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Research Report

The role of organic cation transporter-3 in methamphetamine disposition and its behavioral response in rats

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ABSTRACT

Organic cation transporter-3 (OCT3) is expressed in several tissues including the brain. We have previously demonstrated that rats with behavioral sensitization to methamphetamine (METH) increased the brain penetration of METH with decreased expression of OCT3 in brain. Considering the earlier *in vitro* studies demonstrating that 1) OCT3 could transport dopamine (DA) and 2) the specific transport via OCT3 could be inhibited by METH, these results suggest that decreased OCT3 might decrease the efflux of METH and/or DA from brain, subsequently causing the development of behavioral sensitization. Thus, in the present study, behavioral task related to DA and pharmacokinetic experiment were performed using rats treated with antisense against OCT3 (OCT3-AS) since no specific ligands for OCT3 are still available. The continuous infusion of OCT3-AS into the third ventricle significantly decreased the expression of OCT3 in choroid plexus (CP) epithelial cells. Both METH-induced hyperlocomotion and METH-induced extracellular DA levels in nucleus accumbens and prefrontal cortex were significantly increased in OCT3-AS-treated rats. Moreover, the concentrations of METH were significantly increased in cerebrospinal fluid as well as extracellular areas at the nucleus accumbens in OCT3-AS-treated rats. These results suggested that decreased OCT3 elevated the concentration of METH and/or DA in brain, subsequently enhancing dopaminergic neuronal transmission and increasing METH-induced hyperlocomotion. In summary, OCT3 at the CP could regulate the effect of METH by controlling the levels of METH and/or DA in brain. Thus, these results suggest that OCT3 may be a new molecular target to treat METH-related disorders such as drug abuse and schizophrenia.

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Abbreviations: OCT3, organic cation transporter-3; METH, methamphetamine; OCT3-AS, antisense against OCT3; OCT3-SCR, scrambled antisense against OCT3; PFC, prefrontal cortex; NAcc, nucleus accumbens; MPP^+, 1-methyl-4-phenylpyridinium; CP, choroid plexus; CSF, cerebrospinal fluid; HPLC, high performance liquid chromatography; AUC, area under the blood concentration time curve; DA, dopamine

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1. Introduction

Behavioral sensitization is characterized by the enhancement of locomotor responses to psychostimulant drugs, such as amphetamine (Paulson and Robinson, 1995; Mendrek et al., 1998) methamphetamine (METH) (Szumlinski et al., 2000; Davidson et al., 2001) and cocaine (Pierce et al., 1998; Beurrier and Malenka, 2002) when those drugs are repeatedly administrated. Several researchers have reported that behavioral sensitization to psychostimulant drugs was accompanied by neuronal adaptation in mesocorticolimbic regions, including the prefrontal cortex (PFC), ventral tegmental area and nucleus accumbens (NAcc) (Wolf et al., 1994; Cador et al., 1999; Brady et al., 2005). However, recently, we have found that rats with behavioral sensitization to METH have increased the brain penetration of METH together with the decreased expression of organic cation transporters-3 (OCT3) in the brain (Kitaichi et al., 2003; Fujimoto et al., 2007). Further study revealed that the polymorphisms of *SLC22A3*-coded OCT3 are related to the development of polysubstance use in Japanese patients with METH dependence (Aoyama et al., 2006). Thus, OCT3 might be an important molecule revealing behavioral sensitization to METH. However, the relationship between OCT3 and neuronal functions, including dopaminergic transmission, remains unknown.

OCT3 is expressed in several tissues including the placenta, intestine, heart and brain, and could transport several cations including dopamine (DA) as a sodium- and chloride-independent, transporter (Grundemann et al., 1997, 1998; Kekuda et al., 1998). It has been reported that specific transport of [^{3}H]MPP$^+$ could be inhibited by amphetamine and METH in OCT3-expressed cells, suggesting OCT3 could uptake METH instead of [^{3}H]MPP$^+$ (Wu et al., 1998) although there is no report demonstrating that amphetamine and METH are transported by OCT3. In the brain, OCT3 is highly expressed in the choroid plexus (CP) epithelial cells and circumventricular organs (Haag et al., 2004; Vialou et al., 2004; Amphoux et al., 2006; Gasser et al., 2006). It is well documented that CP plays an important role in detoxifying xenobiotics and endogenous waste by metabolic enzymes and efflux transport systems, which provide a barrier function between cerebrospinal fluid (CSF) and the blood circulation (blood–CSF barrier) to maintain the CNS condition (Ogawa et al., 1994; Kusuhara and Sugiyama, 2004). Additionally, circumventricular areas are implicated in the changes in blood osmolarity and ingestion of salt and water (Vialou et al., 2004), circadian pacemaker (Aston-Jones et al., 2001), and stress-related signal to the hypothalamic–pituitary–adrenal axis (Lowry et al., 2003). These reports suggest that OCT3 might regulate the influx/efflux of cationic compounds between CSF and blood circulation, similar to other influx/efflux transporters at CP epithelial cells (Kusuhara and Sugiyama, 2004), and/or by uptake into cells from extracellular areas, subsequently maintaining the brain functions, especially monoaminergic neuronal functions (Wu et al., 1998; Takeda et al., 2002; Graff and Pollack, 2004; Schildkraut and Mooney, 2004). This assumption is partially supported by recent reports. That is, Vialou et al. showed that salt-intake behavior was altered in OCT3-null mice and Gasser et al. showed that OCT3 regulated the transport of monoamines in dorsomedial hypothalamus (Vialou et al., 2004; Gasser et al., 2006). Moreover, our preliminary studies in mice demonstrated that antisense treatment against OCT3 (OCT3-AS) significantly increased METH-induced hyperlocomotion (Kitaichi et al., 2005).

The hypothesis that OCT3 in CP epithelial cells might play an important role in controlling METH-induced extracellular DA levels in NAcc and PFC is supported by our previous study demonstrating that infusion of OCT3-AS increased METH-induced hyperlocomotion (Kitaichi et al., 2005). Moreover, we expect to alter the distribution of METH in the brain by decrease in OCT3 expression with OCT3-AS, since the brain penetration of METH increased in behavioral sensitization to METH rats together with decreased expression of OCT3 in the brain (Kitaichi et al., 2005). Then, we estimated

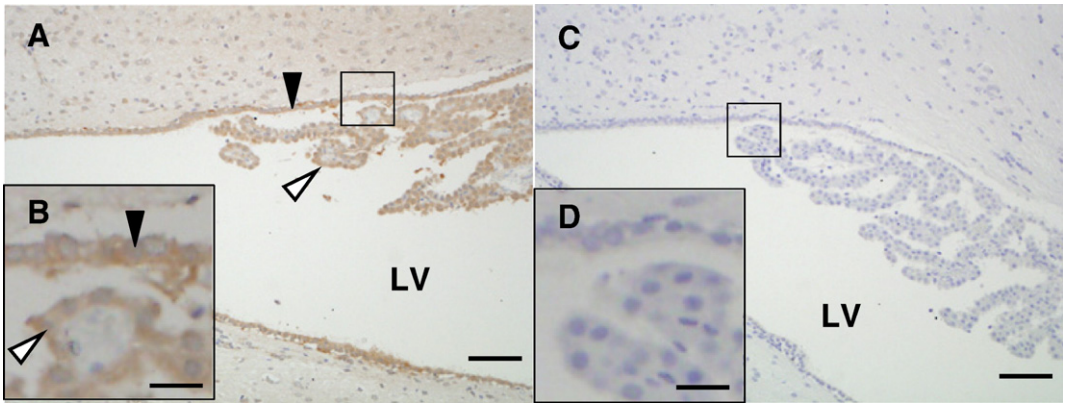

Fig. 1 – Immunohistochemical analysis of OCT3 in rat lateral ventricle (LV). The OCT3 positive signals in LV were detected in CP epithelial cells (white arrowheads) and ependymal cells (filled arrowheads) (A, B). The insert images indicate the higher magnification in black line box (B, D). The OCT3 positive signals were eliminated by incubation of anti-OCT3 antibody with OCT3 blocking peptide (C, D). Scale bars represent 200 μm (A, C), 20 μm (B, D).