

# “D-cell hypothesis” of schizophrenia: Possible theory for mesolimbic dopamine hyperactivity

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## ABSTRACT

The author proposes a new “D-cell hypothesis” for mesolimbic dopamine (DA) hyperactivity of schizophrenia. The “D-cell” is defined as “non-monoaminergic aromatic L-amino acid decarboxylase (AADC)-containing cell”. D-cells produce trace amines, such as tyramine and  $\beta$ -phenylethylamine, and may also take up amine precursors and convert them to amines by decarboxylation. Trace amine-associated receptor, type 1 (TAAR1), a subtype of trace amine receptors, has a large number of ligands, including tyramine,  $\beta$ -phenylethylamine and methamphetamine, that influence on human mental states, and is now regarded to be a target receptor for novel neuroleptics. Recent studies revealed that the reduced stimulation of TAAR1 on DA neurons in the midbrain ventral tegmental area (VTA) increased firing frequency of VTA DA neurons. The author and her colleagues reported the decrease of D-neurons in the striatum and nucleus accumbens of postmortem brains of patients with schizophrenia. This may imply the decrease of trace amine synthesis, resulting the reduced stimulation of TAAR1 on terminals of midbrain VTA DA neurons, and may lead to mesolimbic DA hyperactivity in schizophrenia. The decrease of striatal D-neurons of postmortem brains of schizophrenia is supposed to be due to neural stem cell dysfunction in the subventricular zone of lateral ventricle. The decrease of striatal D-neurons and acts of TAAR1 signals on DA neurons might explain mesolimbic DA hyperactivity of schizophrenia.

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

## 1. INTRODUCTION

Dopamine (DA) dysfunction [1,2], glutamate dysfunction [3,4], neurodevelopmental deficits [5,6], or neural stem

cell 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, produce 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]. Neural stem cell 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-CELL

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-cell contains 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 convert 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 decarboxylation. 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].

### 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 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,  $\beta$ -phenylethylamine (PEA) and psychostimulants, for example, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA) and lysergic acid diethylamide (LSD) [23, 25,29], and is now a target receptor for exploring novel neuroleptics [30,31].

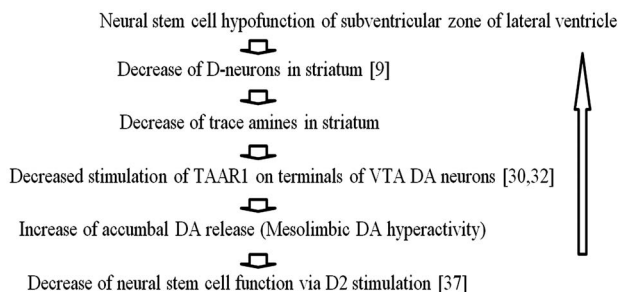
TAAR1 knockout mice showed schizophrenia-like behaviors, with a deficit in prepulse inhibition [32]. TAAR1 knockout mice showed greater locomotor response to amphetamine and released more DA (and norepinephrine) in response to amphetamine than wild type mice [32]. It has been shown that TAAR1 has a thermoregulatory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

A new theory, “D-cell hypothesis”, for explaining mesolimbic DA hyperactivity in pathogenesis of schizophrenia is shown in **Figure 1**.

In brains of patients with schizophrenia, dysfunction of neural stem cells in the subventricular zone of lateral ventricle may cause the decrease of D-neurons in the nucleus accumbens [8,34]. 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 [35,36], a usual finding documented in brain imaging studies of schizophrenia,



**Figure 1.** “D-cell hypothesis” of schizophrenia.

may also be due to dysfunction of neural stem cells of the subventricularzone [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 D2 stimulation of neural stem cells in the striatum inhibited forebrain neural stem cell proliferation [37]. 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 neural stem cell proliferations. It might be consistent with the clinical evidences that D2 blocker is effective for the treatment of schizophrenia.

### 5. CONCLUSION

The D-cell, the trace amine-producer, might be a clue for pathogenesis of DA hyperactivity of schizophrenia. Further exploration of signal transduction of the D-neuron is essential.

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