Striatal Information Signaling and Integration in Globus Pallidus: Timing Matters

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Key Words

Gamma-aminobutyric acid · Basal ganglia · Caudate putamen · Dendrites · Local collaterals · Parkinson's disease · Pauses, globus pallidus neuron activity · Synaptology · Synchrony, globus pallidus neuron discharges

Abstract

Advances in research on globus pallidus (GP) suggest that this 'long thought to be' relay in the 'indirect pathway' plays a unique and critical role in basal ganglia function. The traditional idea of parallel processing within the basal ganglia is also challenged by recent findings. It is now clear that axons of GP neurons form large, perisomatic baskets around target neurons in all major basal ganglia nuclei, thereby exerting a profound influence on the output of the entire basal ganglia. GP neurons are autonomously active both in vivo and in vitro. It is believed that temporal information carried along the corticostriatopallidal pathway is critical for proper motor execution. The importance of appropriately controlled discharge of GP neurons is highlighted by psychomotor disorders such as Parkinson's disease, in which alterations in the pattern and synchrony of discharge in GP

neurons are thought to contribute to motor symptoms. Several lines of evidence suggest that the aberrant activity of GP neurons following dopamine depletion is caused by alteration in the synaptic input from both striatum and subthalamic nucleus. In normal subjects, the capability of striatal input in translating cortical input into precisely timed responses in GP neurons is mediated by (1) the expression of postsynaptic GABA_A receptor composed of subunits with fast kinetic properties; (2) an effective GABA reuptake system in terminating the action of synaptically released GABA, and (3) the existence of dendritic HCN channels that actively abbreviate the time course of the inhibitory postsynaptic potentials and reset rhythmic discharge. Despite the rapid pace in uncovering the elements that shape the activity along the striatopallidosubthalamic pathway, the origin of rhythmic, synchronized bursting of GP neurons seen in parkinsonism has not been fully established experimentally. Further elucidation of the factors that control the information transfer in the striatopallidal synapses is thus critical to our understanding of basal ganglia function and establishing treatment for Parkinson's disease and other basal ganglia disorders.

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Introduction

Over the past few years, there have been several reviews that have summarized advances in various aspects of basal ganglia research. Most of these reviews have focused on midbrain dopaminergic neurons – which degenerate in Parkinson's disease (PD) – or their principal target: the striatum. These reviews have not provided an overview of recent studies suggesting that the globus pallidus (GP) plays a unique role in basal ganglia function. In particular, studies that examined the striatopallidal synapse have suggested that this synapse conveys temporal information necessary for proper motor execution. There also is compelling evidence suggesting that dysfunction of the GP constitutes a central origin of psychomotor disorders, including PD, where there is an alteration in pattern and synchrony of discharge of GP neurons. This review will summarize our current understanding of the GP, focusing on GABAergic signaling mechanisms and their relationship in basal ganglia dysfunction.

The GP Is a Critical Player in the Basal Ganglia

The rodent GP – and its primate equivalent, the external segment of the GP (GPe) – has traditionally been viewed as a mere 'relay' in the 'indirect pathway' [1–4]. However, recent anatomical and electrophysiological studies have shown that the GP is richly interconnected with all other major elements in the basal ganglia macrocircuit [5–13]. GP neurons form large, perisomatic baskets around their target neurons, much like those formed by the 'basket cells' in cortex, hippocampus, and cerebellum [12, 14–17]. Unlike interneurons, which only innervate the local, principal neurons, the axon of a single GP neuron can travel for a very long distance, innervating neurochemically and functionally diverse neuronal types [10, 12, 13, 18, 19]. This broad range of connectivity as well as the perisomatic targeting of their synapses suggest that the GP neuron activity can exert a profound influence on global basal ganglia function.

Cell Types and Synaptic Inputs in the GP

Morphological and electrophysiological studies performed in rodents and primates are in agreement that there is one predominant cell type within the GP [11,

20–25]. These GP neurons express GAD67 and parvalbumin, have discoidally arborizing dendrites, and project an axon to the subthalamic nucleus (STN) [7–9, 18, 26–29]. This population of GP neurons is intermixed with ENK-expressing GABAergic neurons that predominantly project back to the striatum [7, 28–30]. The observed heterogeneity of cellular makeup within the confine of the GP in part is due to a displaced population of basal forebrain cholinergic neurons near the medioventral portion of the GP [27, 31–33]. However, there is no evidence that the properties of GP neurons are discrete, nor is there a definitive correlation between electrophysiological properties and morphological and molecular features of GP neurons. There are suggestions that the properties of GP neurons are overlapping and highly depend on threshold and sensitivity of the assays.

The principal excitatory input to the GP arises from the STN, but it accounts for less than 10% of synapses impinging onto GP neurons. This excitatory input mediates transmission via synaptically localized AMPA and NMDA ionotropic receptors positioned on the long dendrites of GP neurons (up to 1 mm in rodents and 1.6 mm in macaques) [34].

In contrast, the majority (~80–90%) of the synaptic input to GP neurons is derived from the dorsal striatum. Approximately two thirds of these arise from enkephalinergic, dopamine D₂ receptor expressing medium spiny neurons. The remainder originates from collaterals of striatonigral (substance P and dopamine D₁ receptor expressing) neurons [35–37]. This rich GABAergic input primarily targets the dendrites of GP neurons, as first suggested by Golgi staining and immunohistochemistry that showed the 'woolly' fiber structures of pallidal dendrites enmeshed by a plexus of thin, enkephalin- or substance-P-positive putative striatal axons [19, 38–46]. Ultrastructural studies further revealed that dendrites of GP neurons are fully covered by a mosaic of symmetrical synapses. These findings are consistent with the notion that the striatopallidal afferents have a feature that is homologous to that formed between climbing fiber and cerebellar Purkinje neurons [14, 47–49]. Single-axon labeling studies [26, 36, 40, 50] demonstrated that the striatal axon ramifies into branches that ensheath dendrites of pallidal neurons – a morphology characteristic resembling 'woolly' fiber. However, these studies also showed that a single striatal axon only forms a relatively small number (100–250 in both rats and macaques) and a low density (10/100 μm^2 in macaques) of synapses within the confine of GP. In fact, single striatal axons form only a few synapses on individual dendrites of GP neurons. In-

stead, they often contact several pallidal dendrites successively [26, 36, 50–52].

The striatal input to GP is highly convergent. In the rat, there are roughly 3 million striatal neurons, but only 46,000 GP neurons [53]. Assuming all of the neurons in the striatum are pallidal projecting, individual GP neurons should receive input from about 60 medium spiny neurons. The dendritic arbor of GP neurons (with a receptive surface estimated to be $\sim 30,000 \mu\text{m}^2$ in macaques) is oriented perpendicularly to the incoming, radial striatal fibers, creating an ideal anatomical arrangement for intercepting axons from broad striatal regions [13, 26, 36, 40, 54, 55].

In addition to the striatal input, intrapallidal collaterals account for another major source of GABAergic input onto GP neurons. Juxtacellular labeling or intracellular dye loading of GP neurons has revealed the presence of numerous varicosities of various sizes within the dendritic field of parent neurons. Nearly all principal GP neurons have local axon collaterals that terminate on somata and proximal dendrites of their neighboring neurons [8, 11–13, 23, 56]. However, very little is known about the properties of this connection.

GP Activity Patterns

In awake animals, GP neurons maintain a high rate of ambient spiking [22, 57–62]. This tonic ‘background’ activity was originally thought to be dependent upon excitatory synaptic input arising from the STN [2, 63]. However, it is now recognized that neurons within the GP are autonomously active [20, 21, 27, 64, 65]. Thus, discharge rate and pattern seen in vivo likely reflect the interaction between intrinsic and extrinsic synaptic influences [24, 66–68].

Recordings from primate GPe suggest that a phasic neuronal activity is important for generating movement sequences. Transient pauses in GP activity are thought to terminate sustained neuronal activity in the supplementary motor area and to allow the next movement in the sequence to be executed [69]. These pauses or reductions in the activity of GP neurons are likely to be evoked by a striatal or perhaps intrapallidal GABAergic input. Electrical stimulation of various cortical areas (prefrontal, premotor, supplementary motor, and arcuate premotor areas and motor cortex) and striatum inhibits spontaneous discharge of pallidal neurons [60, 61] – an effect that is blocked by local infusion of a GABA_A receptor antagonist into the GP [66, 70]. In addition, electrical

stimulation of the striatum produces cortical and behavioral responses identical to those achieved by direct stimulation of the GPe alone [71]. These observations are supplemented by in vitro studies, showing that pauses in the activity of GP neurons can be produced by a GABAergic synaptic input arising from the striatum [11, 20, 56, 64, 66, 72].

Sculpting GABAergic Signaling at the Striatopallidal Synapse

If the timing of striatally induced pauses in GP activity is critical to movement, then the GABAergic striatopallidal synapse must be capable of faithfully translating striatal activity into precisely timed postsynaptic events. Although much remains to be done in characterizing this synapse, recent work has revealed key features of its operation.

Biophysical Properties of the Striatopallidal Synapse

Striatal stimulation evokes long-latency (4–8 ms in mice and 5–10 ms in rats), inhibitory postsynaptic potentials (IPSPs) in GP neurons with reversal potential close to the predicted equilibrium potential for Cl[−] [56, 73–76]. The slow conduction velocity has been noted in rats (0.8 m/s) [56], in guinea pigs (0.33 m/s) [20], and in primates [60, 61]. The responses typically display paired-pulse facilitation [73–76], indicative of a relatively low release probability of the synapse [77]. IPSPs are blocked by GABA_A receptor antagonists, e.g., bicuculline and SR95531/gabazine. Thus, as predicted by morphological study (symmetrical and high contents of GAD, GABA), the striatopallidal synapse uses GABA [19].

Miniature inhibitory postsynaptic currents (mIPSCs), recorded in the presence of TTX and ionotropic glutamate receptor blockers, can often be separated into two subclasses. The majority of mIPSCs are small in amplitude and have variable time courses. Despite such variability, the rise and decay kinetics of individual mIPSCs are positively correlated. The variability in mIPSC kinetics is consistent with the convergence of many different striatopallidal terminals on a single pallidal neuron and the broad dendritic distribution of these synapses.

In contrast, the large, kinetically fast mIPSCs most likely arise from proximal synapses formed by recurrent collaterals of GP neurons [8, 11–13, 23, 56]. In support of this view, large and regularly spaced IPSCs that are TTX sensitive can be seen in voltage clamp recordings from GP neurons. Although these recurrent synapses

are of clear importance to our understanding of GP circuit dynamics [78], very little is known about them because of the difficulty in selectively isolating these collaterals.

Postsynaptic GABA_A Receptors

GABA_A receptors are ligand-gated Cl⁻ channels. Eight subunit classes have been isolated to date (α 1–6, β 1–4, γ 1–3, δ , ϵ , π , θ , and ρ 1–3). It is thought that most functional GABA_A receptors in vivo are formed by coassembly of two α - and two β -subunits and additional subunits [79–86]. As revealed by a number of approaches, the GABA_A α 1 subunit is expressed at very high levels in the GP [87–93]. The GABA_A α 1 subunit is often found at synapses with fast synaptic currents which are at least in part attributable to fast desensitization [94–96]. Immunocytochemical studies have shown that the striatopallidal synapses are richly invested with α 1 subunits [97, 98]. In accord with this finding, zolpidem, a GABA_A α 1 subunit selective imidazopyridine agonist, slows the decay kinetics of striatal mIPSCs in the GP, leaving their frequency and amplitude unchanged. Zolpidem has a stronger impact on striatopallidal IPSCs than on those arising from local collaterals. In mice with genetic deletions of the GABA_A α 1 subunit, there is a profound loss of GABA_A receptors in the GP, and they exhibit tremor [99]. The linkage of this subunit to PD has been strengthened by the downregulation of GP GABA_A α 1 subunits in PD patients and models and the therapeutic effectiveness of zolpidem (see below).

GABA Transporters

Three GABA transporters have been identified in the brain. GABA transporter subtype 1 (GAT1) is predominantly found in axons, presynaptic terminals, and glial cells. GAT2 is weakly expressed throughout the brain, primarily in arachnoid and ependymal cells. GAT3 is found predominantly on glial cells [100–109]. High levels of mRNAs and proteins for GABA transporters GAT1 and GAT3 have been found in the GP. Moderate levels of mRNA for GAT1 are also found in the striatum [105–107, 110–114]. Consistent with this, systemic administration of the GAT1 antagonist tiagabine increases the extracellular level of GABA [115]. Interestingly, GAT1 knockout mice, like the GABA_A α 1 subunit knockout mice, exhibit tremors [116].

In acutely prepared tissue slices, tiagabine slows the decay kinetics of GP mIPSCs in much the same way as zolpidem [117]. Presumably, blockade of the GABA uptake via GAT1 increases the concentration of GABA at

the synaptic cleft, leading to prolonged activation of postsynaptic GABA_A receptors on GP neurons. In addition, activation of presynaptic GABA_B receptors at the striatopallidal terminals is tightly controlled by GAT1, as the application of tiagabine significantly reduces the frequency of mIPSCs in a CGP55845-sensitive manner. Electron microscopy analysis has shown that GAT1 is predominantly localized in axonal segments and glial juxtaposed at symmetrical synapses. GAT3 is found exclusively on glial processes in the GP [111, 118] that ensheath dendrites and terminals. Better characterizing the role of GABA transporters in shaping GABA transmission will be crucial to our understanding of GP and the development of better therapeutic strategies for movement disorders.

HCN Channels Abbreviate the Time Course of IPSPs and Mediate Synaptic Resetting

Single-cell RT-PCR and immunohistochemical approaches revealed robust expression of HCN2 subunits, as well as significant levels of HCN1 subunits, in GABAergic GP neurons [27, 119]. These voltage-gated channels unlike most others are activated by hyperpolarization and have a reversal potential of about –20 to –30 mV. The admixture of HCN1 channels with HCN2 (the predominant channel type) gives rise to a channel with a faster activation kinetics and a more depolarized voltage of activation. Transient incoming striatal GABAergic input efficiently recruits the dendritic HCN channels. This in turn generates inward currents (depolarization) that abbreviate the duration of the IPSPs, leading to resetting of rhythmic discharge [27]. In this way, the temporally correlated striatopallidal activity would be capable of inducing phase synchrony among a subpopulation of GP neurons. This integrative feature of GP neurons is likely to be important to both the phasic changes in activity seen during voluntary movement as well as the emergence of correlated, rhythmic bursting seen in PD models.

Contribution of GP Dysfunction to the Symptoms of PD

In contrast to the activity patterns seen in normal animals and humans, correlated, rhythmic burst discharge of GP neurons emerges in PD [62, 120–129]. This abnormal activity pattern is thought to be closely linked to rigidity and tremor [130], as well as dyskinesias [121, 123, 125]. Disruption of this aberrant activity pattern with

electrical stimulation alleviates PD symptoms, strengthening the causal linkage in PD [131].

The origin of rhythmic bursting in GP neurons has not been fully established experimentally. Using organotypic cultures, Plenz and Kital [132] reported that STN and GP could form a reciprocally connected oscillatory network. But the critical cellular and molecular determinants of this network have yet to be defined. At present, we have only fragmentary data. Bevan et al. [133] have shown that low-threshold, T-type (Cav3) Ca^{2+} channels in STN neurons create a post-IPSPs burst of activity. This burst could induce an elevation in GP activity by virtue of the glutamatergic projection from the STN. But it is not clear how the pauses in GP activity arise. Modeling work suggests that both recurrent collateral GABAergic connections and striatal GABAergic input are important to the emergence of rhythmic bursting [78]. There are several lines of evidence implicating altered GABA transmission at striatopallidal synapses in PD. Injection of the GABA_A receptor antagonist bicuculline directly into the GP had marked antiparkinsonian effects and increased the locomotor score in a reserpine-treated rodent model of PD [134]. However, local injection of this antagonist into the GPe in normal monkeys induced abnormal posture and contraction [135], dyskinesias [58], or even akinesias [136]. Furthermore, tremor was observed in GABA_A $\alpha 1$ subunit and GAT1 knockout mice [99, 116]. An important feature of dopamine depletion is the dramatic enlargement in striatopallidal terminals (up to ~90%) and the increased GABA synthesis in striatopallidal neurons at the GP level [124, 137–140]. Consistent with an enhanced release of GABA from striatopallidal terminals, the total number of GP GABA_A receptors decreases after a nigrostriatal lesion [141–145]. This is attributed to the downregulation of the $\alpha 1$ -subunit-containing GABA_A receptors [146, 147]. Yet, the overall response to striatal stimulation increases following dopamine depletion. At this point, it is not clear whether there are changes in the composition or in the density of GABA_A receptors localized at these synapses. Why these adaptations occur is not clear. The traditional model argues that the striatopallidal activity increases following dopamine depletion [4, 148–151]. However, recent work by our group has shown that striatopallidal neurons undergo a profound deafferentation following dopamine depletion. In isolation, this would lead to a diminished striatopallidal activity. In simulations of the basal ganglia network reported by Terman et al. [78], any significant change in the striatopallidal activity (in either direction) could induce rhythmic bursting.

Conclusions

Although the static ‘box-and-arrow’ model of the basal ganglia [3, 4] has been of great heuristic value, it clearly does not capture the dynamic properties we know to be critical. It also fails to account for function and importance of the internuclear connectivity of the basal ganglia. These deficiencies are particularly prominent when thinking about the GP. We now know that GP neurons form multiple projections to virtually all major components of the basal ganglia. This challenges the view of sequential, parallel processing within the basal ganglia and argues that GP is not simply a sign inverter in the indirect pathway. These neurons are autonomously active and generate patterns of activity that are critical to basal ganglia function and movement execution. More and more, we are coming to the view that the pattern of activity, rather than the mean rate, is what is important in both health and disease. Our understanding of how synaptic and intrinsic properties of GP neurons shape these activity patterns is rapidly advancing, but much remains to be done.

Acknowledgments

This work was supported by the Morris K. Udall Parkinson's Disease Research Center of Excellence (National Institute of Neurological Disorders and Stroke Grant P50 NS047085) and the Research Grants Council of Hong Kong (Grant CUHK 4175/02M). We thank Drs. Wendy Wu and David Carr for their thoughtful discussion and critical reading of the manuscript.

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