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A possible role of olivary gap-junctions in the generation of physiological and pathological tremors

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Tremor is a potentially disabling pathology that affects millions of people. The inferior olive (IO) has been implicated in several types of tremor.[1,2] In particular, electrical synapses have been shown to be essential for the generation of oscillatory activity in the IO,[3] which may manifest as tremor. In a recent paper,[4] we described how the electrical coupling of non-oscillating cells can generate oscillatory network behavior. Here we apply this dynamic mechanism to the IO and discuss the possible clinical applications.

Physiological tremor is a normal 8–12 Hz oscillatory movement of the outstretched hands, which occurs during maintained posture and to a lesser extent during movement execution. It can be accentuated by stress or fatigue and the dramatic increase in the tremor amplitude, which follows fear has been known from biblical times*. When the amplitude of the physiological tremor becomes large, eg, as a result of hyperthyroidism or aging, the tremor is defined as 'pathological' and is called enhanced physiological tremor.[2]

Essential tremor bears many similarities to enhanced physiological tremor, but with a larger amplitude and a lower frequency. In contrast to physiological tremor, it can also affect the lower limbs, the head and other body parts. While the neurological literature regarding the diagnostic criteria of essential tremor is equivocal, it is considered to be the most common adult movement disorder and affects 0.4–4% of the population.[1] Of particular importance is the alcohol withdrawal tremor, from which many alcoholics suffer. The 6–10.5 Hz tremor of the hands starts 1–3 days after abstinence, and can last up to a week. Prolonged alcohol abuse can result in chronic tremor disorder.[5] Other kinds of pathological tremors,[1] which have different symptoms, will not be discussed here.

The underlying mechanisms that generate the above tremors are still poorly understood. The interaction of heart beat with the mechanical properties of the limbs, the recruitment and firing rate of the motor neurons and the spinal feedback loops, may all contribute.[1,2] However, there is much evidence linking the tremor with processes that occur in the central nervous system (CNS). For example, it has been known for almost a century that damage to the cerebellum abolishes physiological tremor.[6] Moreover, physiological tremor is also diminished by the removal of visual feedback.[2] Young *et al*[7] have shown that the β-adrenergic receptor blocker, propranolol, suppresses tremor when administered systemically, but has very little effect when administered locally to the trembling limb, suggesting that the tremor originates in the CNS. In addition, thalamotomy and thalamic deep brain stimulation are effective tools for controlling essential tremor.[5]

It is possible that pathologies in different parts of the CNS generate similar phenotypes of tremor. However, the most likely source of the above tremors is the IO, a small brainstem nucleus that projects to the cerebellum. The IO hypothesis postulates that the above tremors emerge from synchronous membrane potential oscillations of neurons in the IO. Evidence from different sources supports this contention. Slice recordings have shown that the membrane potential of IO neurons is often not constant, but oscillates in a subthreshold manner with a frequency of 4–10 Hz. When adjacent pairs of IO cells are recorded simultaneously, synchronous oscillations are usually observed.[8] These synchronous oscillations are manifest in the olivary action potentials, measured as complex spikes in cerebellar Purkinje cells. The firing rate of these spikes is oscillatory in the awake rat[9] (but not in the awake monkey), and the spikes are synchronous between adjacent Purkinje cells. The role of the IO in the generation of tremor is further supported by positron emission tomography (PET) studies, which show an increased olivary glucose utilization and cerebellar blood flow in patients who suffer from essential tremor, which are further increased in the presence of tremor.[1] The similarities between the above tremors and the tremor induced by harmaline provide further evidence to the olivary hypothesis. The administration of harmaline generates an 8–12 Hz physiological-like tremor in a variety of animals. Lesions in the brainstem or the lateral cerebellar system reduce the frequency of this tremor, making it essential-like.[1,10] Mutant and lesion studies have shown that the rhythmic activation of motor neurons, which accompanies harmaline-induced tremor, is correlated with a synchronous oscillatory spiking activity of IO neurons.[10]

How are oscillations generated in the IO? The olivary neurons are connected by an elaborate network of dendro-dendritic gap-junctions. Experimental observations suggest that these cells, in isolation, are not oscillatory and that it is the electrical coupling of the

*'When the people saw the thunder and lightning and heard the trumpet and saw the mountain in smoke, they trembled with fear' Exodus 20, 18.

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neurons which generates the oscillations. The subthreshold oscillations are blocked, *in vitro*, by the gap-junction blocker octanol.[3] The frequency or phase of the oscillations measured in a cell is not altered by changing its membrane potential, but rather by network manipulations, eg, by changing the ionic concentration of the bathing fluid.[8] In addition, developmental studies show that gap-junctions appear in the IO of rats between days 10–15 postnatal. Similarly, olivary subthreshold oscillations appear only during the third week postnatal.[11] Interestingly, harmaline is devoid of tremorogenic activity in young rabbits (1–7 days postnatal),[12] suggesting that the harmaline-induced tremor is dependent on the existence of IO gap-junctions.

The emergence of sustained oscillations in a network where identical non-oscillating cells are coupled seems to be paradoxical. If network oscillations were fully synchronized then there would be no voltage difference between the cells, and thus no current flowing through the electrical coupling and the whole network would behave exactly like the single cell does. Therefore, if the single cell does not oscillate the network will be quiescent. Hence, sustained oscillations in such a network must necessarily involve phase differences between the cells. However, phase differences will be suppressed by the electrical coupling that tends to equalize the membrane potentials of the coupled cells. Thus, one would expect that if single cells have a stable rest state it would be maintained in the presence of electrical coupling. Recently[4] we have shown that this intuition is not always correct, and that electrical coupling can not only synchronize oscillations but also generate in-phase membrane potential oscillations in identical quiescent cells. Our mechanism is based on three assumptions: Firstly, individual cells are described by their membrane potentials and additional 'internal variables', eg the amount of activation and inactivation of ionic channels or the concentrations of different ions and proteins. Secondly, these internal variables have a tendency to oscillate. Thirdly, the interaction of the membrane potential with the internal variables provides a negative feedback that prevents the oscillations of these internal variables and stabilizes the cell. Electrical coupling effectively acts as a shunt conductance and thus diminishes the suppression capacity of the potential, thereby giving rise to membrane potential oscillations. Applying this mechanism to the IO neurons, we suggest that it is the coupling of the non-oscillatory IO cells with gap-junctions that generates membrane potential oscillations in these cells. The existence of these oscillations, their amplitude and their synchrony are controlled by the strength of the electrical coupling, which can be altered by the cerebellar cortex via the inhibitory input that the deep cerebellar nuclei provide on the sites of electrical coupling.[2] The state of the network can also be altered by pharmacology, eg, by harmaline and possibly, as we discuss below, by ethanol. An abnormal state of the electrically coupled network can enhance the oscillatory activity of the IO cells and may generate some of the pathological forms of tremor.

This mechanism may provide us with clues to possible pharmacological solutions to the disabling aspects of tremor. For example, we can try to impair the tendency of internal variables to oscillate. Elsewhere,[4] we have proposed that these internal variables are the cytosolic and internal-stores calcium concentrations. The positive feedback of the calcium-induced calcium release current generates their tendency to oscillate. Alternatively, we can enhance the ability of the membrane potential to dampen the oscillations, possibly by increasing the negative feedback that the voltage-dependent calcium current and calcium-dependent potassium current exert on the calcium concentrations oscillations. In addition, weakening the electrical coupling between the olivary cells could terminate the subthreshold oscillations. Furthermore, even if the oscillations are a property of the isolated cell and not of the electrically coupled network (which is not supported by current experimental data), weakening the electrical coupling may desynchronize the network activity, and thereby may prevent the tremor generating rhythmic activity in the motor system.

The hypothesis that olivary subthresold oscillations play an important role in the generation of tremor is consistent with the profound impact of alcohol on tremor. The consumption of small quantities of ethanol has been shown to effectively reduce physiological tremor.[13] Similarly, essential tremor is significantly improved within 10–15 minutes following ingestion of ethanol. However, no change in the tremor was observed with ethanol administered locally to the forearm.[14] This suggests that alcohol suppresses tremor by acting on the CNS. Indeed, PET studies in essential tremor patients have revealed that the suppression of tremor mediated by alcohol is associated with a decrease in cerebellar blood flow and an increase in the blood flow to the IO nucleus.[15]

The administration of ethanol in an IO slice suppresses the oscillations, and after washout, the oscillations reappear with larger amplitude.[16] While this effect is consistent with the proposed mechanism, there may be several ways by which ethanol exerts its influence. One possibility is that ethanol blocks the gap-junctions and thereby diminishes and perhaps even terminates the olivary oscillations.[17] Another possibility is that ethanol diminishes the tendency of the cytosolic and internal stores calcium concentrations to oscillate by blocking the low threshold calcium current, thereby reducing the cytosolic calcium concentration.[16] Similarly, alcohol withdrawal tremor could result from the rebound effect that is seen in the slice. For example, long-term abuse of alcohol, which blocks the gap-junctions, may induce a strengthening of the electrical coupling in the IO. During the first days of abstinence, the excessive electrical coupling causes exaggerated synchronized membrane potential oscillations, which are manifest as a large amplitude tremor.

More experiments are still needed in order to estab-

lish (or disprove) the role of the proposed mechanism in the generation of olivary oscillations. However, we believe that it is the combination of theoretical modeling with experiments that will lead us to a better understanding of olivary dynamics, and perhaps to novel treatment of the pathological forms of tremor.

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