick 1989; Shaikh and Finlayson 2003).

2.5.3 *Neuroleptic-Induced Tremor*

Neuroleptics also cause tremor and parkinsonism, and atypical antipsychotics are more likely to manifest extrapyramidal side effects. These compounds are lipophilic and strongly block the D2 subtype of dopamine receptors (Susatia and Fernandez 2009). Depletion of dopamine in presynaptic terminals causes increased activity of the GABAergic system which reduces the turnover of dopamine in the nigrostriatal system (Susatia and Fernandez 2009; Waldmeier and Maitre 1978; Kabuto et al. 1995). The membrane pathophysiology of neuroleptic-induced tremor is therefore similar to that induced by experimental models of dopamine depletion as described in the section of tremor in Parkinson's disease (section 2.4).

2.5.4 *Tremor in Hyperthyroidism*

Thyroid hormone has many effects on the electrical activity of the cell membrane. The effect of hyperthyroidism on cardiac pacemaker membrane is well studied, but much less is known about the effects on neurons. Thyroid hormone decreases the duration of the monophasic action potential and effective refractory period in cardiac pacemakers, predisposing to cardiac arrhythmias (Yu et al. 2009; Childers 2006). One can speculate that an analogous increased excitability in neurons would increase the propensity of central oscillators to cause tremor. In hippocampal and cortical neurons, thyroid hormone up-regulates fast-acting sodium currents and increases the rate of depolarization and the firing rate (Hoffmann and Dietzel 2004). An increase in the rate of depolarization and reduction of the refractory period in central neurons would increase their excitability. An increase in neural excitability of thalamocortical or olivocerebellar circuit could then result in tremor (Shaikh et al. 2008).

2.5.5 *Caffeine-Induced Tremor*

Caffeine stimulates the brain in many ways. At high, nonphysiological concentrations, caffeine mobilizes intracellular calcium, inhibits phosphodiesterases, affecting depolarizing currents including I_h and I_T . These changes would increase membrane excitability of the thalamocortical and olivocerebellar neurons and could cause tremor. At normal doses, caffeine increases cerebral energy metabolism, decreases cerebral blood flow, decreases pH, and activates noradrenaline (Nehlig et al. 1992). An increase in noradrenergic tone and decrease in pH favors an increase in depolarizing currents including I_h and I_T , reducing the membrane threshold, and increasing membrane excitability (Pape and McCormick 1989; Shaikh and Finlayson 2003, 2005).

2.5.6 Tremor Induced by Adrenergic Agonists

Terbutaline, isoproterenol, epinephrine, amphetamines, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, nicotine, and theophylline all increase adrenergic activity. Adrenergic agonists increase I_h and I_T and thus membrane excitability and so could contribute to tremor (Pape and McCormick 1989; Shaikh et al. 2008).

2.6 Membrane Mechanisms in Pathogenesis of Acquired Pendular Nystagmus and Saccadic Oscillations

Acquired pendular nystagmus (APN) is a rhythmic sinusoidal or quasi-sinusoidal oscillation of the eyes often impairing vision because of excessive motion of images on the retina (Leigh and Zee 2006). APN can be considered the tremor of the eyes and in many ways it can be analogous to tremor of the limbs. Two common causes of APN are multiple sclerosis (MS) and the syndrome of oculopalatal tremor (OPT) (Lopez et al. 1996; Deuschl et al. 1994). Saccadic oscillations are another tremor-like disturbance of the eyes in which there are uncalled for back-to-back saccades which also interferes with vision. They can be unidimensional, pure horizontal, or multidimensional affecting all three axes of rotation. Unidimensional saccadic oscillations are called ocular flutter, when multidimensional, they are called opsoclonus (Leigh and Zee 2006). Paraneoplastic syndromes, postinfectious encephalitis, demyelinating disorders, or poisoning commonly causes continuous or transient saccadic oscillations (Shaikh et al. 2008; Leigh and Zee 2006; Ko et al. 2008). Physiologically they are present in newborns; even some healthy subjects have an innate ability to produce saccadic oscillations, which are called voluntary “nystagmus” (Shaikh et al. 2007, 2010; Hoyt 1977). Experimental and computational studies of APN and saccadic oscillations suggest primary disturbances at the levels of neuronal membranes (Das et al. 2000; Shaikh et al. 2007, 2008, 2010, 2011a, b). In subsequent sections we will describe membrane mechanisms contributing to the pathogenesis of APN in MS and OPT.

2.6.1 Membrane Mechanism for APN in MS

The most accepted hypothesis for APN in MS is that the oscillations are generated because of instability in the neural integrator that normally sends premotor commands to hold the eyes steady in a given orbital position (Das et al. 2000). Evidence for the unstable neural integrator hypothesis is that the perturbation of ongoing oscillations by a velocity signal, e.g., a saccade, resets the oscillation phase (Das et al. 2000).

In this section we will first discuss the membrane mechanisms for neural integration and then discuss the possible abnormality, at the level of cell membrane,

causing instability in the neural integrator. A pulse of neuronal discharge generated by the saccadic burst neurons determines the eye velocity; the burst of neural discharge is then converted to steady-state tonic firing in the motor neurons by a neural integrator in the mathematical sense. The persistent tonic firing rate after the saccade is associated with the step-like changes in the inter-spike membrane potential of velocity-position integrator neurons (Aksay et al. 2001). Amplitude of the inter-spike membrane potential and thus neuronal firing rate is directly proportional to the eye position (Aksay et al. 2001). When the membrane is hyperpolarized, brief intracellular pulses (mimicking the saccade) causes step-like change in inter-spike membrane potential (which would potentially translate into steady change in the gaze position) (Aksay et al. 2001). In contrast, when the membrane is depolarized, there is increasing fluctuations in the inter-spike membrane potential. It is proposed that sustained change in the inter-spike membrane potential is due to the persistent synaptic input. There is a mutually excitatory feedback network amongst ipsilateral neurons and mutually inhibitory feedback between ipsi- and contralateral neurons. Mutually inhibitory connections serve to yoke the firing rate and inter-spike membrane potential above (ipsilateral) or below (contralateral) the equilibrium (Aksay et al. 2007). Within the network of neurons serving as neural integrator, the persistence of the firing rate and the similarity of the persistence (i.e., evidence of integration) is also determined by the circuit's functional architecture; physically closer neurons have relatively similar persistence of the firing rate (Miri et al. 2011). Latter underscores the importance of strong network connections (as expected in closely placed neurons) in efficiency of integration (Miri et al. 2011).

These considerations allow us to predict that a constant hyperpolarization of the membrane or disruption of the interconnections would prevent changes in inter-spike membrane potential and subsequently impair the ability of the neural integrator to maintain a steady state change in the firing rate. Indeed injection of the hyperpolarizing agent, muscimol (a selective GABA_A receptor agonist), at the putative site of the neural integrator in monkeys made the integrator unstable, while depolarization (with glutamate) reversed the effects (Arnold and Robinson 1997; Arnold et al. 1999). In the presence of a visual feedback, the unstable neural integrator would then oscillate (Das et al. 2000). It is therefore hypothesized that the severity of the instability of the neural integrator determines the amplitude of APN in MS patients and the membrane depolarization would reduce the amplitude of APN. Indeed, gabapentin and memantine, which indirectly depolarize the cells of the nucleus prepositus hypoglossi, by blocking the alpha-2-delta subunit of calcium channels and antagonizing NMDA receptors at the cerebellar Purkinje neurons, reduces the amplitude of APN in MS (Shaikh et al. 2011a; Thurtell et al. 2010).

2.6.2 Membrane Mechanism for Pathogenesis of APN in OPT

In OPT, hypertrophic degeneration of the inferior olive causes APN due to a breach in the “Guillain-Mollaret triangle” (a circuit from the inferior olive to the deep

cerebellar nuclei and cerebellar cortex, and then projecting from the cerebellum through the superior cerebellar peduncle, passing through the red nucleus and then descending through the central tegmental tract back to the inferior olive) (Guillain and Mollaret 1931). These oscillations are characteristic because they are irregular, smooth, disconjugate, and have random cycle-by-cycle variability in their shape (Shaikh et al. 2010). It has been proposed that hypertrophic degeneration of inferior olive results in development of somatic connexin gap junctions between neighboring inferior olive neurons, physiologically the gap junctions are restricted to the dendrites of the inferior olive (de Zeeuw et al. 1990). As a result, local inferior olive patches begin to fire in synchrony and act as “pacemaker” for *maladaptive* learning by the cerebellar cortex (Hong and Optican 2008; Shaikh et al. 2010). Maladaptive cerebellar learning causes the irregular character of the oscillations in OPT. The hypothesis was pharmacologically tested in patients with OPT who took gabapentin or memantine (Shaikh et al. 2011a; Thurtell et al. 2010). Both gabapentin and memantine reduced the amplitude of OPT and changed the cycle-by-cycle variability (irregularity) in the frequency. Gabapentin and memantine can reduce the excitability of the cerebellar Purkinje neurons, and thus would reduce the amplitude and affect the frequency irregularity of OPT.

2.6.3 *Membrane Mechanisms for Pathogenesis of Saccadic Oscillation*

The Intrinsic membrane properties of saccade generating burst neurons and the reciprocal innervation between the agonist and antagonist burst neurons are cardinal to generate saccadic oscillations (Shaikh et al. 2007; Ramat et al. 2005). The concept is analogous to the thalamic mechanism (involving reciprocally innervating thalamocortical and thalamic reticular neurons with PIR and external inhibition to prevent oscillations) for tremorgenesis. Saccade burst generators, the excitatory burst neurons (EBN), and the inhibitory burst neurons (IBN) reciprocally innervate those on the opposite side, forming an inherently unstable circuit that is prone to oscillate. Physiologically these oscillations are prevented by the inhibitory projections from the omnipause neurons (OPN). The membrane attributes of these neurons are also suitable for PIR (Shaikh et al. 2007). We proposed that instability in the saccadic burst neuron circuit was due to an imbalance between the burst neuron excitability (e.g., increased excitability due to the increase in strength of PIR) and the external inhibition (e.g., disinhibition due to acquired antagonism or congenital hypofunction of inhibitory glycinergic mechanism) which could cause saccadic oscillations (Shaikh et al. 2007, 2008). Simulations of this model showed that the amplitude of I_h or I_T determined the neural excitability, amplitude of PIR, and therefore the frequency and amplitude of saccadic oscillations (Shaikh et al. 2007; Shaikh and Finlayson 2003, 2005; Perez-Reyes 2003). Furthermore, a beta-blocker, propranolol, decreased the amplitude of saccadic oscillations in a patient with the

syndrome of microsaccadic oscillations and limb tremor (Shaikh et al. 2011b). Ethosuximide, a selective antagonist of I_T , reduced the amplitude and increased the frequency of saccadic oscillations during eye closure in two healthy subjects (Shaikh et al. 2011b).

2.7 Summary and Future Directions

Hypothetical disturbances in membrane properties can account for many aspects of the pathophysiology of tremor of the eyes, head, and limbs. Converging evidence for these hypotheses comes from multiple sources including the mechanism of action of drugs used to treat these disorders, animal models, the effects of novel drug compounds on animal models of tremor, links between the genetic mutations in tremor patients and their effects on physiological membrane function, and physiologically realistic computational models of tremor. Further validation of abnormalities of membrane electrophysiology and their links with genetics in various tremor disorders will point to the development of specific and more effective treatments including gene-based therapy of inherited tremors. Recent studies have shown that the principles underlying the mechanisms for tremor of the eyes, head, and limbs have many features in common. For example, a membrane mechanism for saccadic oscillations is analogous to a mechanism based on thalamocortical circuits for the generation of essential tremor. The mechanism for APN in OPT is analogous to olivo-cerebellar mechanism for essential tremor. Studies comparing and contrasting the phenotype, natural history, and kinematics of eye and limb tremor would further enhance understanding of etiology of eyes and limb movement disorders.

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Disorders

Grimaldi, G.; Manto, M. (Eds.)

2013, XVI, 492 p., Hardcover

ISBN: 978-1-4614-4026-0