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Review

Giant $GABA_A$ receptor mediated currents in the striatum, a common signature of Parkinson's disease in pharmacological and genetic rodent models

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ABSTRACT

Oscillatory giant $GABA_A$ receptor-mediated currents recorded from medium spiny neurons (MSNs) of the striatum in vitro are an electrophysiological signature of dysfunctioning dopaminergic synaptic transmission. This is a common early signature of Parkinson's disease in pharmacological and genetic mice models. Recorded from at least 40% of MSNs, these currents are present both after and up to 10 months before motor signs, and are suppressed by chronic levodopa treatment or chronic lesion of the subthalamic nucleus. Giant $GABA_A$ receptor-mediated currents may result from the diverse changes in the GABAergic striatal circuitry identified after dysfunction in dopaminergic transmission. Fast spiking (FS) interneurons are more strongly electrically coupled and a subpopulation of FS interneurons sprouts onto D2-type MSNs. On the other hand, low threshold spiking (LTS) interneurons shift to an excessive and recurrent bursting pattern. All these effects are likely to lead to profound dysfunction in the striatal GABAergic network, given that MSN responses to cortical inputs are highly dependent on GABAergic inputs and that GABAergic interneurons play a fundamental role in network oscillations.

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Introduction

The striatum is the main input nucleus of the basal ganglia. It transforms converging cortical and thalamic inputs into two output streams, called direct and indirect pathways. The projection neurons of the striatum, the GABAergic medium spiny neurons (MSNs), convey this output information previously treated by feedforward inhibition via GABAergic interneurons (the fast spiking (FS), low threshold spiking (LTS) interneurons and other types of interneurons) and by lateral inhibition via MSNs axon collaterals. Dopamine and acetylcholine, respectively released by terminals of midbrain dopaminergic neurons and cholinergic interneurons, modulate the activity of this GABAergic network.

Abbreviations: FS, fast spiking interneuron; HFS, high frequency stimulation; LTS, low threshold spiking interneuron; MSN, medium spiny neuron; PINK 1, PTEN-induced putative kinase 1; 6-OHDA, 6-hydroxydopamine; STN, subthalamic nucleus; TAN, tonically active neuron.

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The spontaneous $GABA_A$ receptor-mediated activity recorded from MSNs therefore reflects the resultant of all these processes. We will describe here how chronic dysfunction in dopamine signaling, as experienced during Parkinson's disease, affects spontaneous $GABA_A$ receptor-mediated activity in the striatum.

Characteristics of giant $GABA_A$ receptor-mediated currents in the dopamine-deprived striatum

The discovery of giant $GABA_A$ receptor-mediated currents in the pharmacological 6-OHDA mouse model

While investigating the spontaneous activity of GABAergic synapses in striatal slices from juvenile and adult 6-hydroxydopamine (6-OHDA)-treated mice, we discovered that chronic dopamine depletion shifts the pattern in half of the MSN population, from tonic to oscillatory. This oscillatory pattern consists of giant spontaneous $GABA_A$ receptor-mediated postsynaptic currents ($GABA_A$ sPSCs or $GABA_A$ currents) occurring singly or in bursts, with 340 pA mean amplitude as against 35 pA for tonic $GABA_A$ currents (Table 1). Giant $GABA_A$ currents are not associated with changes in the reversal potential for GABA or the resting membrane potential of MSNs [1].

The origin of the giant oscillatory $GABA_A$ currents is intrinsic to the striatum, since they are not modified by mechanical isolation of the striatum from surrounding structures or blocked by ionotropic glutamatergic receptors antagonists. Among likely underlying mechanisms of giant oscillatory $GABA_A$ currents is chronic alteration of the pattern of activity of low threshold spiking (LTS) interneurons which shift to a striking bursting pattern in the absence of dopamine. In contrast the activity of MSNs and/or the fast spiking (FS) interneurons which also impinge on MSNs is unchanged. The former are silent and the latter display the same single-spike firing pattern in vitro before and after dopaminergic depletion [1].

The absence of effect by blockers of nicotinic or muscarinic cholinergic receptors and the similar tonic pattern of activity of cholinergic interneurons (TANs) observed both in the presence and absence of dopaminergic innervation [1] rules out any effect due to alteration of the presynaptic inhibition of GABA release by cholinergic receptors [2,3] or to TANs dysfunctioning [4].

Generalization to familial forms of Parkinson's disease

We identified a similar $GABA_A$ signature in the striatum of 6- to 19-month-old PINK1 deficient mice. Loss-of-function mutations in the mitochondrial protein PINK1 causes autosomal recessive PARK6-linked Parkinsonism, an early onset variant of Parkinson's disease with slow progression [5,6]. *PINK1* encodes the PTEN-induced putative kinase 1 (PINK1), a ubiquitously expressed 581 amino acids protein with a mitochondrial localization signal and a cytoplasmic serine-threonine kinase domain [7]. Though midbrain dopaminergic neurons are preserved throughout the mouse lifetime, striatal dopamine is significantly reduced at 9 months, evoked striatal dopamine release is reduced and synaptic plasticity in PINK1$^{-/-}$ corticostriatal slices is disrupted by 3 months of age, and PINK1$^{-/-}$ mice show reduced spontaneous locomotor activity starting at 16 months [8,9]. In this model, disruption of the motor pathway does not require loss of midbrain dopaminergic (mDA) neurons probably because dopamine release and its actions are altered.

Interestingly, in striatal slices from 19-month-old mice having already developed motor problems [9], PINK1 deficiency profoundly alters transmission through $GABA_A$ receptors in around half of the MSNs, causing spontaneous oscillatory $GABA_A$ currents consisting of giant $GABA_A$ sPSCs, occurring singly and/or in bursts (Fig. 1A–C and Table 1) (Dehorter et al., unpublished observations). This signature is strikingly similar to that identified in the severe dopaminergic deficiency state pharmacologically produced by 6-OHDA injection [1] though mDA neurons in PINK1$^{-/-}$ mice remain intact and their striatal dopamine levels are only moderately reduced (20%) [9].

Birth-dating of giant $GABA_A$ currents

The progressive genetic rodent models of Parkinson's disease enabled us to determine the temporal correspondence between electrophysiological signatures of Parkinson's disease and motor pathology. In order to birth-date giant $GABA_A$ currents, we looked for their presence 10 to 14 months before motor signs. The observation of strikingly large $GABA_A$ currents occurring singly or in bursts in around 70% of the 6-month-old PINK1$^{-/-}$ MSNs assayed (Fig. 1A–C and Table 1) [10] came as a surprise, as PINK1$^{-/-}$ mice display no significant locomotor deficit at this age [9]. This suggests that the dopaminergic dysfunction in the striatum, at least at rest, is more severe than expected from amperometric measurements of the response to local striatal stimulation [8]. The birth-dating procedure involves looking for the $GABA_A$ signature of dopamine dysfunction in the striatum of 2-month-old PINK1$^{-/-}$ mice. Only 11% of the cells showed giant currents or bursts and most of the results for giants (but not all) and all results for bursts are not significantly different from those for age-matched wt mice (Fig. 1C and Table 1). We propose that dysfunctioning dopaminergic transmission in the striatum becomes critical after 2 months in PINK1$^{-/-}$ mice, and is maximal at 6 months i.e. long before the first motor signs (16 months). The PINK1$^{-/-}$ mouse model of Parkinson's disease is thus a useful tool to study early stages of the disease process, where reversible

Table 1
Characteristics of giant $GABA_A$ currents in wt mice and mice models of Parkinson's disease at different ages.

Mice age (months)	Control wt	wt + 6-OHDA	PINK1$^{-/-}$		
	2–7	1–2	2	5–7	19
Single giant $GABA_A$ sPSCs					
Recorded in % MSNs	25 (n = 50)	45 (n = 45)	29 (n = 17)	70 (n = 27)	47 (n = 34)
Mean amplitude (pA)	274 ± 17	340 ± 6[a]	300 ± 25	340 ± 25[a]	314 ± 6[a]
Mean frequency (Hz)	0.11 ± 0.02	0.29 ± 0.07[a]	0.09 ± 0.04	0.23 ± 0.06[a]	0.27 ± 0.14
Mean current charge (nA ms)	162 ± 30	1311 ± 142[c]	364 ± 56[a]	1096 ± 289[c]	630 ± 176[a]
% of GABA current charge in giants	10	60	35	38	40
Bursts of $GABA_A$ sPSCs					
Intra-burst amplitude (pA)	51.3 ± 1.0	95.9 ± 2.6[c]	81 ± 19	82.5 ± 7.6[c]	68.5 ± 6.8[c]
Intra-burst frequency (Hz)	29.3 ± 1.1	58.7 ± 1.3[c]	23 ± 6	38.5 ± 3.8[c]	41.4 ± 5.6[c]

All data were compared to wt.
[a] $P < 0.05$.
[c] $P < 0.001$.

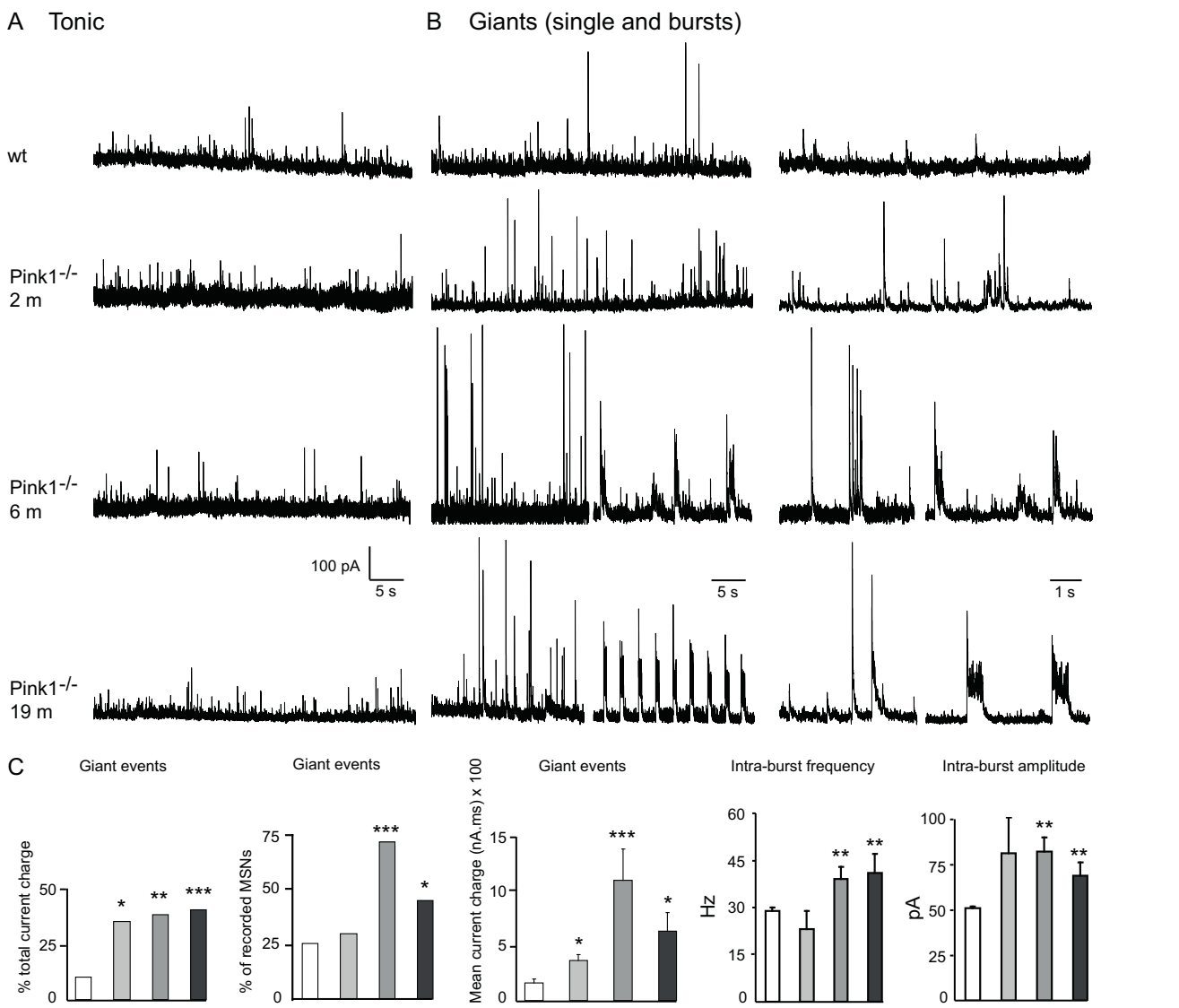

Fig. 1. Birth dating of giant $GABA_A$ receptor-mediated currents in $PINK1^{-}/^{-}$ striatum. (A) and (B) Spontaneous $GABA_A$ currents recorded from MSNs in basal ganglia slices from wt mice (wt) and 2- to 19-month-old $PINK1^{-}/^{-}$ mice (2 m, 6 m, 19 m). (A) Tonic pattern of $GABA_A$ currents. (B) Giant pattern of $GABA_A$ currents at two different time scales. Left column traces of 6 m and 19 m are divided into two to show single giants (left) and bursts of giants (right). Right column traces are expanded from left column traces. (C) Quantification of data from wt (white), 2-month-old (light gray), 6-month-old (dark gray) and 19-month-old (black) $PINK1^{-}/^{-}$ MSNs. (Voltage clamp recording mode, whole-cell configuration, $V_H = -10$ mV, intracellular recording medium Cs-gluconate, reversal potential for GABA −58 mV).

neuronal dysfunction rather than irreversible neuron loss dominates in the brain.

The suppression of giant $GABA_A$ receptor-mediated currents by Parkinson's disease treatments

We hypothesized that giant $GABA_A$ currents could be considered as a signature of Parkinson's disease if they were suppressed/decreased by treatments for Parkinson's disease, such as lesion of the subthalamic nucleus (STN) or chronic L-dopa treatment of $PINK1^{-}/^{-}$ mice. Consistent with our observation that STN neurons of 5- to 7-month-old $PINK1^{-}/^{-}$ mice display the characteristic electrophysiological signature of mild [11] or severe [12,13] dopaminergic depletion i.e. recurrent, spontaneous bursts of glutamatergic EPSPs giving rise to bursts of spikes, kainic acid lesion of the STN reversed the $GABA_A$ activity to the control low-frequency, low-amplitude, regular pattern without single giant currents or bursts in 79% of the MSNs (Table 2). Similarly, after chronic levodopa treatment of $PINK1^{-}/^{-}$ mice, all recorded MSNs (100%) displayed a tonic pattern of $GABA_A$ sPSCs similar to those recorded from wt MSNs of the same age i.e., without giant currents or bursting events in the slices [10] (Table 2).

Generalization: consequences of dopamine depletion/dysfunction on GABA interneurons of the striatum

The GABAergic striatal microcircuitry primarily consists of projection neurons, MSNs, with a small population of two main groups of GABAergic interneurons, FS and LTS [14]. FS interneurons comprise roughly 1% of striatal neurons, receive convergent inputs from a wide range of distinct cortical regions and provide robust feedforward perisomatic inhibition on hundreds of surrounding MSNs of the direct and indirect pathway (D1 and D2 MSNs) [15–20]. FS interneurons are interconnected by electrical and GABAergic synapses [17] but avoid cholinergic interneurons and sparsely contact LTS interneurons [21,22]; see review in [23]. FS spontaneous firing is regular in vitro but mainly shows a stuttering pattern (high frequency firing interrupted by periods of silence) in

Table 2
Suppression of giant $GABA_A$ currents by treatments.

Mice and treatment	wt	PINK1$^{-/-}$ + levodopa	PINK1$^{-/-}$ + STN lesion	PINK1$^{-/-}$
Age (months)	5–7	5–7	5–7	5–7
Single giant $GABA_A$ sPSCs				
Recorded in % MSNs	30 ($n=10$)	0 ($n=9$)	21 ($n=38$)	70 ($n=27$)
Mean amplitude (pA)	219 ± 5	0	241 ± 4	340 ± 25[c]
Mean Frequency (Hz)	0.032 ± 0.004	0	0.20 ± 0.11	0.23 ± 0.06[a]
Mean current charge (nA ms)	343 ± 218		287 ± 65	1096 ± 289[c]
% of GABA current charge	9	–	5	30
Bursts of $GABA_A$ sPSCs				
Intra-burst Amplitude (pA)	–	–	–	82.5 ± 7.6
Intra-burst Frequency (Hz)	–	–	–	38.5 ± 3.8

All data were compared to wt.
[a] $P<0.05$.
[c] $P<0.001$.

vivo [19]. FS interneurons appear to mediate the bulk of feedforward inhibition [18,23] because they receive strong cortical innervation [24] and respond with faster latency to cortical stimulation than MSNs [25].

LTS interneurons comprise roughly 1% of striatal neurons and contain other neurotransmitters such as neuropeptide Y, nitric oxide synthase and somatostatin that may have different functional roles. A subgroup of LTS provides robust inhibition on MSNs [26]. They display complex autonomous firing patterns (regular, irregular and bursting) [21,27]. By contrast, MSN–MSN GABAergic synapses tend to be distal to the MSN cell body and are individually weak, albeit large in number [28,29].

Decreased dopaminergic transmission in the striatum affects this striatal GABAergic network at different loci: it (i) removes the presynaptic inhibitory control of GABA release by D2 dopaminergic receptors [30] except for lateral connections between MSNs whose activity is in contrast down regulated by reserpine or 6-hydroxydopamine (6-OHDA) treatment in mice [31], (ii) shifts the spontaneous pattern of GABAergic LTS interneurons to bursty [1], (iii) increases the connectivity of GABAergic FS interneurons to D2 MSNs causing a target-specific reorganization of the feedforward inhibitory circuit through selective enhancement of FS connections, driven by the sprouting of FS axons [32] (but see [33] for controversial results obtained after a longer period), without changing their spontaneous activity [1] and (iv) increases electrical coupling between FS interneurons [34] (Fig. 2). Therefore spontaneous giant $GABA_A$ currents occurring singly or in bursts may result from the synchronous activity of an increased number of FS interneurons terminals [35] and the bursting activity of LTS interneurons, both effects being amplified by the removal of presynaptic DA inhibition of GABA release at GABAergic interneuron-MSN synapses.

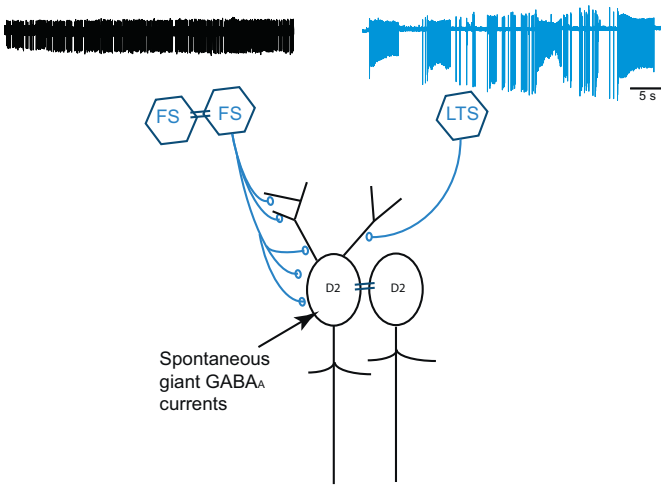

Fig. 2. The GABAergic striatal network after depletion or dysfunction of the dopaminergic transmission. Changes in morphology (FS) or activity (LTS) of GABAergic interneurons are indicated in blue. The double bar indicates gap junctions. We chose to illustrate changes at the level of D2 MSNs because they are the most affected by FS interneurons sprouting. See the text for explanations.

Giant $GABA_A$ currents likely destabilize striatal function by profoundly altering the resting state activity of at least half of the MSNs and as a consequence their response to cortical inputs. During down states, GABA-induced depolarization decreases the impact of the hyperpolarization-activated inward rectifier K^+ current that prevents MSNs from excitation-induced rapid firing [36,37]. GABA-induced depolarization drives the MSN membrane to a potential (−65 mV) at which its input resistance and time constant are close to maximal [38], which may facilitate glutamatergic inputs and lead to the generation of action potentials [39]. Along the same lines, the blockade of spontaneous and tonic $GABA_A$ synaptic transmission decreases the cortically evoked excitation recorded from MSNs in the cell-attached configuration [40]. In contrast, during the up states that are more frequent in the DA-depleted striatum (MSNs spend a longer time in up states in chronically 6-hydroxydopamine-lesioned rats [41]), giant $GABA_A$ currents should efficiently and transiently inhibit cortical inputs, preventing information transfer and integration.

D2 MSNs could be the specific target of this pathological $GABA_A$ activity since giant $GABA_A$ currents are recorded in around half of the MSNs (which corresponds to the percentage of D2 MSNs) and because FS axons specifically sprout onto D2 MSNs [32]. However, the double immunocytochemical characterization we performed on the recorded MSNs failed to show any preference by giant $GABA_A$ currents for D1 or D2 MSNs [1]. This needs to be confirmed by identifying MSNs during recordings in genetically engineered mice.

GABAergic interneurons are known to play a significant role in the generation of oscillations [42]. Low-frequency LFP oscillations (<55 Hz) are amplified by dopamine depletion in the sensorimotor striatum in vivo during the performance of complex well-learned tasks involving action initiation, decision making, and reward. By contrast, high-frequency (>65 Hz) oscillations are uniformly diminished with dopamine depletion. These changes could reflect temporally restricted increases in network synchrony or increased responsiveness to task-modulated inputs [43]. The role of giant and bursting $GABA_A$ currents in these changes remains to be determined.

The striatal $GABA_A$ signature of dysfunctioning dopamine signal also provides an interesting early read-out [44] to assess the severity of the pathology in genetic mouse models of Parkinson's disease.

Conflict of interest

The authors declare no competing financial interests.

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