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BRAIN RESEARCH

Research Report

Decreased reuptake of dopamine in the dorsal striatum in the absence of alpha-synuclein

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ABSTRACT

The presynaptic protein alpha-synuclein (α-syn) plays a role in dopaminergic neurotransmission in the nigrostriatal dopaminergic system. Mutations in this protein have been linked to pathogenesis of Parkinson's disease. However, the details of regulation of dopamine homeostasis by α-syn and its molecular targets are generally unknown. We investigated the effect of α-syn deletion on striatal dopaminergic homeostasis. Two α-syn deficient mouse lines, one carrying a spontaneous deletion of α-syn locus and the other a transgenic α-syn knockout, were used in the study. Stimulated and basal extracellular dopamine levels were determined in the dorsal striatum by *in vivo* voltammetry and *in vivo* microdialysis, respectively. Dopamine transporter expression was studied by immunohistochemistry. Stimulated dopamine overflow and basal extracellular dopamine levels were higher in mice lacking α-syn with a concomitant decrease in dopamine transporter expression and reuptake in the dorsal striatum. We show that α-syn deletion produces significant adaptive changes in the striatal dopaminergic system via modulation of reuptake.
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1. Introduction

Mutations in alpha-synuclein (α-syn) have been linked to certain forms of familial Parkinson's disease (PD) and other neurodegenerative disorders (Spillantini et al., 1997; Lee and Trojanowski, 2006). α-syn plays a role in dopamine synthesis (Perez et al., 2002), alters the compartmentalization of dopamine storage pool (Cabin et al., 2000) and neurotransmitter release (Abeliovich et al., 2000). α-syn appears to have a minor effect on DA release at short, relatively weak stimuli but plays an important role in recycling of dopamine storage pool at intense (Yavich et al., 2004; Nemani et al., 2010) or during repetitive stimuli (Abeliovich et al., 2000; Yavich et al., 2004). Neurotransmission during burst stimulation, which mimics repetitive firing of dopamine neurons, is sustained by effective reuptake (Stevens and Wesseling, 1999). Efficient reuptake replenishes the readily releasable pool (RRP), which is the primary source of presynaptic dopamine available for release during bursting. Several *in vitro* studies have shown that α-syn plays a role in the trafficking of the dopamine transporter (DAT) (Lee et al., 2001; Wersinger and Sidhu, 2003). However, modulation of reuptake in α-syn knockout mice has not been revealed at least in *ex vivo* experiments in slices (Abeliovich et al., 2000; Senior et al., 2008).

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Previous studies have demonstrated alterations of dopamine neurotransmission in mice lacking α-syn such as faster recovery of DA release after paired-pulse stimulation (Abeliovich et al., 2000) and facilitation of DA release following burst stimulation (Yavich et al., 2004). However, the evidence on alterations in DA tissue content in the absence of α-syn is conflicting. Abeliovich et al. (2000) reported lower striatal DA content while Chandra et al. (2004) and Robertson et al. (2004) found no change in the striatal DA content. So far, no studies have examined the extracellular levels of DA in the absence of α-syn.

In this study, we investigated stimulated dopamine overflow, DAT expression, and basal extracellular DA levels in mice lacking α-syn. The dorsal striatum is one the most severely affected brain regions in PD (Bergstrom et al., 2001), and a site where significant alterations in dopamine neurotransmission have been reported in mice lacking α-syn (Abeliovich et al., 2000; Yavich et al., 2004). Therefore, we focused on the dorsal striatum in the present study. Our *in vivo* voltammetry, *in vivo* microdialysis, and immunohistochemistry data indicate that dopamine release and reuptake is altered in α-syn deficient mice. These data also show that α-syn is an important player in maintaining dopaminergic homeostasis and permanent adaptive changes occur in the dopaminergic system following its deletion.

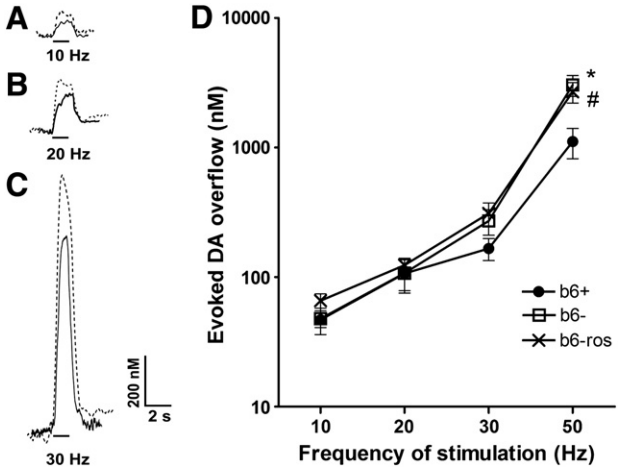

Fig. 1 – Evoked DA overflow following stimulation of the MFB in the dorsal striatum of wildtype mice and two mouse lines lacking alpha-synuclein (α-syn). Panels A, B, and C show a representative recording of evoked DA overflow after 2-s bursts of stimulation at 10, 20, and 30 Hz, respectively. Solid line shows recordings from b6+ line while dashed line shows recordings from b6– mice. The horizontal line below the recordings indicates the length of stimulation (see also Fig. 4A for an example of DA overflow following 50 Hz stimulation). D. Evoked DA overflow following stimulation of the MFB at increasing frequencies from 10 to 50 Hz. Two mouse lines lacking α-syn showed significantly higher evoked DA overflow than the wildtype mice at 50 Hz stimulation (statistical significance indicated by * and # in b6– and b6– ros mice, respectively; for statistics, see Section 2.1).

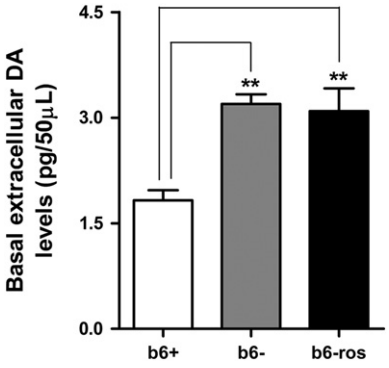

Fig. 2 – Basal extracellular DA levels in the dorsal striatum in mice with and without α-syn. The basal extracellular DA levels were 75% and 69% higher in b6– and b6– ros mice, respectively, in comparison with b6+ mice. There was no significant difference between b6– and b6– ros mice.

2. Results

2.1. *Evoked DA overflow is α-syn dependent*

Three mouse lines were used in these experiments. C57BL/6J line was used as the wildtype 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 5.1). Using *in vivo* voltammetry, we investigated evoked DA overflow in the dorsal striatum following stimulation of the medial forebrain bundle (MFB) at 10–50 Hz. The response to different stimulus frequencies was found to be α-syn dependent (Fig. 1). Evoked DA overflow was higher in b6– and b6– ros mice than in b6+ mice with increasing frequency of stimulation. Statistical analysis revealed a significant genotype × frequency interaction (RM ANOVA, $F_{4,30}=3.1$, $p=0.03$, $n=7$ per group). The DA overflow in b6– ros ($p=0.002$) and b6– ($p=0.005$) mice was significantly higher at 50 Hz stimulation than in b6+ mice (Tukey's *post hoc* test).

2.2. *Basal extracellular dopamine levels are higher in α-syn deficient mice*

To study the effect of α-syn deletion on basal extracellular DA levels, we used *in vivo* microdialysis. The basal extracellular DA levels in b6– and b6– ros mice were 75% and 69% higher than in b6+ mice, respectively (Fig. 2, one-way ANOVA, $F_{2,22}=6.4$, $p=0.007$, $n=8$ per group). In Tukey's *post hoc* test, both b6– ros ($p=0.0004$) and b6– ($p=0.0006$) mice differed significantly from b6+ mice while there was no difference in the extracellular DA levels between b6– and b6– ros mice ($p=0.75$).

2.3. *Decreased DAT expression in the dorsal striatum in mice lacking α-syn*

Based on the data on elevated extracellular DA levels, we hypothesized that the expression and/or functional activity of the striatal dopamine transporter may be lower in α-syn

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