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Short Communication

Catecholaminergic neuronal network dysfunction in the frontal lobe of a genetic mouse model of schizophrenia

Iritani S, Sekiguchi H, Habuchi C, Torii Y, Kuroda K, Kaibuchi K, Ozaki N. Catecholaminergic neuronal network dysfunction in the frontal lobe of a genetic mouse model of schizophrenia.

Background: The precise aetiology of schizophrenia remains unclear. The neurodevelopmental hypothesis of schizophrenia has been proposed based on the accumulation of genomic or neuroimaging studies.
Objective: In this study, we examined the catecholaminergic neuronal networks in the frontal cortices of disrupted-in-schizophrenia 1 (DISC1) knockout (KO) mice, which are considered to be a useful model of schizophrenia.
Methods: Six DISC1 homozygous KO mice and six age-matched littermates were used. The animals' brains were cut into 20-μm-thick slices, which were then immunohistochemically stained using an anti-tyrosine hydroxylase (TH) monoclonal antibody.
Results: The TH-immunopositive fibres detected in the orbitofrontal cortices of the DISC1 KO mice were significantly shorter than those seen in the wild-type mice.
Conclusion: These neuropathological findings indicate that the hypofrontal symptoms of schizophrenia are associated with higher mental function deficiencies or cognitive dysfunction such as a loss of working memory.

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Keywords: animal model; DISC1; frontal lobe; schizophrenia; tyrosine hydroxylase

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Significant outcome

- Impaired catecholaminergic neuronal networks were detected in a genetic mouse model of schizophrenia.
- The hypofrontality exhibited by schizophrenic symptoms might be related to neuronal network deficits.

Limitations

- This paper only describes the neuropathological findings obtained in a genetically altered model mouse of schizophrenia; that is, it does not describe behavioural observations.
- The findings of this study should be verified in human schizophrenic brains.

Introduction

Despite the fact that schizophrenia is a common neuropsychiatric disease and great effort has been made to elucidate its pathophysiology, the pathogenesis of the condition remains unknown. The neurodevelopmental hypothesis, which suggests that the pathogenesis of schizophrenia involves deficits in

neuronal transmission, synaptic function, neuronal network formation, and/or neuronal migration during growth or maturation, etc., is supported by the findings of many biological studies (1). However, no definitive neuropathological findings that are specific to the schizophrenic brain have been identified. One reason for this is that various confounding factors affect post-mortem human brains including the state of the brain in the agonal stage; coexisting physical disease; and the use of neuroleptic drugs, which can affect the neuropathological condition of brain tissue (2). To overcome these problems, studies involving animal models with clearly defined biological backgrounds that are not affected by such confounding factors would be useful, as their findings could provide clues about the pathophysiology of schizophrenia.

Genetic investigations of the pathogenesis of schizophrenia have identified several candidate genes. Most of these candidate genes play a role in neurodevelopmental functions including neuronal migration/differentiation, neuronal network formation, or neuronal fibre extension, etc., in the central nervous system (CNS) (3). Disrupted-in-schizophrenia 1 (DISC1) is potent candidate gene for schizophrenia and was found to co-segregate with major mental illnesses in a Scottish family (4). An *in vitro* study indicated that DISC1 is involved in neurogenesis, neuronal migration, and neuronal network formation (5). DISC1 might also play a role in the development of the cerebral cortex, and it was suggested that the loss of DISC1 function might underlie the neurodevelopmental dysfunction seen in schizophrenia (6). DISC1 plays important roles in neuronal formation, and the loss of DISC1 function might contribute to neuropsychiatric disease. In addition, a molecular brain imaging study detected subcortical dopaminergic deficits in a DISC1 mutant animal model (7).

Many kinds of animal models have been developed for use in studies of the pathogenesis of schizophrenia, including genetically modified, pharmacologically treated, and environmentally stressed animal models. From the point of view of examining the neurodevelopmental hypothesis, genetically modified animal models in which DISC1 is targeted are considered to be a useful model of schizophrenia (8). In addition, various kinds of mutant mice have been used to elucidate the function of DISC1 during the neurodevelopment of brain tissue. For example, a mutant mouse containing a single nucleotide polymorphism in the DISC1 gene exhibited altered brain cortex development (during histological examinations). However, it did not display any gross brain phenotypes or behavioural abnormalities (9). Little is known concerning how DISC1 influences the development of neuronal networks or brain tissue maturation. Previous studies have suggested that DISC1 might act by regulating Wnt signaling through glycogen synthase kinase 3β (10,11) or interacting with DIX (Dishevelled-Axin) domain containing-1 (12). Furthermore, another study indicated that DISC1 activity is essential for postnatal dopaminergic maturation in the frontal cortex and the normalisation of behavior during the pre- and perinatal stages of development (13).

In the clinical setting, frontal lobe impairments, including cognitive deficits and negative symptoms, are important targets for treatment in schizophrenia (14), and neuroimaging studies have indicated that the orbitofrontal cortex plays an important role in the development of severe negative symptoms in schizophrenic patients (15). The orbitofrontal cortex is considered to be involved in cognitive processing and decision-making, and dysfunction of this region might play a role in human neuropsychiatric disorders. On the other hand, tyrosine hydroxylase (TH) is a catecholaminergic marker, and catecholamines such as dopamine and noradrenaline are closely associated with the pathophysiology of schizophrenia (16).

In this study, we used mutant mice that lacked exons 2 and 3 of the DISC1 gene. The mice were produced by homologous recombination in embryonic stem cells. These mutant mice are viable and fertile, and do not exhibit any gross anatomical abnormalities. However, they do display some electrophysiological abnormalities; that is, long-term potentiation (17). Most of these characteristics resemble the clinical features of schizophrenic patients. Moreover, these mutant mice exhibit some gender-specific differences in neuronal development (18); thus, we also investigated whether there were any gender differences in the examined parameters.

Aim of the study

We examined the catecholaminergic neuronal networks in the orbitofrontal cortices of genetically modified DISC1 knockout (KO) mice using an immunohistochemical technique involving the use of an anti-TH antigen. In particular, we focused on the middle layer of the orbitofrontal cortex, where interneurons are abundant. We considered that a neuropathological investigation of the TH-positive neuronal structures present in this animal model might aid the elucidation of the pathogenesis of schizophrenia. In addition, we examined the density of TH-positive fibres according to gender and the density of TH-positive neurons in the ventral tegmental area (VTA), which is one of the major nuclei of origin.

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Materials and methods

Subjects (animal model)

A total of 12 mice were used in this study. Six 15-week-old DISC1 homozygous KO (–/–) mice (three males and three females) and the same number of age-matched littermates (wild-type) (three males and three females) were used. All of the mice were bred and maintained under the same conditions. The mice were placed under deep anaesthesia and then perfused with a tissue fixative solution (4% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4). After the perfusion procedure, their brains were immediately removed. There was no significant difference (p-value > 0.05) between the brain weights of the wild-type (mean: 0.61 ± 0.12 g) and DISC1 KO mice (mean: 0.59 ± 0.09 g). The prefrontal regions were cut into 20-μm-thick coronal sections on a cryostat. All animal experiments were performed according to the guidelines for animal experiments of Nagoya University. All efforts were made to minimise the suffering of the animals used in this study and to reduce the number of animals used.

Immunohistochemistry

TH. The brain sections were rinsed in Tris-buffered saline [0.1 M Tris-HCl (pH 7.4) and 0.9% NaCl] containing 0.3% Triton X-100 and 2% normal goat serum for 30–60 min at room temperature. An anti-TH monoclonal antibody was employed as the primary antibody in this study (catalogue no. MA1-18038, lot no. #1381031, dilution 1 : 4000; Thermo Fisher Scientific, Waltham, MA, USA). The brain sections were incubated with the primary antibody for 48 h at 4°C. Avidin biotin complex (ABC) staining was performed using the VECTASTAIN ABC system® (Vector Laboratories, Burlingame, CA, USA). Finally, the sections were reacted with the ImmPACT® DAB substrate (DAB peroxidase substrate kit; Vector Laboratories).

Measuring the lengths of TH-immunopositive fibres

Immunostained coronal brain sections were observed under a light microscope (Figs 1c and d). A digital image of each specimen was taken using a microscopic digital camera (Digital DP72; Olympus, Shinjuku, Tokyo, Japan). We arbitrarily placed two square regions of interest (width: 100 μm) on the middle layer of the anterior medial orbitofrontal cortex of each specimen (Fig. 1a). We extracted the immunopositive fibres from the digital images using the ImageJ 1.41 software package (free software provided by NIH: http://www.rsb.info.nih.gov/ij/) (Fig. 1b). We extracted the immunopositive fibres using the same detection threshold level in each specimen. The lengths of the TH-positive fibres in each region of interest were measured using a digital map meter (FS-DSC101; Firestar, Japan). All measurements were performed in a blinded manner. The total length of the TH-positive fibres in each region of interest was then calculated, and the difference in total TH-positive fibre length between the DISC1 KO and wild-type mice was examined using the Mann–Whitney U-test. We also investigated fibre length in each gender in the same manner in order to examine the gender-dependency of our finding. In addition, we counted the number of TH-positive neurons that were present in a 200-μm square of the VTA to investigate the condition of the nuclei of origin (Fig. 1d). Neurons that contained a clearly defined nucleus were regarded as TH-positive neurons.

Results

The DISC1 KO mice exhibited a significantly shorter total TH-positive fibre length than the wild-type mice. The total TH-positive fibre length was 420.58 ± 16.97 μm in the DISC1 KO mice and 675.17 ± 22.95 μm in the wild-type mice ($p < 0.01$) (Fig. 2a). This indicated that the DISC1 KO mice possessed fewer and/or shorter TH-positive neuronal fibres than the wild-type mice, which might mean that the TH-positive neuronal networks in the frontal cortex developed defectively in the DISC1 KO mice. In addition, the total TH-positive fibre length of the DISC1 KO mice was significantly shorter than that of the wild-type mice in both genders ($p < 0.01$) (638.67 ± 51.06 μm in the male wild-type mice versus 413.67 ± 73.72 μm in the male DISC1 KO mice; 711 ± 89.98 μm in the female wild-type mice versus 427.50 ± 45.34 μm in the female DISC1 KO mice). The total TH-positive fibre length did not differ significantly between the genders in the wild-type or DISC1 KO mice (Fig. 2b). There was no significant difference in the density of TH-positive neurons in the VTA between the wild-type and DISC1 KO mice (14.4 ± 3.3 neurons/200-μm square in the wild-type mice versus 13.2 ± 3.1 neurons/200-μm square in the DISC1 KO mice) (Fig. 2c).

Discussion

In the present study, we found that DISC1 KO mice have shorter and/or fewer TH-positive neuronal fibres in their frontal cortices than wild-type mice; however, they possess the same number of TH-positive cells in their VTA. This study also obtained evidence that the TH-positive neuronal fibres in the middle layer of the medial orbitofrontal cortex develop defectively in DISC1 KO mice, although

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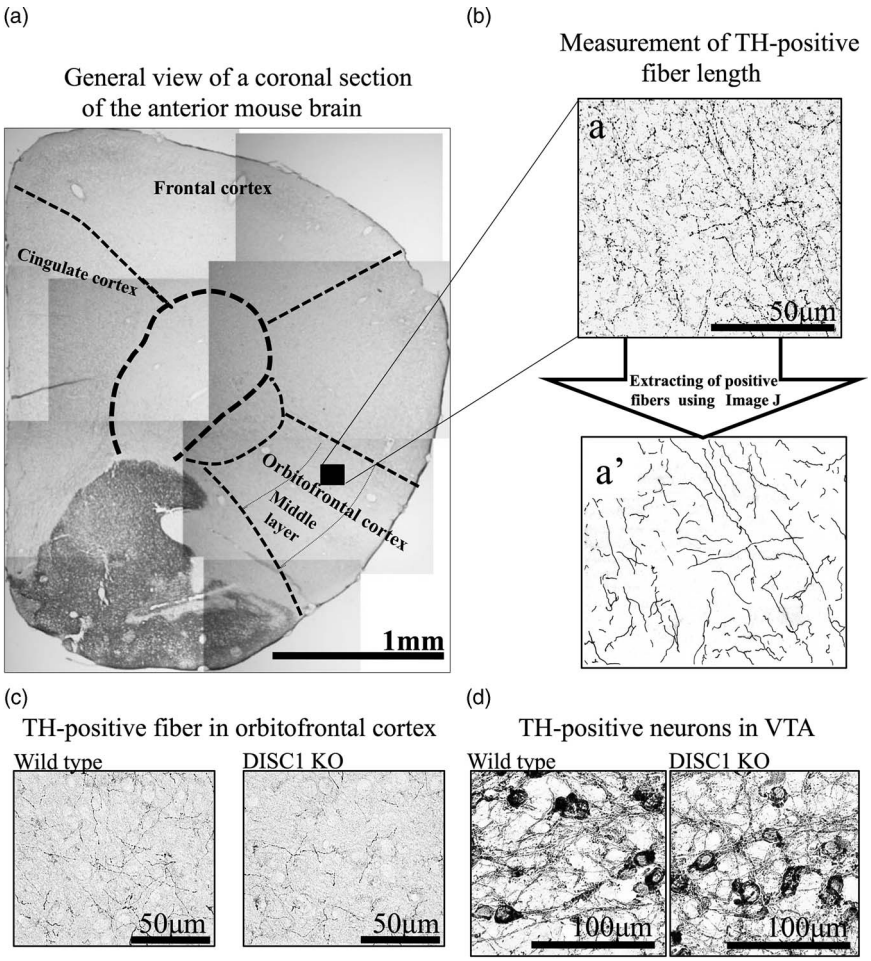

Fig. 1. (a) General view of a coronal section of the anterior mouse brain. The middle layer of the orbitofrontal cortex (OFC) contained the region of interest. In each animal's brain, we randomly placed two square regions of interest (width: 0.1 mm) in the middle layer of the OFC (the black square is shown as an example). (b) Measurement of tyrosine hydroxylase (TH) positive fibre length. We took digital images of immunostained specimens from the disrupted-in-schizophrenia 1 knockout (DISC1 KO) and wild-type mice using a microscopic digital camera (DP72; Olympus, Japan) (a). TH-positive fibres were extracted from these digital images using the ImageJ 1.41 software package (a'). In figure a', the length of each TH-positive fibre was manually measured using a digital map meter. Then, the total length of all TH-positive fibres in each region of interest was calculated. (c) Photomicrographs of TH-positive fibres in specimens obtained from wild-type (left) and DISC1 KO mice (right). (d) Photomicrographs of TH-positive neurons in specimens obtained from wild-type (left) and DISC1 KO mice (right). VTA, ventral tegmental area.

previous studies have detected marked interneuronal activity in this area of the frontal cortex. TH-positive fibres are considered to be a constitutive part of the interneuronal circuits within the frontal cortex. In previous studies, it was suggested that a deficit of interneurons in the frontal cortex; that is, a neuronal network deficit, might be one of the pathogenic mechanisms responsible for schizophrenia (19). In this study, we did not detect any gender-dependent differences in the density of TH-positive fibres in the frontal cortex, which disagrees with the findings of previous studies. For example, gender-specific histological alterations were observed in the hippocampal GABAergic neuronal network, and the level of methamphetamine-induced DA release in the nucleus accumbens was also reported to vary according to gender (18). Taking these findings together with ours, the actions of DISC1 in each brain region might be gender-dependent, and a deficiency of DISC1 could accentuate gender-dependent sensitivity to psychostimulants (20).

TH and schizophrenia

TH is the rate-limiting enzyme in the production of catecholamines including dopamine, and alterations in dopamine regulation have been suggested to be involved in the pathogenesis of schizophrenia (21). Our results suggest that catecholaminergic neuronal network malformation occurs in the frontal cortices of animal models of schizophrenia. We previously

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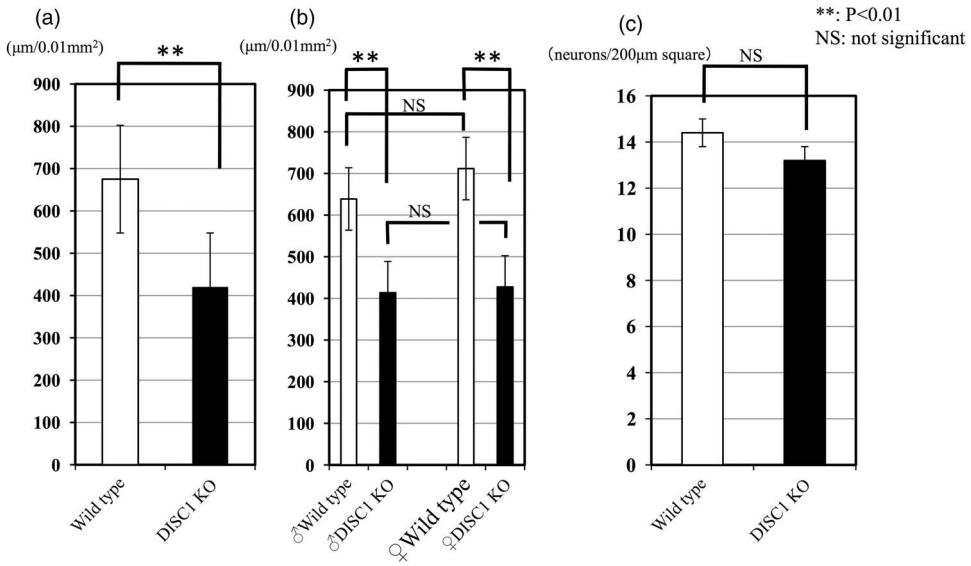

Fig. 2. (a) Total tyrosine hydroxylase (TH) positive fibre length. The disrupted-in-schizophrenia 1 knockout (DISC1 KO) mice displayed a significantly shorter total TH-positive fibre length than the wild-type mice ($p < 0.01$). (b) Total TH-positive fibre length according to gender. The total TH-positive fibre length of the DISC1 KO mice was significantly shorter than that of the wild-type mice in both genders ($p < 0.01$), and there were no significance differences between the total TH-positive fibre lengths of the male and female mice in either the wild-type or DISC1 KO mice. (c) The number of TH-positive neurons in the ventral tegmental area did not differ significantly between the wild-type and DISC1 KO mice.

detected the same phenomenon in another mouse model of schizophrenia (22).

Some reports have indicated that TH itself contributes to the aetiology of schizophrenia (23), and mutations in the TH gene have been shown to affect the clinical symptoms of the condition including patients' cognitive abilities (24) and the risk of suicide (25). Thus, TH might play a role in the pathogenesis of schizophrenia, and dopamine could be a particularly important mediator of the symptoms of the condition.

The function of DISC1 and animal models of schizophrenia

The aetiology of schizophrenia is considered to be multifactorial and to involve both genetic and environmental factors. A number of candidate genes that are considered to contribute to the pathogenesis of schizophrenia have been identified in molecular biological studies. Many of these candidate genes have been suggested to play important roles in the neuronal maturation of the CNS. DISC1 is one of these candidate genes and was originally identified at the breakpoint of a chromosomal translocation found in a rare case series of familial schizophrenia (4). Based on these clinical findings, DICS1 KO mice are considered to be a useful genetic animal model for studying schizophrenia. Previous studies have suggested that DISC1 plays important roles in the pathogenesis of schizophrenia (26). The DICS1 gene is considered to be involved in the neurogenesis of the CNS, synapse formation, axonal targeting, oligodendrocyte differentiation, and interneuron elongation, etc. (27). DISC1 might also contribute to the formation of neuronal networks composed of TH-positive fibres in the frontal cortex, as was suggested in the present study. These findings strongly support the neurodevelopmental hypothesis of schizophrenia.

Hypofrontality in schizophrenia

Examinations of frontal cortex function; that is, executive function, are considered to be important for assessing the prognosis of schizophrenia patients (28). A hypodopaminergic state in the frontal cerebral cortex might induce hypobulia, a lack of motivation, and a flattening of affect, etc., which frequently occur as negative symptoms of schizophrenia (29). The decline of working memory in schizophrenia has also been described as a frontal function deficit. Assuming that schizophrenia involves the maldevelopment of TH-positive neuronal networks in the frontal cortex and frontal function deficits, a hypodopaminergic state might be one of the core pathophysiologies of the disease. The various neurotransmitters found in the CNS are intricately involved with each other; therefore, a hypodopaminergic state would result in the abnormal development of neuronal structures associated with other neurotransmitters, which could cause a variety of clinical symptoms. Studies of DISC1 might help to identify novel drug targets and aid

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the development of more relevant animal models of schizophrenia for compound testing.

Future directions

To further our knowledge about the aetiology of schizophrenia, it would be useful to determine whether neuropathological findings acquired using genetically modified model animals can be applied to the clinical setting. The neuronal findings obtained in the present study might provide significant clues about the pathophysiology of schizophrenia. Therefore, we should develop methods that would make it possible to investigate whether the phenomena observed in the present animal model are replicated in the brains of schizophrenic patients. In addition, it was suggested that investigating the relationship between the neuropathology and genetics of schizophrenia would improve our understanding of the disorder at the neurological systems level (30). We hope that this study will also help to bridge the gap in translational psychiatry between experimental neuropathological findings and clinico-neuropathological observations of the human brain.

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Conflicts of Interest

The authors have no conflicts of interest.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals.

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