NSC-induced D-neurons are decreased in striatum of schizophrenia: Possible cause of mesolimbic dopamine hyperactivity

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ABSTRACT

Neural stem cell (NSC) hypofunction is an etiological hypothesis of schizophrenia. Although dopamine (DA) dysfunction is also a widely accepted hypothesis, molecular background of mesolimbic DA hyperactivity has not yet been well known. Here, the author proposes “D-cell hypothesis”, accounting for molecular basis of mesolimbic DA hyperactivity of schizophrenia, by NSC hypofunction and decrease of putative NSC-induced D-cells. The “D-cell” is defined as “non-monoaminergic aromatic L-amino acid decarboxylase (AADC)-containing cell”. D-cells produce trace amines, and also take up amine precursors and convert them to amines by decarboxylation. The author reported “dopa-decarboxylating neurons specific to the human striatum”, that is, “D-neurons” in the human striatum, and decrease of striatal D-neurons in patients with schizophrenia. Trace amine-associated receptor, type 1 (TAAR1), a subtype of trace amine receptors, having a quite number of ligands such as tyramine, β-phenylethylamine (PEA) and methamphetamine, has modulating functions on monoamine neurons. It has been known that reduced binding of ligands to TAAR1 receptors on DA terminal of DA neurons of the midbrain ventral tegmental area (VTA) increased firing frequency of VTA DA neurons. In brains of schizophrenia, NSC hypofunction in the subventricular zone of lateral ventricle may cause decrease of D-neurons in the striatum and nucleus accumbens, and may result in decrease of trace amine signals. Decrease of trace amine signals to TAAR1 on VTA DA neurons may increase firing frequency of VTA DA neurons, and may finally cause mesolimbic DA hyperactivity. Increased stimulation to DA D2 receptors of NSCs might suppress NSC proliferation, and may induce additional mesolimbic DA hyperactivity as well as D-cell decrease. This novel theory, “D-cell hypothesis”, possibly explains mesolimbic DA hyperactivity in pathogenesis of schizophrenia.

Keywords: Dopamine; D-Neuron; Ventral Tegmental Area; Schizophrenia; TAAR1

1. INTRODUCTION

Dopamine (DA) dysfunction [1,2], glutamate dysfunction [3,4], or neurodevelopmental deficits [5-8] are widely accepted hypotheses for etiology of schizophrenia. Nevertheless, molecular mechanism of mesolimbic DA hyperactivity [1,2] as DA dysfunction has not yet been well known. In the present review, the author proposes “D-cell hypothesis”, for explaining mesolimbic DA hyperactivity of schizophrenia, in which neural stem cell (NSC) dysfunction, and decrease of putative NSC-induced D-cells [9] in the striatum and nucleus accumbens [10] are involved.

1.1. Is “D-Cell” NSC-Like Cell?

The “D-cell” was described, by Jaeger et al. [11] in 1983, in the rat central nervous system, and was defined “non-monoaminergic aromatic L-amino acid decarboxylase (AADC)-containing cell” [11]. D-cells produce trace amines [12,13], and may also act as an APUD (amine precursor uptake and decarboxylation) system that takes up amine precursors and converts them to amines by decarboxylation [14]. The localizations of D-cells were specified into 14 groups, from D1 (the spinal cord) to D14 (the bed nucleus of stria terminalis), in caudo-rostral orders of the rat central nervous system, using AADC immunohistochemistry [15,16]. In this usage of classification term, “D” meant decarboxylation. In rodents [14, 17,18], a small number of D-cells were described in the striatum, rostral to D14, and confirmed to be neurons by
electro-microscopic observation [14].

The author reported in 1997, “dopa-decarboxylating neurons specific to the human striatum [19-22]”, that is, “D-neurons” in the human striatum [21,23] (classified to be D15) [21], and later in 2003, the decrease of D-neurons in the striatum and nucleus accumbens of patients with schizophrenia [10,23]. The decrease of D-neurons must be caused by NSC hypofunction in the subventricular zone of lateral ventricle.

Whereas, it is known that the number of striatal D-neurons increased in parkinsonian model rats with unilateral 6OH-DA lesion in the substantia nigra, and the D-neurons synthesized DA after administration of L-dopa [18].

1.2. Trace Amine-Associated Receptor, Type 1 (TAAR1) Modulates DA Function

Since the cloning of trace amine receptors in 2001 [24,25], enormous efforts have been made for exploring signal transduction of these G-protein coupled receptors located on chromosome focus 6q23.1 [26]. The receptors have been shown to co-localize with dopamine or adrenaline transporters in monoamine neurons, and to modulate the functions of monoamines [27-29].

The trace amine-receptor, type 1 (TAAR1) has been shown to have a quite number of ligands, including tyramine, β-phenylethylamine (PEA), octopamine, and psychostimulants, for example, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA) and lysergic acid diethylamide (LSD) [24,26,30], and is now a target receptor for exploring novel neuroleptics [31,32].

TAAR1 knockout mice displayed schizophrenia-like behaviors, with a deficit in prepulse inhibition [33]. TAAR1 knockout mice showed greater locomotor response toamphetamine and released more DA (and noradrenaline) in response to amphetamine than wild type mice [33].

It has been clarified that signal increase to TAAR1 receptors on cell membranes of DA neurons in the midbrain ventral tegmental area (VTA) reduces firing frequency of VTA DA neurons [26,31,33].

1.3. D-Cell Hypothesis of Schizophrenia

In Figure 1, “D-cell hypothesis”, the novel theory for mesolimbic DA hyperactivity in pathogenesis of schizophrenia is outlined. In brains of patients with schizophrenia, NSC hypofunction in the subventricular zone of lateral ventricle [34-36] may induce reduction of D-neurons in the striatum and nucleus accumbens [10], and may result in decrease of trace amines. For example, the ventricular enlargement, noticed in brain imaging studies of schizophrenia, may be caused by NSC hypofunction of the subventricular zone of lateral ventricle [35,36].

The reduction of simulation to TAAR1 on VTA DA neurons may increase firing frequency of VTA DA neurons [31,32], and may cause mesolimbic DA hyperactivity.

DA hyperactivity in the striatum [1,2] might inhibit forebrain NSC proliferation by increasing the stimulation to DA D2 receptors [37], and may lead additional decrease of striatal D-neurons, which may induce additional hyperactivity of mesolimbic DA system.

2. Conclusion

Putative NSC-induced D-cells in the striatum, as trace amine producer, are clue to molecular basis of mesolimbic DA hyperactivity of schizophrenia. Further exploration of signal transduction of D-cells is essential.
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REFERENCES


