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Shati/Nat8l knockout mice show behavioral deficits ameliorated by atomoxetine and methylphenidate

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ABSTRACT

We previously identified a novel molecule, SHATI/NAT8L, as having an inhibitory effect on methamphetamine dependence. We generated *Shati/Nat8l* knockout (KO) mice and found that they showed neurochemical changes and behavioral abnormalities related to attention deficit/hyperactivity disorder (AD/HD). In this study, we assessed validities of the *Shati/Nat8l* KO mice as a new animal model for AD/HD through a behavioral pharmacology approach. We conducted a locomotor activity test in a novel environment, a cliff avoidance test, and an object-based attention assay using *Shati/Nat8l* KO mice at the ages of 4 and 8 weeks. We found that at the ages of both 4 and 8 weeks, *Shati/Nat8l* KO mice showed hyperactivity in locomotor activity test, shortened jumping latency in cliff avoidance test, and lower recognition index in object-based recognition test. Moreover, we evaluated the effects of atomoxetine (ATX) and methylphenidate (MPH) on the behavioral deficits in *Shati/Nat8l* KO mice. As the result, almost all behavioral deficits were improved by the treatment of both ATX and MPH. Our findings suggest that *Shati/Nat8l* KO mice have an impaired neural system similar to AD/HD pathophysiology. *Shati/Nat8l* KO mice might serve as a novel and a useful animal model for the pathophysiology of AD/HD.

1. Introduction

Attention deficit/hyperactivity disorder (AD/HD) is a neurodevelopmental disorder with a prevalence of 5.0–7.1% in children and adolescents worldwide [1,2]. Patients with AD/HD show developmentally abnormal levels of hyperactivity, impulsivity, and inattention [3,4]. Prospective follow-up studies have found that the symptoms in approximately 50% of children with AD/HD persisted into adulthood [5–7]. Some epidemiologic studies have estimated a high heritability of 60–90% [8], suggesting that AD/HD is strongly related to genetic background. Despite these genetic evidences, specific genes and gene sets causally linked to AD/HD remain to be elucidated.

A number of studies have revealed dopaminergic impairments in AD/HD patients. Some genetic studies showed that genetic variations in dopamine transporter (DAT) and dopamine (DA) receptor D4 are associated with AD/HD [9,10]. Moreover, an imaging study using positron emission tomography (PET) found that AD/HD is associated with reduced levels of DAT and DA D2/D3 receptor availability in some brain regions such as the nucleus accumbens (NAC) [11–13]. DAT knockout (DAT-KO) mice have been thoroughly investigated as a genetic animal model for AD/HD. They have been demonstrated to display high levels of spontaneous locomotion activity in a novel environment [14] and impulsive behavior in the cliff avoidance test [15], and exhibit persistently and profoundly elevated extracellular DA levels in the striatum (STR) and the NAC, but not the prefrontal cortex (PFC) [16]. Moreover, the impairment of dopaminergic transmission in AD/HD is supported by pharmacological evidence that AD/HD symptoms can be improved by treatment with methylphenidate (MPH), which acts

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Table 1
Dopaminergic function in *Shati/Nat8l* KO mice.

	Shati/Nat8l KO mice dopaminergic function[1]	Effect on synaptic DA[2]	
		ATX	MPH
PFC	Hypofunction ↑ - Decreased DA turnover	↑	↑
NAC	Hyperfunction ↓ - Increased basal DA level - Increased DA release after METH administration - Increased DA turnover	—	↑

↑: increase, ↓: decrease, —: no change.
[1] Toriumi et al. 2015.
[2] Bymaster et al. 2002.

by blocking the DAT and noradrenaline transporter (NAT).

We have previously identified SHATI/NAT8L as a novel inhibitory factor against methamphetamine (METH) dependence, one of the most well-known abusive drugs [17,18]. Downregulation of *SHATI/NAT8L* by the treatment of its antisense oligonucleotide led to an elevated synaptic DA concentration in the NAC and major behavioral manifestations in mice, including heightened locomotor activity, increased rate of sensitization development, and conditioned place preference (CPP) responses to METH. Furthermore, we previously generated *Shati/Nat8l* KO mice [19] and demonstrated that they showed significantly increased DA turnover and basal levels of extracellular DA in the NAC. The DA release after METH treatment was also significantly increased in the NAC of *Shati/Nat8l* KO mice [20]. Consistent with these findings, *Shati/Nat8l* KO mice displayed hyperlocomotion in a habituated environment and enhanced METH-induced sensitization and CPP [21]. These results strongly suggest that *Shati/Nat8l* KO mice have dopaminergic abnormalities (Table 1), which may lead to behavioral deficits.

Behavioral abnormalities such as hyperlocomotion and neurochemical changes such as decreased DA reuptake observed in *Shati/Nat8l* KO mice appear to be similar to those observed in other animal models for AD/HD, such as DAT-KO mice. Thus, in the present study, we assessed the validity of *Shati/Nat8l* KO mice as a new animal model for AD/HD. In addition to the basal hyperactivity under a novel environment, we found that *Shati/Nat8l* KO mice showed shortened jumping latency in cliff avoidance test and lower recognition index in object-based recognition test. Moreover, these behavioral deficits were ameliorated by treatment with therapeutic agents for AD/HD, MPH and atomoxetine (ATX). These findings suggest that the behavioral impairments of *Shati/Nat8l* KO mice might be caused by an impaired neural system similar to AD/HD pathophysiology.

2. Materials and methods

2.1. Animals

Adult C57BL/6J *Shati/Nat8l* KO mice exhibiting behavioral deficits were used in this study, as previously reported [19]. *Shati/Nat8l* wild-type (WT) littermates were used as controls. They were housed in plastic cages and maintained in a regulated environment (25 °C ± 1 °C, 50% ± 5% humidity) in a 12 h light/dark cycle (lights switched on at 8:00 AM and off at 8:00 PM). Food (CE2; Clea Japan Inc.) and tap water were available ad libitum.

The experimental procedures were approved by the Animal Experiment Committee of Meijo University (YakuJitsu-No. 10 (2011); 12 (2012); 25 (2013); PE-9 (2014); PE-25 (2015); PE-11 (2016)). Procedures involving animals and their care were conducted according to international guidelines (National Research Council Committee 2011).

2.2. Locomotor activity test

The locomotor activity test was performed as described previously with minor modifications [21,22]. Locomotor activity was measured when mice were aged 4 and 8 weeks. Mice were placed individually in a transparent acrylic cage with a black frosted Plexiglas floor (W45 × D26 × H40 cm). The locomotor activity was measured at

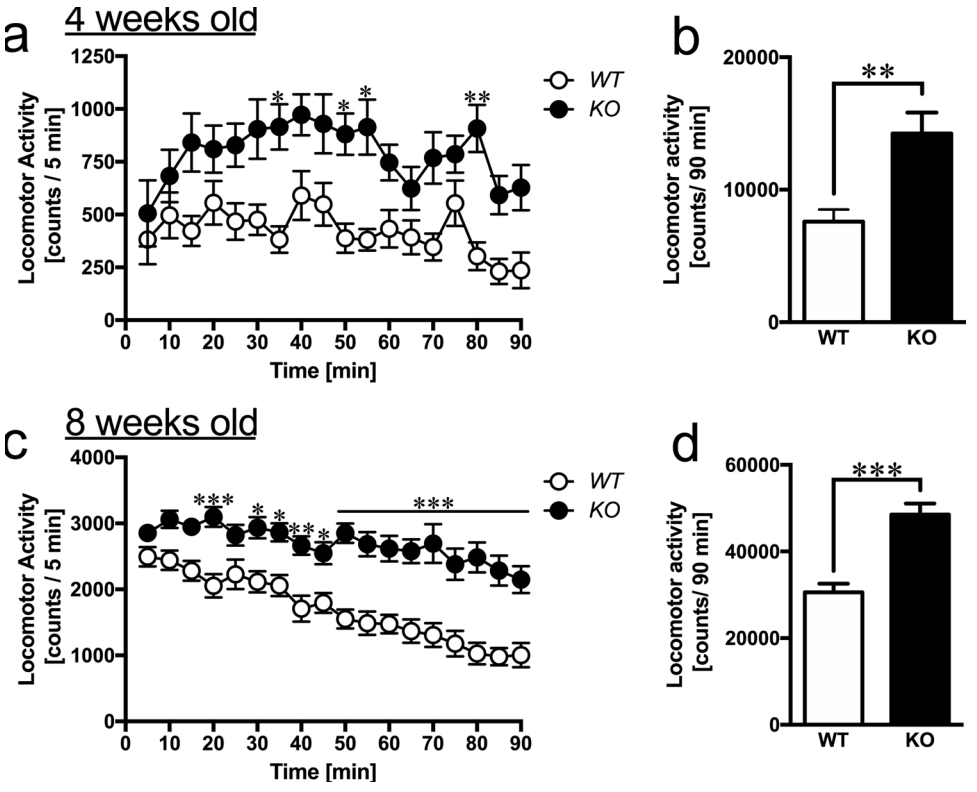

Fig. 1. Hyperlocomotion in *Shati/Nat8l* KO mice.
Locomotor activity test was conducted at the ages of 4 and 8 weeks. At 4 weeks, (a) time course of locomotor activity [Two-way ANOVA with repeated measurements: $F_{Interaction(17,544)} = 1.36$, $p > 0.05$; $F_{Time(17,544)} = 3.47$, $p < 0.001$; $F_{Genotype(1,32)} = 10.5$, $p < 0.05$] and (b) the total locomotor activity in WT and *Shati/Nat8 l* KO mice were shown (N: WT/KO = 14/20). At 8 weeks, (c) time course of locomotor activity [Two-way ANOVA with repeated measurements: $F_{Interaction(17,493)} = 3.14$, $p < 0.001$; $F_{Time(17,493)} = 17.6$, $p < 0.001$; $F_{Genotype(1,29)} = 30.8$, $p < 0.001$] and (d) the total locomotor activity in WT and *Shati/Nat8l* KO mice were shown (N: WT/KO = 14/20). $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ using an unpaired *t*-test.
Note: WT, wild-type; KO, knock out; ANOVA, analysis of variance

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