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Involvement of monoamine oxidase-B in the acute neurotoxicity of MPTP in embryonic and newborn mice

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ABSTRACT

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces damage to the nigrostriatal system and subventricular zone (SVZ) of mice. While there have been many researches on the neurotoxicity of MPTP in adult mice, there have been few reports concerning that in embryonic and newborn mice. Very recently, we revealed that such neurotoxicity of MPTP and 1-methyl-4-phenylpyridinium (MPP^+), a metabolite of MPTP, is observed not only in adult mice but also in embryonic and newborn mice; however, the mechanism of acute toxicity is not well elucidated. In the present study, we attempted to reveal the involvement of monoamine oxidase B (MAO-B) in the metabolism of MPTP to MPP^+ and dopamine transporter (DAT) in the neuronal cellular uptake of MPP^+ during the acute toxicity of MPTP in both embryonic and newborn mice. Immunohistochemistry and double-labeling immunofluorescent staining demonstrated an increase of MAO-B-positive glial cells in the brain only in MPTP-treated mice, indicating the involvement of MAO-B in the metabolism of MPTP to MPP^+ during the acute neurotoxicity of MPTP in both embryonic and newborn mice. The expression of DAT was not observed in the nigrostriatal zone of embryonic mice and in the zone and SVZ of newborn mice. The mechanism of how MPP^+ is taken up into those neuronal cells remains unknown. In conclusion, MAO-B is involved in the acute neurotoxicity of MPTP in embryonic and newborn mice.

1. Introduction

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes damage to dopaminergic (DA) neurons in the nigrostriatal system, similar to that seen in Parkinson's disease (PD) patients (Mandel et al., 2007; Yokoyama et al., 2008). MPTP-treated C57BL/6J mice (Melamed et al., 1990; Teismann et al., 2001; Xiao et al., 2004; Smeyne et al., 2005), common marmosets (Jenner, 2009) and cynomolgus monkeys (Johnston et al., 2010) are representative animal models for idiopathic PD (Schapira, 2007). When MPTP is injected into mice, the chemical penetrates the brain through the blood-brain barrier (BBB) and is converted to 1-methyl-4-phenylpyridinium (MPP^+) by monoamine oxidase-B (MAO-B) in astrocytes (Levitt et al., 1982; Singer et al., 1986; Di Monte et al., 1992; O'Callaghan and Seidler, 1992; Ghosh et al., 2007; Chen et al., 2008; He et al., 2008a,b; Sonsalla et al., 2010). MPP^+ has high affinity for the dopamine transporter (DAT) on DA cells (Javitch and Snyder, 1984; Chiba et al., 1985; Lotharius and O'Malley, 2000; Obata, 2006), and is taken up into the cell (Reinhard et al., 1987; Daniels and Reinhard, 1988; Del Zompo et al., 1993; Obata, 2006). MPP^+ is then accumulated in the mitochondria and causes neuronal cell death (Muñoz et al., 2006; Seo et al., 2006; Schapira, 2007).

Recently, several studies (He et al., 2006, 2008a,b; Shibui et al., 2009; Ito et al., in press-a) have confirmed that MPTP is toxic not only to DA neurons in the nigrostriatal system but also to neuroblasts in the subventricular zone (SVZ). Intraperitoneal (i.p.) injection of MPTP provokes apoptosis of DCX-positive neuroblasts in the SVZ of C57BL/6J mice (He et al., 2006). In addition, pretreatment with deprenyl, a selective MAO-B inhibitor, protected the decline of the nigrostriatal dopamine level and reduced the number of apoptotic cells in the SVZ induced by MPTP, suggesting the involvement of MAO-B in the metabolism from MPTP to MPP^+ (He et al., 2008a,b); however, inhibitors of DAT, serotonin transporters and noradrenaline transporters did not rescue MPTP-induced apoptosis in the SVZ (Shibui et al., 2009; Ito et al., in press-a). These findings indicate the involvement of an unknown MPP^+ uptake system in neuroblasts in the SVZ.

There have been many researches on the neurotoxicity of MPTP in adult mice (He et al., 2008a,b; Shibui et al., 2009; Berry et al., 2010; Dehay et al., 2010; Ito et al., in press-a,b), but very few reports

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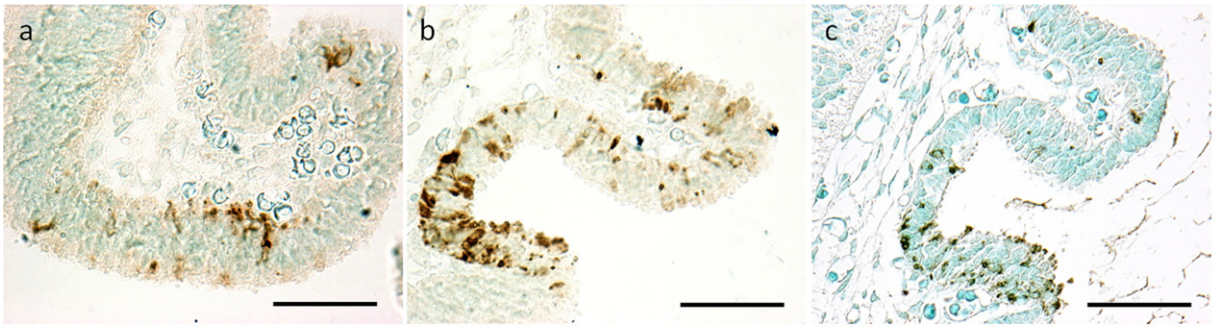
Table 1
List of treatment conditions to tissue preparation for histological analysis of mice.

	Treated materials (number of groups)	Number of animals/group	Age	Dose (mg/kg)	Number of samples/group
Embryo	Saline, MPTP, MPP^+ (3)	4 pregnant mice	Pregnant day 12 (10–20 week old maternal mice)	MPTP 25.0 MPP^+ 17.1	8 embryos (2 embryos/pregnant mice)
Newborn	Saline, MPTP, MPP^+ (3)	4 newborns (2 males and 2 females)	9-day old	MPTP 25.0 MPP^+ 10.0	Striatum: 4 SN: 4



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	Mean ± SE (Each value of MAO-B expression level)
Control	11452.1 ± 2336.2 (24440.6, 6856.8, 16812.6, 7484.1, 9808.7, 5220.8, 14236.7, 6756.3)
MPTP	16092.8 ± 4377.5 (32323.4, 17247.0, 10766.7, 41672.5, 9988.6, 33277.5, 11426.6, 14938.7)
MPP^+	8855.3 ± 1299.9 (8144.5, 8811.0, 12391.7, 3670.1, 11837.3, 12989.4, 3529.7, 9468.7)

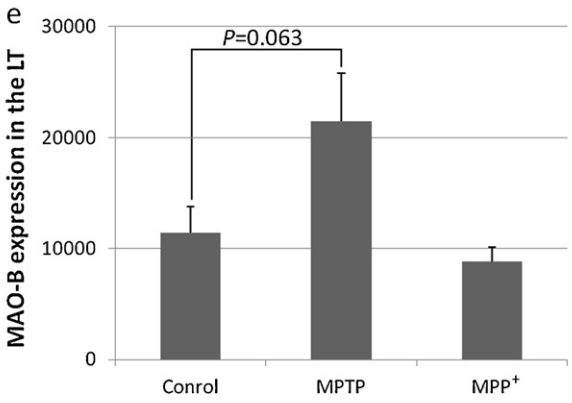

Fig. 1. MAO-B expression was increased in the LT of MPTP-treated embryos. (a) Control; (b) MPTP; (c) MPP^+. (d) Mean and SE of MAO-B expression level of each treatment group and each value of MAO-B expression level in the LT of embryonic mice. (e) MAO-B expression level was increased in MPTP-treated mice, although the difference was not significant. Values are shown as the mean ± SE. Scale bars = 50 μm.

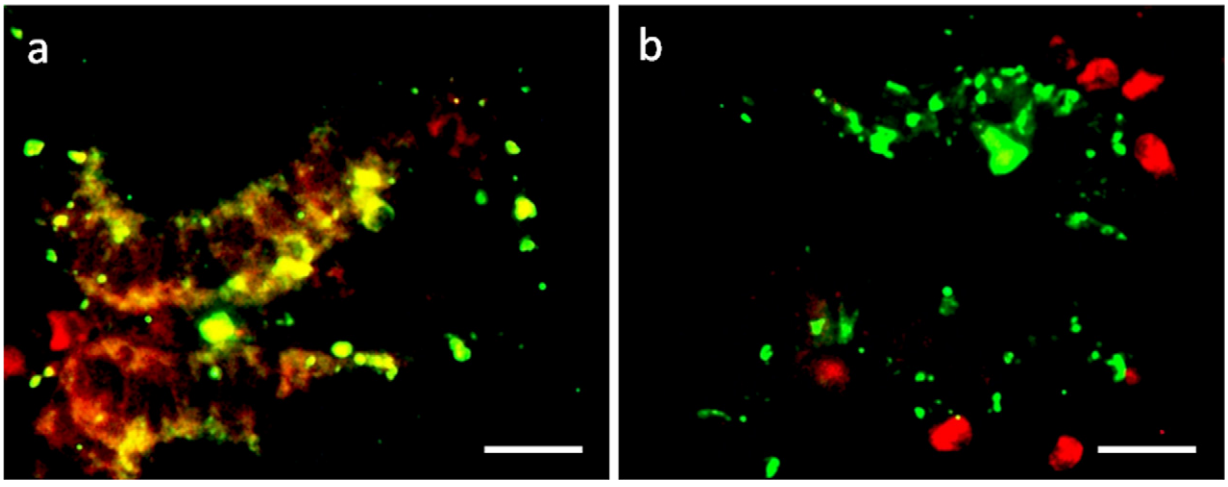

Fig. 2. MAO-B expression in immature glial cells in the LT of MPTP-treated embryos. Green fluorescence indicates MAO-B expression, and red fluorescence indicates nestin (a) or Dcx (b). MAO-B was expressed in nestin-positive immature glial cells (a), not in Dcx-positive neuroblasts (b). Scale bars = 20 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)