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Is the loss of thalamostriatal neurons protective in parkinsonism?

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Abstract

Neuronal loss in Parkinson's Disease (PD) is more widespread than originally thought. Among the extrastriatal sites in which significant loss of neurons has been reported in PD is the centremedian-parafascicular (CM-PF) complex of the thalamus, which provides one of the three major afferent sources to the striatum. The functional significance of CM-PF loss in PD is unclear. Interestingly, several recent small trials have suggested that deep brain stimulation of the CM-PF improves motor function in PD. We discuss the possible transsynaptic determination of CM-PF loss secondary to nigrostriatal dopamine degeneration, and suggest that expression of the glycoprotein cerebellin1 (Cbln1) in CM-PF neurons may play an important role in striatal synaptic remodeling in parkinsonism.

Keywords

cerebellin1; dendritic spine; dopamine; medium spiny neuron; Parkinson's Disease; parafascicular nucleus; thalamus

Parkinson's Disease (PD) is a progressive neurological disorder characterized by debilitating motor symptoms and varying degrees of non-motor symptoms. Over the past decade there has been an increasing realization that the symptoms of PD are not restricted to motor dysfunction and that the pathology of PD is not restricted to the nigrostriatal system. It is now clear that there are widespread pathological changes in PD, as revealed by the presence of α -synuclein-positive inclusion bodies and synuclein-positive neurites [1]. While dysfunction of these affected areas offers insights into the pathophysiological underpinnings of non-motor (and motor) symptoms, the presence of Lewy bodies and neurites does not correlate directly with overt cell loss.

One of the extra-striatal regions in which both α -synuclein-positive neurites and inclusion bodies are present is the thalamus. In particular, both synuclein-positive elements and overt cell loss have been reported in the centremedian-parafascicular (CM-PF) complex of the thalamus [2-4]. In particular, Henderson et al. [4] have reported that the numbers of neurons

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Conflicts of interest

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in the CM-PF is decreased by 30-40% in PD, with neighboring nuclei (including the ventral anterior and ventrolateral posterior nuclei) being spared.

The CM-PF is one of three major sources of afferents to the striatum, together with the substantia nigra and cerebral cortex. While the general anatomical organization of the CM-PF complex has been appreciated for some time [5,6], the functional role of the CM-PF neurons and their projections to the striatum is relatively poorly understood. In particular, the role of the CM-PF in Parkinson's Disease is not clear, although there are tantalizing hints from several recent studies. We will discuss the role of CM-PF neurons in regulation of striatal function and conclude with some speculations on a possible paradoxical beneficial role of CM-PF in parkinsonism.

Anatomy of thalamostriatal projection system

Neurons in a number of different thalamic nuclei send projections to the striatal complex. However, the major thalamic projection to the caudate-nucleus and putamen originates in the CM-PF, which provides a topographically organized glutamatergic projection to the striatum [5,6]. In primate species the centromedian preferentially innervates the sensorimotor striatum, while PF projections target the associative sectors of the striatum [7,8].

In contrast to primates, rodents lack a clearly defined CM. The lateral PF of the rat, which innervates the lateral striatum, has been suggested to be homologous to primate CM [5,9]. The medial PF of rodents appears to correspond to the primate PF and project to the medial striatum [9]. In rodents a more anterior group of thalamic nuclei, including the central medial, paracentral, and centrolateral nuclei (which we will collectively designate the CL) also provide striatal projections.

The striatal targets of thalamostriatal neurons include both interneurons and medium spiny neurons (MSNs). Thalamostriatal CM neurons innervate somatostatin- and parvalbumin-positive interneurons as well as cholinergic interneurons [10]. Excitation of cholinergic neurons can be achieved through direct glutamatergic innervation from thalamic afferents, and inhibition can be achieved disynaptically through thalamic activation of medium spiny neurons that send a GABAergic projection onto cholinergic neurons [11].

In the rat both direct pathway (D₁-expressing) and indirect pathway (D₂-expressing) MSNs appear to receive CM-PF inputs [12]. However, in primate species CM-PF axons mainly synapse with direct pathway striatonigral MSNs [10,13]. CM-PF neurons of the rat form synaptic contacts with both MSN dendritic spines and dendritic shafts [14,15], with CL-derived axons primarily synapsing onto dendritic spines [16]. Targets of PF neurons are more heterogeneous, with some PF neurons synapsing exclusively onto the dendritic shaft, others exclusively forming axospinous synapses with MSNs, and still other PF axons targeting both the dendritic shaft and spine [16]. Other minor thalamic afferents to the striatum (including those originating in the midline intralaminar nuclei, mediodorsal nucleus, and anteroventral nucleus) primarily contribute to axospinous synapses with MSNs [16].

Thalamic degeneration and parkinsonism

The extensive loss of CM-PF neurons in PD does not correlate with age of onset of illness, duration of illness, or severity (stage) of parkinsonism [4]. The substantia nigra has long been recognized as sending projections to the CM-PF, although almost exclusively from the pars reticulata. It has recently become apparent that there is a relatively widespread dopaminergic innervation of the thalamus, particularly in primate species [17,18]. However, this dopaminergic innervation is heterogeneous within the primate, with sparse innervation of the CM-PF, and in the rodent only rare axons innervate the PF and CL of the rat [18].

Nonetheless, the possibility that loss of dopamine neurons in the substantia nigra (SN) in PD might result in the transsynaptic result in loss of thalamostriatal cells is intriguing. Aymerich et al. [19] reported that 6-hydroxydopamine (6-OHDA) lesions of the median forebrain bundle led to a loss of PF neurons that are retrogradely-labeled from the striatum. This study did not show loss of neurons, but instead suggested a dysfunction of (tracer accumulation or retrograde transport) in thalamostriatal neurons.

We have searched for a dopamine innervation of the CL and PF in rats using a variety of anatomical approaches. Although anterograde transport after biotinylated dextran amine into the SN resulted in extensive axon labeling in the CL and PF, immunohistochemical studies using dopamine antibodies failed to detect any significant dopamine innervation of the CL complex or PF of the rat. Similarly, dual staining tyrosine hydroxylase (TH) and dopamine- β -hydroxylase (DBH) revealed a relatively extensive noradrenergic innervation of the CL and PF, but very rarely labeled dopaminergic axons in the PF or CL. Moreover, retrograde tracers iontophoretically deposited into the PF or CL resulted in a moderate number of labeled neurons in the SN, primarily of the pars reticulata, but none of these labeled neurons was dopaminergic. It therefore appears that almost all of the anterogradely-labeled fibers in PF and CL seen after intranigral tracer deposits represent a non-dopaminergic innervation originating in the GABAergic cells of the pars reticulata.

In order to determine if SN dopamine lesions result in a multisynaptic dysfunction of cells that ultimately impacts PF neurons, we determined if 6-OHDA lesions of SN nigrostriatal dopamine neurons result in CM-PF cell death. Rats were sacrificed at various intervals between two days and six weeks after the lesion, and tissue was processed to reveal degenerating neurons as revealed by Fluoro-Jade C staining. We saw no evidence of degenerating cell bodies in the thalamus at any of these time points, although very sparse Fluoro-Jade C axonal labeling was observed, presumably reflecting a small degree of non-specific involvement of the SN GABAergic projection to the thalamus.

We also used stereological methods to determine the number of PF neurons after 6-OHDA neurons, which was almost identical to the number seen in control animals, again consistent with the lack of dopaminergic innervation of the CM-PF complex in the rat and lack of transsynaptic degeneration of thalamostriatal neurons in response to nigrostriatal dopamine loss. This observation is consistent with that of Henderson et al. [20].

Dopamine depletion-induced alterations in PF neurons

Although we found no indication of any significant dopamine innervation of the CL or PF in the rat, previous data indicated that lesions of median forebrain bundle (MFB) result in the loss of PF cells retrogradely labeled from the striatum [19]. This may suggest a functional effect of dopamine depletion on thalamostriatal neurons without degeneration. However, given the lack of a dopaminergic innervation of the rodent CL and PF, it was not clear how a lesion of dopaminergic nigrostriatal neurons would impact thalamostriatal neurons.

Injections of 6-OHDA into the MFB can lesion norepinephrine (NE) as well as dopaminergic axons. We therefore compared the effect of intra-nigral injections of 6-OHDA with intra-MFB injections of the toxin, and further examined the consequences of 6-OHDA-induced lesions of dorsal noradrenergic bundle (DNAB), which carries much of the thalamic NE innervation.

The 6-OHDA SN- and MFB-lesioned groups were indistinguishable from the sham-lesioned animals, i.e., there was no decrease in the numbers of retrogradely-labeled PF neurons. Rats subjected to 6-OHDA lesions of the DNAB showed a non-significant trend toward a decrease in the number of retrogradely-labeled PF cells. However, there was no change in the total number of PF neurons, as assessed by stereology. Thus, our data indicate that nigrostriatal

dopamine denervation does not cause a loss in PF neurons nor does it result in a decrease in retrograde labeling of thalamostriatal neurons. Nor does NE denervation of the thalamus appear to compromise retrograde transport in thalamostriatal neurons in any significant manner.

In summary, our anatomical data indicate that lesions of the nigrostriatal dopamine system do not alter the numbers of thalamostriatal neurons, as determined either by stereology (overt loss of neurons) or retrograde transport (a functional disturbance of thalamostriatal neurons). Nor is there any significant dopaminergic innervation of the thalamostriatal neurons. However, these data do not address any functional effect of dopamine denervation on PF or CL physiology.

Yan et al. [21] reported that the firing rate of PF neurons is decreased at three weeks after 6-OHDA SN lesions, but by the fifth week increases. Recently, Parr-Brownlie et al. [22] recorded single unit and field potential activity in the PF of rats subjected to 6-OHDA lesions. They found that dopamine denervation resulted in fewer PF neurons being detected over the first two weeks post-operatively, i.e., that fewer PF cells showed spontaneous activity. However, the firing rates of those spontaneously active PF cells that were detected was unchanged. Moreover, they showed that lesions resulted in an increase in the proportion of PF spike trains at 0.3-2.5 Hz oscillations, but that PF-STN spike oscillations were in phase, leading the authors to conclude that dopamine loss does not directly drive changes in PF-STN oscillatory activity.

One final means of identifying an effect of dopamine depletion on thalamostriatal function is to focus on the striatum, by assessing if the thalamostriatal axons synapse in the normal pattern and frequency in animals with dopamine denervation of the striatum as compared to intact subjects. Raju et al. [23] noted that in MPTP-treated primates the ratio of VGluT2-immunoreactive (–ir) axospinous to axodendritic synapses is increased in MSNs. Thus, the distribution of thalamostriatal synapses, and presumably the functional characteristics of MSNs, will be changed in the dopamine-denervated striatum. The physiological impact of this change in the spatial pattern of thalamostriatal synapses on MSN dendritic integration (and hence MSN activity) is not yet known.

A non-glutamatergic regulation of MSNs by thalamostriatal neurons

An obvious means to study the functional impact of the loss of thalamostriatal neurons on the intact or dopamine-denervated striatum is to simply examine the consequences of lesions of the thalamic nuclei that innervate the striatum. Unfortunately, the shape and size of the CL and PF in the rat make it exceedingly difficult to lesion these thalamic nuclei without significantly damaging other thalamic (e.g., mediodorsal nucleus) and epithalamic (the habenula) nuclei. Because these nuclei directly influence cortical and midbrain dopamine inputs to the striatum it is difficult to untangle the relative contributions of direct thalamostriatal influences on the striatum and indirect cortico- and nigro-striatal effects in animals with striatal dopamine depletion.

We reasoned that we might be able to circumvent such problems by identifying a protein or proteins expressed by thalamostriatal neurons but not by adjacent thalamic nuclei, and using this information to generate transgenic animals with molecular lesions of the thalamostriatal neurons.

Murray et al. [24] examined the expression profile of the primate thalamus to identify mRNAs unique to the thalamus or to specific thalamic nuclei. They identified a number of transcripts enriched in the thalamus. Among these was a mRNA encoding for cerebellin1 (*cbn1*), a protein involved in synaptic development and maintenance [25,26], the expression of which was abundant but essentially restricted to the CM-PF. In rodents the *cbn1* transcript is expressed only in the PF but not in CL neurons [27].

Cbln1 is a glycoprotein that is the prototype of a subfamily (Cbln1-4) of the C1q/TNF α superfamily of proteins [28,29]. Hitherto studied exclusively in the cerebellum, where granule cells express and secrete Cbln1, the protein is thought to bind to an as yet unidentified receptor on Purkinje cell dendrites [30]. In mice lacking *cbln1*, the number of granule cell-Purkinje cell synapses is reduced, and many of the Purkinje cell dendritic spines lack presynaptic partners [25]. Cbln1 is heterogeneously expressed in the CNS of rodents [27,30], including moderate expression levels in the PF. Because Cbln1 is critical for synaptic development and maintenance, we examined Cbln1 in thalamostriatal neurons, hypothesizing that Cbln1 regulates PF synapses onto striatal MSNs.

Cbln1 in thalamostriatal neurons

Using an antibody that recognizes Cbln1 but not other members of the *cbln* family, we found that all Cbln1-ir cells in the PF expressed neuronal but not glial markers [31]. We then deposited the retrograde tracer FluoroGold (FG) into the striatum, and observed that all retrogradely-labeled PF cells were also immunoreactive for Cbln1. In contrast, retrogradely-labeled cells in the CL did not express Cbln1-ir. Cbln1-ir PF cells could also be retrogradely-labeled from the cortex, consistent with the known projections of the PF to the striatum and somatomotor cortex.

Striatal neurons do not contain *cbln1* mRNA [27], and we did not observe any striatal cells that at the light microscopic level expressed Cbln1. We did, however, see clusters of axons scattered in the dendritic trees of MSNs, consistent with a Cbln1 projection from the PF to the striatum. We found that in MSNs that were intracellularly filled with Lucifer Yellow and then processed to reveal Cbln1-ir, the Cbln1-ir puncta were in close apposition to both MSN dendritic spines and dendritic shafts [31]. Ultrastructural examination confirmed these light microscopic impressions [31], revealing the presence of axospinous Cbln1-ir synapses as well as some axodendritic synapses.

We next assessed MSN dendritic morphology in *cbln1* knockout ($-/-$) mice. We and others have shown that striatal dopamine depletion in animals results in a substantial loss of MSN dendritic spines [32-35]. Golgi staining revealed a significant 22% increase in MSN spine density of *cbln1* knockout relative to wildtype littermate mice [31]; no significant change in dendritic length or spine type was noted. Because in the cerebellum of the *cbln1* $^{-/-}$ mouse the density of synapses is decreased and there is an increase in the number of naked spines (those spines lacking presynaptic partners), we examined the spines of MSN dendrites at the electron microscopic level. In contrast to the picture in the cerebellum, the increased density of MSN spines in the *cbln1* knockout was not due to an increase in naked spines: we observed a 21.7% increase in the density of axospinous synapses, thus effectively showing that the loss of *cbln1* has opposite effects in cerebellum and striatum [31].

We were curious to see if the increase in MSN spine density seen in the *cbln1* mutant was also seen after genetic deletion of other members of the *cbln* family. In contrast to the increase in MSN spine density and axospinous synapses seen in the *cbln1* $^{-/-}$ mouse, no changes in the structure of MSN dendrites, including spine number, were seen in *cbln2* or *cbln4* knockout mice; we did not examine the *cbln3* $^{-/-}$ mouse because *cbln3* is not expressed in the PF.

Finally, we assessed if the increase in spine density and synapses seen in the *cbln1* $^{-/-}$ mouse were accompanied by changes in the numbers of PF neurons or striatal levels of the vesicular glutamate transporter 2 (VGluT2), marker of thalamostriatal projections [36]. Stereological assessment of the PF uncovered no difference across *cbln1* genotypes in PF cell number, and immunoblot studies found no change in VGluT2 levels [31]. These observations suggest that the increase in spine density and axospinous synapses in the *cbln1* $^{-/-}$ mouse is not attributable to a greater number of PF neurons innervating the striatum, and that *cbln1* deletion does not compromise the glutamatergic phenotype of PF thalamostriatal neurons.

Is CM-PF degeneration a compensatory process in PD?

Although it has long been recognized that neurons in the vicinity of the PF respond to pain, temporally tuned CM-PF neurons respond to multiple type of sensory stimuli [37,38]. The CM-PF neurons have been suggested to participate in attentional processes [38] and appear to respond to differences in reward expectation and the actual reward delivered [39]. As such, CM-PF neurons are thought to play a key role in integrating behaviorally salient information to appropriately guide motor output [37,40].

There are relatively few data on the effects of lesions of the CM-PF neuron. Lesions of the PF reduce striatal GAD₆₇ mRNA levels, and reverse the increase in GAD₆₇ seen in the dopamine-denervated striatum [41,42]. In particular, the effects of PF lesions appear to target indirect pathway (enkephalin-containing) neurons. Thus, PF lesions partially reverse the increase in striatal preproenkephalin mRNA levels seen in the dopamine-denervated striatum, but have minimal effects on direct pathway neurons, as reflected by changes in preprotachykinin levels [42,43].

In rodents with nigrostriatal dopamine depletion, deep brain stimulation (DBS) of the PF has been reported to attenuate motor impairment [44]. While the mechanism of deep brain stimulation remains unclear, most scenarios suggest a locus of inhibition in the target area caused by the high frequency stimulation, i.e., suggest the presence of a functional “lesion”. Several recent small clinical trials of CM-PF DBS in idiopathic PD have also reported a decrease in motor symptoms, particularly tremor, and a decrease in levodopa-induced dyskinesias [45-48]. Taken together, these data suggest that disruption of thalamostriatal neurons may attenuate or reverse motor dysfunction in the dopamine-denervated striatum.

Thalamostriatal neurons are glutamatergic but also express Cbln1. It is not clear if the putative beneficial effects of disruption of thalamostriatal signaling on striatally-dependent motor function are related to changes in glutamate dynamics, Cbln1 release, changes in both glutamate and Cbln1 release, or some other process. The observation that genetic deletion of Cbln1, which does not appear to alter the glutamatergic innervation of the striatum, but increases dendritic spines in the *cbln1* knockout mouse, tentatively suggest that Cbln1 is an important player in alleviating motor dysfunction secondary to striatal dopamine depletion.

Loss of striatal afferents as a protective mechanism in parkinsonism

The CM-PF suffers a major loss of neurons in PD. It is not clear when this neuronal loss begins, particularly because the loss is comparable across individuals with less and more severe illness, as reflected by Hoehn and Yahr scores (4). This raises the possibility that the loss of CM-PF neurons can antedate the emergence of motor symptoms sufficient for diagnosis of PD.

The CM-PF is thought to play a key role in guiding of motor behavior through sensory processes, and as such may offer a means through which external cues can improve the deficits in initiation of movements in PD. Moreover, the PF and ventrally contiguous sub-parafascicular nucleus have long been known to be key thalamic relays for pain and lesions of the PF have been used to treat intractable pain [49]. It is therefore difficult to reconcile loss of PF neurons with the fact that pain is one of the most frequent non-motor presentations of PD [50], or how loss of PF neurons in PD might improve motor function. We have no answer to this puzzle. However, the observation that loss of Cbln1 in PF neurons leads to increases in dendritic spines, where dopamine receptors reside, offers one potential mechanism. Consistent with this suggestion is the observation that lesions of the PF in the rat result in an increase in the density of striatal D2 receptors at 70 days post-lesion [51].

Continued work will be required to elucidate the roles of the CM-PF in Parkinson's Disease. There has been a surge in interest in the thalamostriatal systems and motor function over the past decade, and it has been 25 years since *cbln1* was first described [52]. We can only hope that more rapid progress will occur over the next few years and lead to new therapeutic modalities for PD and related disorders.

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