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Research Report

Sub-regional differences and mechanisms of the short-term plasticity of dopamine overflow in striatum in mice lacking alpha-synuclein

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ABSTRACT

Mice lacking the pre-synaptic protein alpha-synuclein (α-syn) demonstrate enhanced facilitation of dopamine (DA) overflow in dorsal striatum following repeated, high-frequency burst stimulation of the dopaminergic pathways. Dorsal striatum is most vulnerable to neurodegeneration in Parkinson's disease. The role of α-syn in facilitation of DA overflow in the ventral striatum, which is less vulnerable to neurodegeneration, is unknown. We investigated the link between the absence of α-syn and the plasticity of DA overflow in the dorsal and ventral striatum by in vivo voltammetry and the possible mechanisms of modulation of the plasticity of DA overflow. We show that the facilitation of DA overflow following paired-burst stimulation is significantly enhanced in the dorsolateral but not in the ventral striatum of mice lacking α-syn. Re-uptake inhibitor, GBR12909, completely eliminated the facilitation of DA overflow regardless of the presence of α-syn in both dorsal and ventral striatum, indicating that re-uptake is critical for maintenance of paired-burst facilitation (PBF). Inhibition of D2 autoreceptors by haloperidol decreased PBF only in mice lacking α-syn. However, the basal function of D2 autoreceptors tested by paired-pulse depression of DA overflow was not different between the lines. Therefore, alterations in the D2 autoreceptor system do not explain the different effect of haloperidol on PBF in mice with and without α-syn. This indicates that neither re-uptake nor D2 autoreceptors differentiate the PBF between the genotypes. We propose that modification of DA vesicles in α-syn knockout mice, as reported in several studies, may be a factor underlying the enhanced PBF in these mice.

1. Introduction

Activity-dependent increase in neurotransmitter release following repeated stimulation has been reported in dopamine (DA) (Yavich, 1996), glutamate (Stevens and Wesseling, 1999) and GABA-ergic neurons (Wang and Kaczmarek, 1998). This facilitation of neurotransmitter release reveals a form of short-term plasticity, which involves reorganization of pre-synaptic vesicular storage pools (Stevens and Wesseling, 1999; Yavich, 1996; Yavich et al., 2004). The mechanisms and regulation of this

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Abbreviations: α-syn, alpha-synuclein; DA, dopamine; DAT, dopamine transporter; FSCV, Fast-scan cyclic voltammetry; MFB, medial forebrain bundle; PBF, paired-burst facilitation; PD, Parkinson's disease; PPD, Paired-pulse depression; RRP, readily releasable pool; SNARE, Soluble N-ethylmaleimide-sensitive factor attachment protein receptor

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form of plasticity have not been described in detail. Repeated stimulation of the ascending dopaminergic pathways produces enhanced facilitation of DA overflow in the dorsal striatum in mice with spontaneous deletion of α-syn in comparison with wild type mice (Yavich et al., 2004). Additionally, we recently reported an increase in the stimulated and extracellular DA levels and decreased re-uptake in the dorsal striatum in mice lacking α-syn (Chadchankar et al., 2011). However, the impact of these alterations on the short-term plasticity of DA overflow in striatum is unknown. Moreover, these studies reported dopamine neurotransmission in α-syn knockout mice from predominantly one location in the dorsal striatum, which does not address the well known heterogeneity in DA release (Garris and Wightman, 1994) and plasticity of DA release (Cragg, 2003) in the striatum. Understanding the mechanisms underlying short-term plasticity of DA overflow in the sub-regions of the striatum and the role of α-syn in this process is potentially important due to the possible link between α-syn dependent plasticity of DA overflow and sub-regional differences in the vulnerability of the striatum to neurodegeneration. These differences have been reported following administration of neurotoxin (Garris et al., 1997) and in progression of PD in humans (Kish et al., 1988; Morrish et al., 1996).

One of the factors underlying heterogeneous release of DA in the striatum is the levels of dopamine transporter (DAT) expression (Javitch et al., 1985). DA recycled by re-uptake forms a significant proportion of the readily releasable pool (Jones et al., 1998). It is likely that this recycled DA, similar to other neurotransmitters (Rizzoli and Betz, 2005; Wang and Kaczmarek, 1998), is an immediate source for release following repeated stimulation. Therefore, the plasticity of DA overflow may depend on DA re-uptake. D2 autoreceptors also mediate DA overflow following repeated burst stimulation (Kita et al., 2007; Yavich, 1996). We suggest that these two factors may play a role in the short-term plasticity of DA overflow in mice without α-syn.

In this study, short-term plasticity of DA overflow in two α-syn deficient mouse lines was studied after high frequency, paired-burst stimulation of the ascending DA pathways. We used the ratio of peak DA overflow after second burst stimulation to that after the first burst stimulation to characterize the short-term plasticity of DA overflow. For ease of terminology, we have referred to this ratio as paired-burst facilitation (PBF). The roles of the DAT and D2 autoreceptors in the phenomenon of PBF and its possible dependence on α-syn were also studied. We found that PBF is selectively enhanced in the dorsolateral striatum of mice lacking α-syn while it remained unchanged in the ventral striatum. We also found that when re-uptake of DA was inhibited by GBR12909, paired-burst facilitation was eliminated in both dorsal and ventral striatum in all genotypes. Haloperidol decreased the PBF but did not eliminate it. The function of D2 autoreceptor was not different in mice lacking α-syn.

2. Results

2.1. *Enhanced facilitation of dopamine overflow in the dorsolateral but not in the ventral striatum of alpha-synuclein deficient mice*

Three mouse lines were used in these experiments. C57BL/6J line was used as the wild type control line (b6+). C57BL/6JOlaHsd line carrying a spontaneous deletion of α-syn locus (b6–) and B6;129X1-*Snca*^{tm1Rosl}/J, a transgenic knockout for α-syn (b6–ros), were used as α-syn deficient mouse lines (For details, see Section 4.1). DA overflow was measured in the sub-regions of striatum after paired-burst stimulation. Consistent with an earlier study (Yavich et al., 2004), higher PBF was seen at locations in the dorsal striatum. PBF in the dorsal striatum of b6– and b6–ros mice was 3 to 4 times larger than in the control mice (Fig. 1C, pooled data from the dorsal striatum, n=10). RM ANOVA revealed a significant sub-region × genotype interaction ($F_{2,75}$=36.5, p=0.001). Furthermore, the PBF in the dorsal striatum was significantly higher in comparison with the PBF in the ventral striatum in b6– and b6–ros mice (RM ANOVA, $F_{1,75}$=257, p=0.001).

To further elucidate the sub-region specific alterations in PBF, we generated a two-dimensional map of PBF (Fig. 2) using the brain atlas of Franklin and Paxinos (2007) as a template. A map of isolines permits to predict, using routine mathematical approach, the levels of PBF outside the actual measuring locations, the same as isolines on geological map show elevation outside the actual measurement points (see Section 4.4). This representation revealed that PBF follows a dorsolateral–ventromedial gradient (Fig. 2). The highest PBF was observed in the dorsolateral striatum of both b6– and

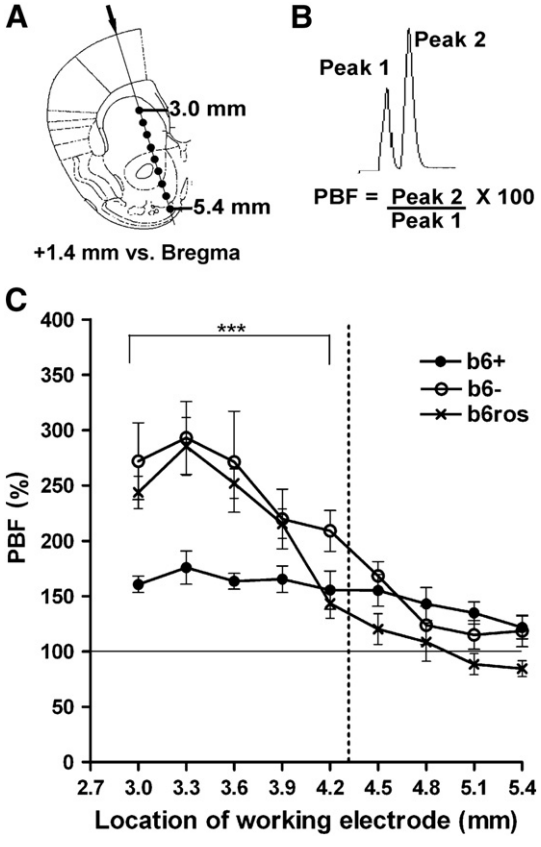

Fig. 1 – Paired-burst facilitation in striatal sub-regions of mice with and without α-syn. A. Insertion path of the working electrode in the striatum. Each dot indicates a recording location. B. Calculation of PBF from a real recording of dopamine overflow following two 50 Hz, 2 s stimuli at 5 s interval. C. Mean values of PBF at recording locations indicated in (A).