

Why D-neuron? Importance in schizophrenia research

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ABSTRACT

Recent pharmacological discovery on trace amine-associated receptor, type 1 (TAAR1) has emphasized importance of trace amines in pathogenesis of psychoses, such as schizophrenia. TAAR1 has many ligands, including tyramine, β -phenylethylamine (PEA), amphetamines, and 3'-iodothyronamine. So-called D-neurons are putative producer of trace amines, endogenous ligands of TAAR1. The D-neuron is defined "the aromatic L-amino acid decarboxylase (AADC)-containing neuron, but not dopaminergic nor serotonergic", *i.e.* not containing tyrosine hydroxylase nor tryptophan hydroxylase. AADC is an enzyme, also called dopa decarboxylase (DDC). The localization of D-neurons in the central nervous system has been specified into 15 groups, from the spinal cord (D1) to striatum (D15). We showed the decrease of D-neurons in D15 in postmortem brains of schizophrenia, where midbrain dopamine (DA) neurons are heavily innervated. Decrease of D-neurons may cause reduction of trace amines in the striatum, and may also decrease stimulation of TAAR1 on striatal terminals of ventral tegmental area (VTA) DA neurons. This might increase firing frequency of VTA DA neurons, and causes DA hyperactivity in the striatum and nucleus accumbens. In the present article, the author introduces the novel theory, "D-cell hypothesis", for mesolimbic DA hyperactivity of schizophrenia. Some clinical and/or experimental evidences that support this hypothesis are mentioned. The D-neuron, as a trace amine producer, is a clue for elucidating pathogenesis of psychoses, as well as human mental functions. Thus, signal transduction of D-neurons should be investigated.

Keywords: Dopamine; D-neuron; Ventral Tegmental Area; Schizophrenia; TAAR1; Aromatic L-Amino Acid Decarboxylase

1. INTRODUCTION

Dopamine (DA) dysfunction [1,2], glutamate dysfunction

[3,4], neurodevelopmental deficits [5,6], or neural stem cell (NSC) dysfunction [7,8] are well-known hypotheses for etiology of schizophrenia. DA dysfunction hypothesis suggests that mesolimbic DA hyperactivity causes positive symptoms such as paranoid-hallucinatory state of schizophrenia [1,2]. It is also explained by the efficacy of DA D2 blocker for paranoid-hallucinatory state, and also by hallucinogenic acts of DA stimulants, including methamphetamine or amphetamine [1,2]. Glutamate dysfunction theory was induced by the fact that intake of phencyclidine (PCP), an antagonist of NMDA receptor, produces equivalent to negative symptoms of schizophrenia, such as withdrawal or flattened affect, as well as positive symptoms [3,4]. The neurodevelopmental deficits hypothesis implicates that schizophrenia is the consequence of prenatal abnormalities resulting from the interaction of genetic and environmental factors [5,6]. NSC dysfunction has also been shown to be a cause of schizophrenia [7,8].

Although mesolimbic DA hyperactivity [1,2] has been well documented in pathogenesis of schizophrenia, the molecular basis of this mechanism has not yet been detailed. In the present article, the author hypothesized the involvement of striatal D-neurons and trace amine-associated receptor, type 1 (TAAR1) in the pathogenesis of mesolimbic DA hyperactivity of schizophrenia [9].

2. D-NEURON

The "D-cell" was described, by Jaeger *et al.* [10] in 1983, in the rat central nervous system, and was defined "non-monoaminergic aromatic L-amino acid decarboxylase (AADC)-containing cells" [10]. Namely, the D-cells contain AADC but not dopaminergic nor serotonergic [10]. D-cells produce trace amines [11,12], 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 [13]. 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 [14,15]. In this usage of classification term, "D" means decar-

boxylation. In rodents [13,16,17], a small number of D-cells in the striatum were rostrally described and confirmed to be neurons by electron-microscopic observation [13].

I reported in 1997, “dopa-decarboxylating neurons specific to the human striatum [18-21]”, that is, “D-neurons” in the human striatum [20,22] (classified to be D15) [20], and later in 2003, and reduction of the number of D-neurons in the striatum and nucleus accumbens of patients with schizophrenia [9,22] (**Figure 1**). These neurons lacked the immunoreactivity for antibodies against tyrosine hydroxylase and tryptophan hydroxylase, indicating non-dopaminergic and non-serotonergic [10, 18,20].

3. TRACE AMINE-ASSOCIATED RECEPTOR, TYPE 1 (TAAR1)

Cloning of trace amine receptors in 2001 [23,24], elicited enormous efforts for exploring signal transduction of these G-protein coupled receptors whose genes are located on chromosome focus 6q23.1 [25]. The receptors

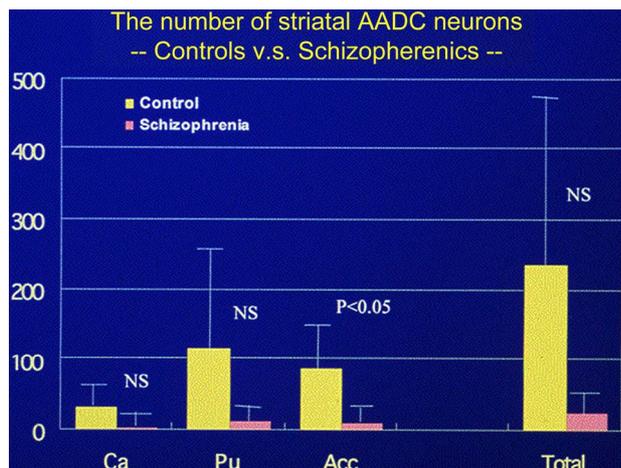


Figure 1. Number of D-neurons reduced in the striatum of post-mortem brains of patients with schizophrenia. As the average number of AADC-positive neurons per one section of 50 μ m thick in the striatum reduced in the brains with longer post-mortem period to death (PMI), analysis was performed using brain samples with PMI less than 8 hours. Controls: n = 5 (27 - 64 y.o.), Schizophrenics: n = 6 (51 - 78 y.o.) [9].

Table 1. Ligands of trace amine-associated receptor, type 1 (TAAR1) [23,25].

Trace amines	Tyramine, beta-phenylethylamine (PEA)
Other amines	d- and l-amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), 3-iodothyronamine (TIAM)
Catecholamine metabolites	3-Methoxytyramine(3-MT), 4-methoxytyramine (4-MT), normetanephrine, metanephrine
DAT blocker	Nomifensine
DA agonists	Apomorphine, bromocriptine
Hallucinogen	Lysergic acid diethylamide (LSD)

are shown to co-localize with dopamine or adrenaline transporters in monoamine neurons, and to modulate the functions of monoamines [26-28].

The trace amine-associated receptor, type 1 (TAAR1) has a large number of ligands, including tyramine, β -phenylethylamine (PEA) and psychostimulants, for example, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA) and lysergic acid diethylamide (LSD) [23,25,29] (**Table 1**), and is now a target receptor for exploring novel neuroleptics [30,31].

TAAR1 knockout mice showed schizophrenia-like behaviors, with a deficit in prepulse inhibition [32]. TAAR1 knockout mice showed greater locomotor response to amphetamine and released more DA (and noradrenaline) in response to amphetamine than wild type mice [32]. It has been shown that TAAR1 has a thermoregulatory function [33].

It was clarified that increased stimulation of TAAR1 receptors on cell membranes of DA neurons in the mid-brain ventral tegmental area (VTA) reduces firing frequency of VTA DA neurons [30-32].

4. A NEW “D-CELL HYPOTHESIS” OF SCHIZOPHRENIA (FIGURE 2)

A new theory, “D-cell hypothesis”, for explaining mesolimbic DA hyperactivity in pathogenesis of schizophrenia is shown in **Figure 2** [34-37].

In brains of patients with schizophrenia, dysfunction of NSC in the subventricular zone of lateral ventricle may cause the decrease of D-neurons in the nucleus accumbens [8,38]. This may lead to the decrease of the amounts of trace amines in the nucleus, though direct evidences have not yet been demonstrated. Enlargement of the lateral ventricle [39,40], a usual finding documented in brain imaging studies of schizophrenia, may also be due to dysfunction of NSC of the subventricular zone [7,8].

The reduction of TAAR1 stimulation on DA terminals of VTA DA neurons, caused by decrease of striatal trace amine synthesis, may increase the firing frequency of VTA DA neurons [30,32]. This may lead to the increase of DA release in the nucleus accumbens, that is, mesolimbic DA hyperactivity.

It has been shown that stimulation of D2 receptors on NSC in the striatum inhibited forebrain NSC proliferation [41]. Then, striatal DA hyperactivity may lead to additional decrease of D-neurons, which might induce additional hyperactivity of mesolimbic DA system by above mentioned mechanisms. Actions of D2 blocking agents in pharmacotherapy of schizophrenia might partially be explained by the decrease of inhibition to forebrain NSC proliferations. It might be consistent with the clinical evidences that D2 blocker is effective for long

term treatment of schizophrenia, and that serum concentration of brain derived neurotrophic factor (BDNF) is decreased in patients with schizophrenia [42].

5. CLINICAL AND/OR EXPERIMENTAL EVIDENCES SUPPORTING “D-CELL HYPOTHESIS”

In **Table 2**, clinical and/or experimental evidences for supporting this hypothesis were summarized.

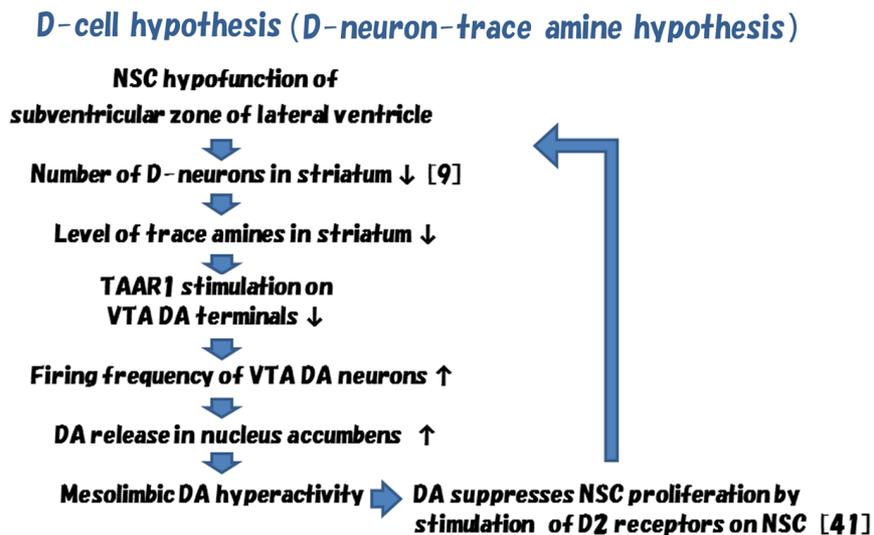


Figure 2. Scheme of D-cell hypothesis (D-neuron-trace amine hypothesis) of schizophrenia [34-37].

Table 2. Clinical and/or experimental evidences supporting “D-cell hypothesis” (D-neuron-trace amine hypothesis) of schizophrenia.

MAOB (=degrading enzyme of trace amines)
1. Striatal PEA be increased in MAOB knockout mice [43].
2. Therapeutic usage of MAOB inhibitor for hypersomnia. (Due to PEA increase?).
3. Higher methylation rate of MAOB gene in the nucleus accumbens of brains of patients with schizophrenia [44]. (Compensation for reduced trace amines?).
Neural stem cell (NSC)
1. NSC dysfunction hypothesis of schizophrenia.
2. Ventricular enlargement of brains of patients with schizophrenia.
3. D-neuron decrease in striatum and nucleus accumbens of patients with schizophrenia.
4. Reduced BDNF level in patients with schizophrenia [42].
Trace amine
1. Decrease of putative trace amine-producing neurons (=D-neurons) in post-mortem brains of schizophrenics.
2. Disturbance of sleep-wake-rhythm of patients with schizophrenia. (insomnia and/or daytime hypersomnia from clinical observation).
3. Decreased anxiety-related behaviors in PEA-elevated MAOB knockout mice [43].
4. “Phenylalanine hypothesis of affective behavior” by Sabelli & Mosnaim (1974) [45].
NSC suppression via DA D2 receptors on NSC
Preventive effects of chronic administration of D2 blocking agents for recurrent psychoses.

6. CONCLUSION

The D-neuron, *i.e.* the trace amine-producing neuron, and TAAR1 is a clue for pathogenesis of DA hyperactivity of schizophrenia. Exploration of signal transduction of the D-neuron is essential.

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