MODULATION OF PARKINSON'S TREMOR VIA DOPAMINERGIC AND NORADRENERGIC INTERACTION IN THE POSTERIOR VENTROLATERAL THALAMUS

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Abstract

Parkinson's disease is the second most common neurodegenerative disease with a worldwide incidence of 1-2 per 1000, of which 60% of the patients are tremor dominant. Despite parkinsonian tremor being highly burdensome, its pathophysiology remains enigmatic. In vivo neuroimaging studies have sparked new insights into the mechanisms and neurotransmitters underlying Parkinson's tremor. In this mini-review, we discuss the pathophysiology and most recent findings and ultimately present a novel model for Parkinson's tremor. In the past years, the "dimmer-switch" model has been established as the leading model for Parkinson's tremor. In this model, tremor-initiating input from the basal ganglia activates the cerebello-thalamic loop which maintains and dictates tremor amplitude. Evidence indicates distinct roles of dopaminergic and noradrenergic input onto the posterior ventrolateral thalamic nucleus. In particular, studies investigating the effect of cognitive stress have unmasked the stimulating effect of noradrenaline on Parkinson's tremor. Clinical and dopamine neuroimaging studies have not yet managed to fully explain the unpredictable and variable response of tremor to levodopa medication. Interestingly, levodopa medication response appears to be also determined by cognitive stress. Incorporating these recent findings, we suggest that Parkinson's tremor modulation occurs due to a mismatch of dopaminergic and noradrenergic innervation in the posterior ventrolateral thalamic nucleus. Future research combining dopaminergic and noradrenergic neuroimaging is needed to study these thalamic interactions.

Background

Parkinson's disease (PD) is a neurodegenerative disorder characterised by the presence of bradykinesia and rigidity or 4-6 Hz resting tremor. Despite Parkinson's tremor being one of the most burdensome symptoms in PD, its exact mechanism remains unknown [1].

In recent years, large in vivo neuroimaging studies have greatly expanded our knowledge of the pathophysiology of Parkinson's tremor. In particular, functional magnetic resonance imaging (fMRI), dopamine transporter single-photon emission computed tomography (DAT-SPECT), and positron emission tomography (PET) studies have made a vital contribution to this [2-4]. These studies, in combination with neurocognitive experiments, have shed light on the possible role of cognitive stress and noradrenaline, besides dopaminergic dysfunction, in Parkinson's tremor.

In this mini-review, we discuss the current leading model for Parkinson's tremor and the most recent findings concerning the pathophysiology. Ultimately, we present a novel model for Parkinson's tremor that incorporates both noradrenergic and dopaminergic function in the thalamus.

Current model Parkinson's disease

The current leading hypothesis is that the basal ganglia initiate a tremor by activating the cerebello-thalamo-cortical brain circuit that maintains and dictates the tremor amplitude [2, 3, 5]. This hypothesis is based on findings from fMRI studies that demonstrated that activation of the globus pallidus internus (GPi) precedes a tremulous episode. The subsequent activity of the cerebellothalamic circuit correlates strictly with tremor amplitude [2, 3]. However, it is unclear which neurotransmitters are involved in triggering and dictating the tremulous activity, and other brain structures also appear to play a role [6-10]. We believe that the evidence for this model is compelling. In order to make it of more clinical significance, further studies determining the neurotransmitters involved are needed, using PET neuroimaging, for instance.

Dopaminergic function

Dopamine depletion in the substantia nigra and the striatum is considered the pathological hallmark of PD [11]. Whether and how dopaminergic depletion in the basal ganglia relates to Parkinson's tremor is still under debate. While tremor can have a markedly good clinical response to levodopa, even better than bradykinesia and rigidity, the response can also be very mild or absent [12]. Interestingly, the effect of levodopa seems to get reduced by cognitive stress [13]. This enigmatic and unpredictable response to levodopa is underscored by the fact that tremor does not strongly correlate with the degree of nigrostriatal dopamine deficits, while bradykinesia and rigidity do [14]. Thus, the assumption that merely dopaminergic dysfunction would be responsible seems incorrect based on several reasons. First, the severity of tremor correlates poorly with nigrostriatal dopaminergic deficits and clinical response to dopaminergic medication varies greatly between patients and is often even absent [8, 15, 16]. Second, reduced raphe nuclei serotonin transporter availability correlates with tremor severity [17]. However, direct evidence of serotonergic influence on parkinsonian tremor is lacking. Third, activation of the locus coeruleus (LC) (the predominant source of noradrenergic projections in the brain) by an audio-visual task or cognitive stress markedly leads to the onset and worsening of resting tremor [6, 9]. This leads to the idea that other neurotransmitters and cerebral systems are involved in the pathophysiology of Parkinson's tremor.

Noradrenergic involvement in Parkinson's tremor

Multiple studies support that noradrenaline via the LC is involved in the generation and/or modulation of Parkinson's tremor. Post-mortem studies show that in tremor-dominant patients (TD+) the neuronal loss in the LC is limited relative to patients with a non-tremor dominant (TD-) phenotype [18]. Interestingly, noradrenergic terminals are relatively preserved in TD+ PD patients, especially in the thalamus [4, 19]. In line with this, noradrenergic receptor binding is also increased in TD+ patients [20]. While pharmacological suppression of noradrenergic transmission generally leads to a reduction in tremor, intravenous injection of noradrenaline ,in turn, leads to a more intense tremor [21-23]. Nonetheless, proper experiments showing the possibility of noradrenergic medication for reduction of tremor are lacking. There is an abundance of evidence demonstrating that motor symptoms of PD worsen during psychological stress [24, 25]. When patients are asked to perform an arithmetic task (e.g., counting backwards from one hundred in steps of seven) and thereby experiencing cognitive stress, tremor amplitude and severity increase dramatically [6, 26]. More interestingly, the study by *Dirkx et al.* showed that an increase in cognitive stress was associated not only with increased tremor amplitude but also with enlarged pupil diameter and increased heart rate, both of which indicate activation of the LC [6].

Cognitive stress leads not only to a profound exacerbation of the tremor, but also to a reduced effect of levodopa medication [13]. Thus, there seems to be a subtle interaction of noradrenergic and dopaminergic systems causing modulation of parkinsonian tremor.

The posterior ventrolateral thalamic nucleus as a modulatory centre in Parkinson's tremor

The noradrenergic neurons originating from the LC have a profound effect on the activity of almost all the nuclei and cortices of the brain [27, 28]. α1-Adrenoreceptors and β-adrenoreceptors are present on the thalamus, and these are likely to be stimulated by the large noradrenergic projections from the LC [29, 30]. Indeed, the posterior ventrolateral thalamic nucleus pars ventralis (VLpv) is specifically the area through which noradrenergic innervation (by cognitive load, referring to the amount of working memory used when performing a task) appears to influence tremor [6]. Dopaminergic innervation is also abundant in the thalamus [31]. The exact dopaminergic innervation onto the posterior ventrolateral thalamic nucleus (VLp) originates predominantly from the retrorubral area (RRA), and not from the substantia nigra. A small post-mortem study demonstrated increased dopaminergic degeneration in the RRA in TD+ patients, but this finding has not yet been replicated in a larger study in vivo using neuroimaging [32]. Levodopa reduces activity in the VLp and pallidal activity, and is correlated with concurrent tremor activity [33]. Dopamine transporter depletion in nigro-pallidal regions (measured with (DAT-SPECT)) correlates with tremor severity [3]. Transcranial stimulation studies confirm that the thalamus, specifically the VLp, modulates Parkinson's tremor. Namely, stimulation of the thalamus at a frequency similar to the patient's tremor frequency resulted in the tremor adapting to the phase of the electrical stimulation [34].

It has been demonstrated that dopaminergic inhibition of the VLp reduces tremulous activity and that noradrenergic activation of the VLpv amplifies Parkinson's tremor [6, 33]. In the model of Helmich, Parkinson's tremor on- and offset is generated in the globus pallidus internus (GPi) by activating the motor cortex via the anterior ventrolateral thalamic nucleus (VLa), and the cerebello-thalamic circuit is responsible for modulating tremor amplitude. Building on this previous model of PD, we hypothesise that Parkinson's tremor modulation occurs due to a mismatch of dopaminergic and noradrenergic innervation in the VLp, in which noradrenergic hyperactivity may be inadequately inhibited by the impaired dopaminergic innervation, leading to tremor exacerbation (figure 1) [5]. Future research combining dopaminergic (e.g. DAT-SPECT) and noradrenergic (e.g. 11C-MeNER PET) neuroimaging is warranted to test this suggested model of Parkinson's tremor.

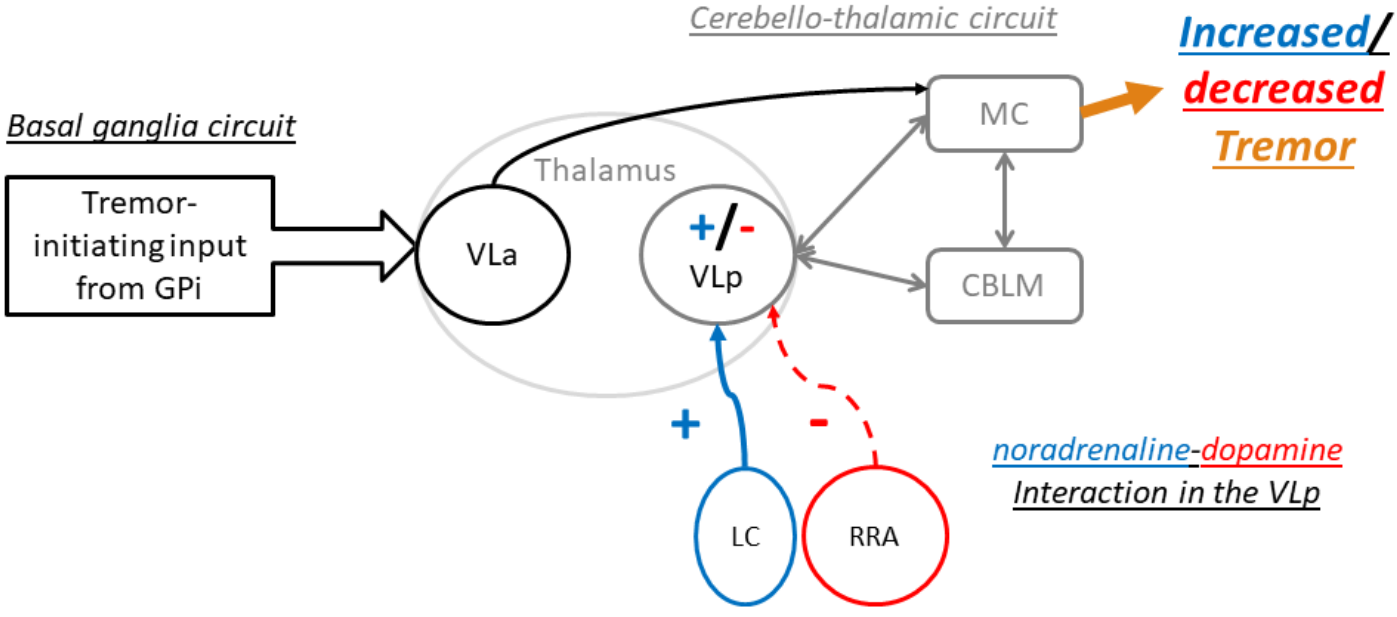

Figure 1: *A hypothetical model of the pathophysiology of Parkinson's tremor. We propose that an interplay of dopaminergic inhibition from the retrorubral area and noradrenergic inhibition from the locus coeruleus can inhibit or activate the posterior ventrolateral nucleus, respectively. Whereby an activation, due to a preserved noradrenergic activation (intact blue line) exceeding degenerated dopaminergic inhibition (dashed red line), will lead to a pro-tremor brain output from the posterior ventrolateral nucleus to the cerebello-thalamic circuit. Abbreviations: cerebellum CBLM,; GPi, globus pallidus internus; LC, locus coeruleus; motor cortex MC; posterior ventrolateral thalamus VLp* ; anterior ventrol*ateral thalamus VLa; retrorubral area RRA.*

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