Review

The search for a role of the caudal intralaminar nuclei in the pathophysiology of Parkinson’s disease

José L. Lanciego, Iciar P. López, Alberto J. Rico, María S. Aymerich, Mónica Pérez-Manso, Lorena Conte, Carolina Combarro, Elvira Roda, Carmen Molina, Nancy Gonzalo, María Castle, Teresa Túnón, Elena Erro, Pedro Barroso-Chinea

Area de Neurociencias, Centro de Investigación Médica Aplicada (CIMA) y Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Facultad de Medicina, Universidad de Navarra, Spain

Servicio de Anatomía Patológica, Centro de Investigación Biomédica, Hospital de Navarra, Servicio Navarro de Salud, Spain

Servicio de Neurología, Centro de Investigación Biomédica, Hospital de Navarra, Servicio Navarro de Salud, Spain

Abstract

The situation of the caudal intralaminar thalamic nuclei within basal ganglia circuits has gained increased attention over the past few years. Although initially considered as a “non-specific” thalamic nuclei, tract-tracing studies carried out over the past two decades have demonstrated that the centromedian–parafascicular thalamic complex (CM–Pf) is connected to virtually all basal ganglia components and related nuclei. Although the anatomical basis sustaining the thalamic modulation of basal ganglia circuits has long been characterized, the functional significance of these transverse circuits still remain to be properly accommodated within the basal ganglia model, both under normal conditions as well as in situations of dopaminergic depletion. However, the recent demonstration of primary (e.g., non-dopamine related) neurodegenerative phenomena restricted to the CM–Pf in Parkinson’s disease (PD) has renewed interest in the role played by the caudal intralaminar nuclei in the pathophysiology of PD. Concomitantly, evidence has become available of increased metabolic activity in the caudal intralaminar nuclei in rodent models of PD. Finally, CM–Pf neurosurgery in patients suffering from PD has produced contrasting outcomes, indicating that a consensus is still to be reached regarding the potential usefulness of targeting the caudal intralaminar nuclei to treat movement disorders of basal ganglia origin.

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1. Brain circuits linking the caudal intralaminar nuclei with basal ganglia structures: thalamostriatal and thalamousubthalamic projections

1.1. Thalamostriatal pathway

Research on the thalamostriatal system began in the 40s–50s with the pioneering studies of Vogt and Vogt [83] and Powell and Cowan [62]. Since then, a number of studies have attempted to characterize the thalamostriatal system. Although many of the key issues have now been addressed from an anatomical point of view, very little is currently known about the functional role of the thalamostriatal pathway within the basal ganglia system.

At present, the thalamostriatal pathway is recognized as a major source of excitatory afferents to the striatum [61,58,67–69,72,26,19,20,70,22,23,66,35,80,74,2]. At the striatal level, virtually all the resident neurons are approached by glutamatergic terminals from thalamic sources, both the projection neurons [35,74,21,71,15,48,4] as well as all the major subtypes of striatal interneurons [66,71,55,50,51,16,17]. When we consider the medium spiny striatal neurons (MSN), there is a marked segregation of the postsynaptic elements approached by either corticostriatal or thalamostriatal afferents. Glutamatergic terminals coming from cortical sources make asymmetrical synapses with dendritic spines of MSNs, whereas thalamic projections to the striatum preferentially reach the dendritic shafts of MSNs [68,74,71,72]. Such a sharp segregation has been challenged by recent data showing that when originating from thalamic nuclei other than the centromedian–parafascicular complex (CM–Pf), thalamostriatal afferents also target dendritic spines. Therefore, only the dendritic shafts are exclusively approached by afferents that originate at the level of CM–Pf [64].

Although it is well known that any given cortical or thalamic afferent reaching the striatum is glutamatergic in nature, these two pathways are characterized by the presence of a different vesicular transporter for glutamate trafficking. In this regard, antibodies against isoforms 1 and 2 of the vesicular glutamate transporter (VGLUT1 and VGLUT2) have commonly been used as putative markers for striatal glutamatergic terminals from cortical or thalamic sources, respectively [64,45,32,33,63]. By combining in situ hybridization with retrograde tract-tracing, we have demonstrated that VGLUT2 is the only vesicular glutamate transporter used by thalamostriatal-projecting neurons located in the midline and intralaminar nuclei [5]. However, it must be born in mind that VGLUT1 mRNA expression has been found within thalamic locations other than the midline and intralaminar nuclei [42,28,29,30,79,6], locations that mainly include the principal thalamic relay and association nuclei. Since these nuclei are also substantial contributors to the thalamostriatal system [7,8,73,10,54,24,25,78], it might also be worth addressing whether VGLUT1 (with or without the additional involvement of VGLUT2) is engaged in glutamatergic transmission within the thalamostriatal system. Recent data from our group have demonstrated that both VGLUT mRNAs may be co-expressed within a single thalamostriatal-projecting neuron when located within thalamic territories other than the midline and intralaminar nuclei [5]. Indeed, at the subcellular level, the mRNA clusters related to either VGLUT1 or VGLUT2 transcripts appear to be largely complementary. However, when these two VGLUTs co-localize it notable that the expression of VGLUT2 mRNA is by far the most abundant transcript and therefore, the moderate expression of VGLUT1 mRNA might not be translated into sufficient VGLUT1 protein to be detected by immunocytochemistry.

In summary, the thalamostriatal pathway is currently seen as a dual system, involving preponderant VGLUT2-expressing projections that arise from the midline and intralaminar nuclei, together with another substantial population of projections that originate from the ventral and associative relay nuclei containing both VGLUTs.

1.2. Thalamousubthalamic pathway

The subthalamic nucleus (STN) receives substantial innervation from the caudal intralaminar nuclei. Thalamousubthalamic projections are preserved across species and have been demonstrated in rats, cats and primates [68,70,15,48,75,76,65,52]. Besides corticousubthalamic projections, these thalamic axons are one of the main sources of excitatory glutamatergic inputs to the STN [56,57]. There are several interesting features that characterize the thalamousubthalamic pathway. Firstly, thalamic axons reaching the STN are topographically organized. As such, the lateral territories of the STN (motor-related) are preferentially innervated by afferents originating from lateral areas of the CM–Pf, whereas neurons located in the medial CM–Pf regions target medial territories (limbic and associative-related) of the STN [69,48]. Secondly, although thalamostriatal and thalamousubthalamic projections mainly arise from different neuronal populations within CM–Pf [26], it is also worth noting that a subpopulation of CM–Pf neurons innervating both the striatum and the STN through axon collaterals has been reported elsewhere [20]. Thirdly, any type of STN efferent neuron is a postsynaptic target for thalamousubthalamic afferents, irrespective of whether they project to the external pallidum (GPe) or to the substantia nigra reticulata (SNr) [15]. Finally, and most importantly, thalamousubthalamic projections are bilateral, i.e.: the activity of one STN is modulated by strong ipsilateral thalamic innervation together with weaker inputs from the contralateral CM–Pf [15]. Indeed, contrasting changes in the electrical activity recorded in the ipsi- and contralateral STNs have been documented after drug-induced stimulation or inhibition of the CM–Pf in rodents [57].

2. Increased metabolic activity of the caudal intralaminar nuclei after dopaminergic removal

The current model of basal ganglia function explains the increased activity in the STN as the result of reduced GABA outflow received from a hypoactive GPe nucleus [17,18]. During the past few years, experimental evidence has challenged the current dogma of decreased GPe activity under circumstances of dopaminergic depletion (Fig. 1). The basal ganglia model predicts that the increased STN activity is the ultimate result of decreased levels of GABA received from a hypoactive GPe, the latter being the consequence of reduced levels of dopamine reaching D2-containing striatopallidal-projecting neurons. However data available in the literature have demonstrated that the STN increased activity apparently is an early phenomenon among the events that take place in the basal ganglia after dopamine depletion [82,59]. Furthermore, increased expression of subunit I of cytochrome oxidase (CO-I) was found in the GPe in different animal models of Parkinson's disease [81]. When thinking of candidates other than the GPe to sustain the increased activity of the STN, both the CM–Pf as well as the pedunculopontine nucleus (PPN) emerge as attractive choices. In this regard, recent studies carried out in rats with unilateral dopaminergic depletion have shown that both PFF and PPN neurons innervating the STN display a remarkable increase in their metabolic activity [60,43]. Subsequently, it was demonstrated that a lesion of the PF in intact rats has a strong impact on the activity of almost all the major basal ganglia nuclei, in keeping with the removal of direct glutamatergic innervation [3]. Indeed, similar PF lesions carried out...
in dopamine-depleted rats resulted in a normalization of the activity that typically accounts for both the STN and the basal ganglia output nuclei after dopaminergic removal [4]. When considering the thalamostriatal pathway, our group recently demonstrated a marked up-regulation in both CO-I and VGLUT2 gene expression within thalamostriatal-projecting neurons under circumstances of unilateral dopaminergic depletion [2]. In summary, there is growing evidence that thalamic projections reaching both the striatum and the STN are hyperactive after nigrostriatal damage. Overall, the glutamatergic overflow coming from the CM–Pf and reaching the key basal ganglia structures has paved the way to consider the CM–Pf as a potential therapeutic target for the surgical treatment of movement disorders of basal ganglia origin, as will be discussed later on in this review.

3. Ongoing neurodegeneration of the caudal intralaminar nuclei under conditions of dopamine depletion

Pioneer work by Henderson et al. has recently demonstrated that neurodegeneration in Parkinson's disease may be restricted to the CM–Pf without involving any other neighboring thalamic nuclei [38,39]. This is the first evidence of degenerative phenomena outside the dopaminergic system in post mortem brains from patients suffering from Parkinson's disease, although equivalent degenerative changes have been found in rodent models of Parkinson's disease [2,31,34]. Such primary, non-dopaminergic degeneration is apparently restricted to thalamostriatal-projecting neurons [2], whereas thalamic neurons innervating the STN do not seem to degenerate as a result of dopaminergic removal [60]. Furthermore, CM–Pf degeneration cannot be considered as an end-stage phenomenon, since it is already evident in early stages of Parkinson’s disease and it persists, displaying no noticeable changes, until Hoehn and Yahr’s stage 5. Indeed, behavioral studies suggested that thalamic degeneration is not a late event provoked by dopaminergic loss [41]. In summary, thalamic and nigral degeneration are probably concurrent yet apparently unrelated phenomena. Indeed, it has already been suggested that CM–Pf degeneration might be the result of an age-related process, since thalamic nerve cell loss has also been found in neurodegenerative disorders where there is no dopaminergic etiology such as Alzheimer’s disease [85]. It is likely that this is also the case when considering progressive supranuclear palsy and Huntington’s disease [39,37,46].

4. Are the caudal intralaminar nuclei a potential surgical target for the treatment of basal ganglia disorders?

There is a clear consensus that the STN can be considered as the most effective target for deep brain stimulation (DBS) to try and ameliorate the key motor symptoms characteristic in Parkinson's disease [36]. Although the ultimate mechanism of action of STN-DBS is still a matter of debate, high-frequency stimulation apparently normalizes the increased metabolic status of the STN under circumstances of dopaminergic depletion. A question that remains to be resolved is the origin of the increase in STN activity itself. The basal ganglia model explains STN overactivity as the net consequence of reduced GABA levels coming from the hypoactive GPe nucleus [17,1,18]. However, experimental evidence from animal models with dopaminergic lesions has challenged this line of reasoning [82,59,81,11]. As such, the caudal intralaminar nuclei have recently emerged as attractive candidates to sustain the increased STN activity. On the one hand, Pf neurons giving rise to thalamo-subthalamic projections are hyperactive in rodents with unilateral dopaminergic depletion [60,43], augmenting the glutamate outflow reaching the STN. On the other hand, the chemical ablation of the Pf in rodents has a direct effect on the STN, normalizing the hyperactivity typically observed after unilateral nigrostriatal damage [4]. Such promising results from animal models of PD have paved the way to reconsider the caudal intralaminar nuclei as potential surgical targets for PD, in order to minimize the increased glutamate reaching the STN from thalamic origins. However, as a part of our ongoing research with primates, we have shown that kainate-induced lesions within restricted CM boundaries failed to improve the motor syndrome induced by the neurotoxin MPTP. Indeed, only a mild, transitory effect that lasts no more than 3 weeks post-surgery has been noticed in the “off” period, without any significant impact on levodopa-induced dyskinesias [49]. The different outcomes from approaches directed towards the CM–Pf in animal models of PD have also been replicated when comparing the pioneering clinical studies carried out to date in PD patients. During the past two decades, several groups have reported posi-
tive results by placing DBS electrodes within CM–Pf territories. For instance, the best relief in terms of motor benefit was obtained in a series of French patients when the DBS electrode was placed nearer to the CM–Pf than the ventral intermediodorsal thalamic nucleus [12–14]. Indeed, similar approaches (DBS in the CM–Pf) produced marked alleviation of resting tremor and levodopa-induced dyskinesias [47,84]. More recently, positive results have been reported by approaching the CM–Pf in combination with GPI targeting, not only in PD patients [53] but also in severe forms of Tourette’s syndrome [44]. Finally, it is also worth noting that these positive effects following DBS in the CM–Pf have been challenged in another study showing a marked worsening in bradykinesia and rigidity in one patient treated in a similar manner [40].

5. Concluding remarks

There is growing experimental evidence that clearly demonstrates an increase in the metabolic activity of CM–Pf neurons innervating the striatum and the STN. When considering animal models of PD and for some reasons that remain to be elucidated, dopaminergic depletion either directly or indirectly induces degenerative phenomena within thalamostriatal-projecting neurons without affecting the number of thalamostriatal-thalamic-projecting neurons. However, this is not the case when dealing with patients suffering from PD, in whom nigrostriatal and thamic CM–Pf degeneration are two apparently unrelated issues. At present, we consider that neurodegeneration of the thalamostriatal system together with increased activity of PF neurons innervating the striatum probably reflect self-compensatory mechanisms. Indeed, surviving PF projection neurons might increase their activity in an attempt to maintain the amount of glutamate reaching the striatum from thalamic sources within normal levels.

Bearing this in mind, the main debate is now focused on whether a brain nucleus such as the CM–Pf, which displays ongoing neurodegenerative changes, might be considered as a useful candidate for DBS surgery, irrespective of the increases in the metabolic activity of the CM–Pf under circumstances of dopaminergic depletion. Several contributions to this Special Issue of Brain Research Bulletin provide further background on this particular issue, which we hope will help readers to reach their own conclusions regarding such an interesting topic.

Acknowledgements

Supported by grants from Ministerio de Educación y Ciencia Ref: BFI2006-06744, Fondo de Investigaciones Sanitarias Ref: P050137, Fundación de Investigación Médica Mutua Madrileña, CIBERNED Ref: CB06/05/006 and by the Proyecto UTE/Fundación de investigación Médica Aplicada (F.I.M.A.).

References