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Research Article

TAAR1 Ligands as Prospective Neuroleptics: From Research of So-Called D-Neuron (Trace Amine Neuron)

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Abstract

Recent pharmacological studies has been shown the importance of trace amine-associated receptor, type 1 (TAAR1), a subtype of trace amine receptors, as a prospective target receptor for novel neuroleptics. The author introduces so-called D-neuron (trace amine (TA)-producing neuron) research in psychiatric field. Although dopamine (DA) dysfunction is a well-known hypothesis of etiology of schizophrenia, its molecular basis has not yet been clarified. To explain this, modulating function of TAs on DA neurotransmission was noticed. The TAAR1 has a large number of ligands, including tyramine, β-phenylethylamine and methamphetamine that influence on human mental state. Reduced stimulation of TAAR1 on DA neurons in the midbrain ventral tegmental area (VTA) has been revealed to increase firing frequency of VTA DA neurons. Significant D-neuron decrease has been reported in the nucleus accumbens (Acc) of postmortem brains of patients with schizophrenia. This implies the decrease of TA synthesis and consequent TAAR1 stimulation reduction on terminals of midbrain VTA DA neurons, that leads to mesolimbic DA hyperactivity in schizophrenia. D-neuron decrease in Acc of postmortem brains, due to neural stem cell (NSC) dysfunction in the subventricular zone of lateral ventricle, might be pivotal in etiology of schizophrenia. The new "D-cell hypothesis (TA hypothesis)", in which D-neurons and TAAR1 are involved, is in agreement of recent reports showing effectiveness of TAAR1 ligands for schizophrenia model animals.

Keywords: Dopamine; D-neuron; Trace amine; Schizophrenia; TAAR1; Dopa Decarboxylase (DDC)

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 suggested that mesolimbic DA hyperactivity caused positive symptoms such as paranoid-hallucinatory state of schizophrenia [1,2] (Table 1A). It is also explained by the efficacy of DA D2 blockers 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] (Table 1A). 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 so-called D-neurons in the striatum and trace amine (TA)-associated receptor, type 1 (TAAR1) in the pathogenesis of mesolimbic DA hyperactivity of schizophrenia [9].

Table 1.

A. Schizophrenia

Symptoms

- Paranoid hallucinatory state
- Excitement
- Disorganized thought and "behavior, Hypobulia"
- Withdrawal
- Flattened affect
- Cognitive deficits
- Interpersonal and social deficits

Etiology

- Abnormality of neural network DA hypothesis
- Glutamate dysfunction
- Neurodevelopmental dysfunction
- NSC dysfunction

Schizophrenia susceptible genes

- DISC-1, Neureglin, Reelin, COMT, BDNF, Calcineurin, etc.

B. Trace amine (TA) -associated receptor, type 1 (TAAR1) [23, 25, 29]

Human

Chromosome locus 6q23.1

- Schizophrenia
- Bipolar Disorder

G protein-coupled receptor (GPCR)

Ligands

TAs

- Tyramine, tryptamine, octopamine, β-phenylethylamine (PEA)

Other amines

- *d*- and *l*-amphetamine
- methamphetamine
- 3,4-methylenedioxymethamphetamine (MDMA)
- 3-iodothyronamine (T1AM)

Metabolites of catecholamines

- 3-methoxytyramine (3-MT)
- 4-methoxytyramine (4-MT)
- normetanephrine, metanephrine

Dopamine transporter (DAT) blocker

- nomifensine

Dopamine (DA) agonist

- apomorphine, bromocriptin

Hallucinogen

- lysergic acid diethylamide (LSD)

D-neuron

The "D-cell" was described in 1983 in the rat central nervous system and was defined "the aromatic L-amino acid decarboxylase (AADC)-containing cell", but neither contains DA nor serotonin [10]. D-cells produce TAs [11,12], and may also act as an APUD (amine precursor uptake and decarboxylation) system that takes up amine precursors and transforms 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, the 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, the reduction of the number of D-neurons in the nucleus accumbens (Acc) of patients with schizophrenia [9,22] (Figure 1). Acc is partially overlapped with neural stem cell (NSC) area.

Trace Amine (TA)-Associated Receptor, Type 1 (TAAR1)

Cloning of TA 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] (Table 1B). The receptors have been shown to co-localize with dopamine or adrenaline transporters in monoamine neurons and to modulate the functions

of monoamines [26-28]. The TA-associated receptor, type 1 (TAAR1) having 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 1B), has become 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]. membranes of DA neurons in the midbrain ventral tegmental area (VTA) reduced firing frequency of VTA DA neurons [30-32].

A New "D-Cell Hypothesis" ("TA Hypothesis") of Schizophrenia (Figure 2)

A new theory, "D-cell hypothesis" ("TA hypothesis"), for explaining mesolimbic DA hyperactivity in pathogenesis of schizophrenia is shown in Figure 2. In brains of patients with schizophrenia, dysfunction of NSCs in the subventricular zone

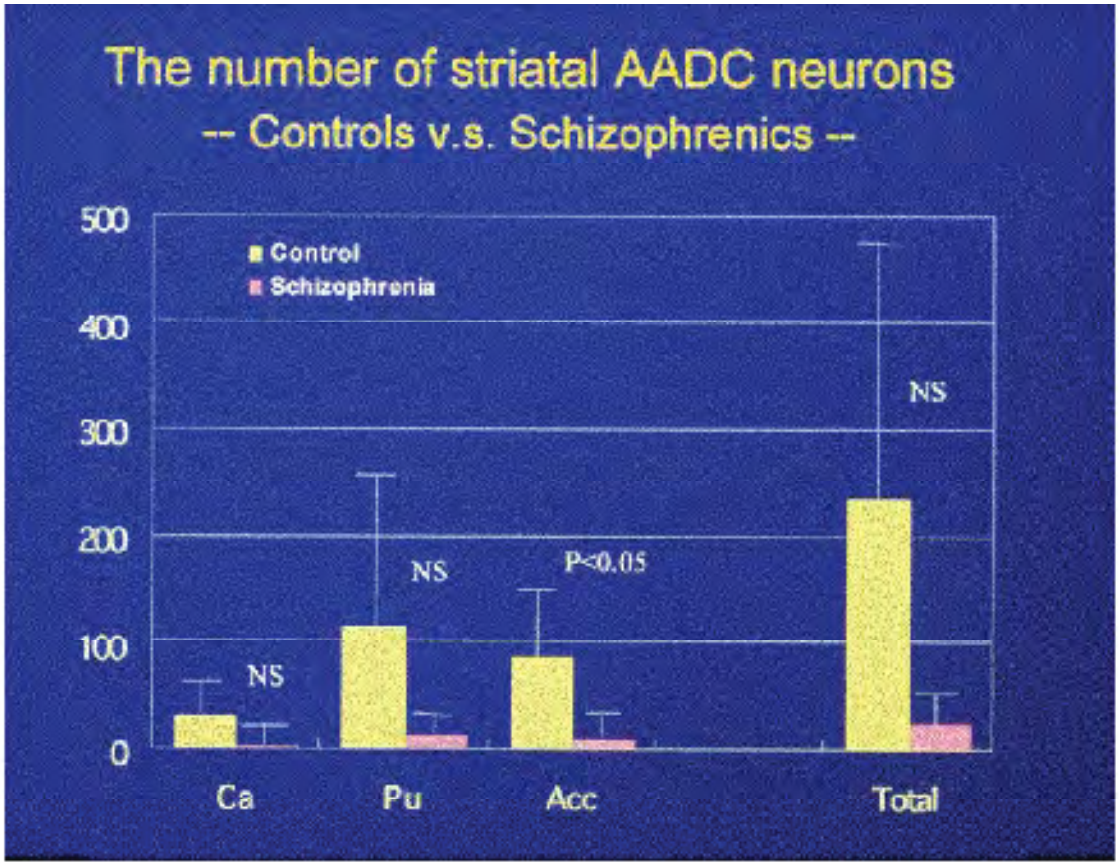
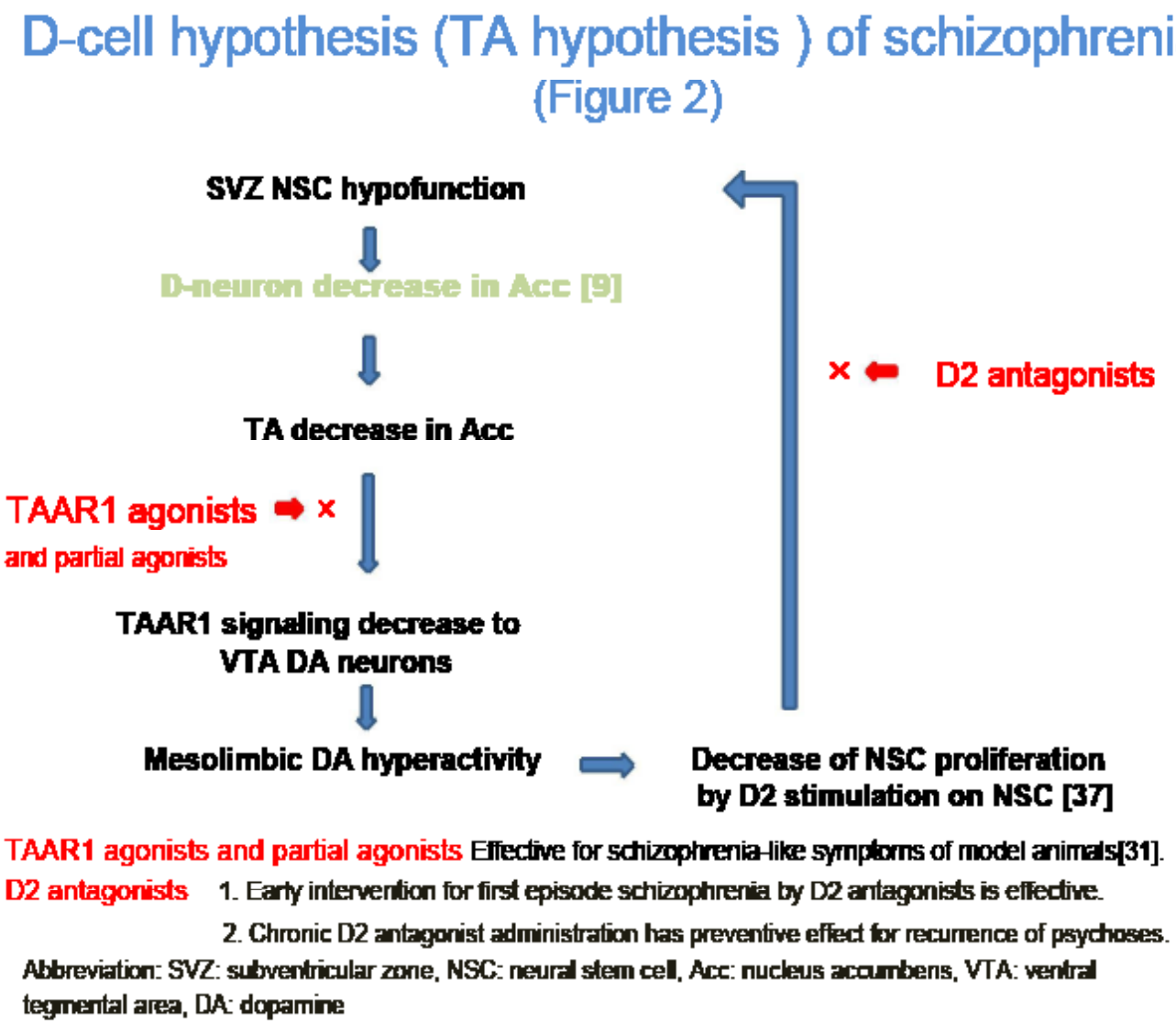


Figure 1. Number of D-neurons reduced in the Acc of post-mortem brains of patients with schizophrenia. As the average number of AADC-positive neurons per one section of 50 μm thick in the striatum reduced in the brains with longer postmortem period to death (PMI), analysis was performed using fresh brain samples with PMI less than 8 hours [9].

Controls: n=5 (27-64 y.o.)
Schizophrenics: n=6 (51-78 y.o.)

Abbreviation: AADC: aromatic L-amino acid decarboxylase,
Ca: caudate nucleus, Pu putamen, Acc: nucleus accumbens



(SVZ) of lateral ventricle causes D-neuron decrease in Acc [8,34]. This leads to TA decrease in Acc, 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, is possibly due to dysfunction of SVZ NSCs [7,8]. TAAR1 stimulation decrease on DA terminals of VTA DA neurons, caused by TA decrease, would increase the firing frequency of VTA DA neurons [30,32]. This increases DA release in Acc, resulting in mesolimbic DA hyperactivity. It has been shown that D2 stimulation of NSCs in the striatum inhibited forebrain NSC proliferation [37]. Then, striatal DA hyper activity may accelerate D-neuron decrease, which accelerates hyperactivity of mesolimbic DA system. Actions of D2 blocking agents in pharmacotherapy of schizophrenia might partially be explained by the decrease of inhibition to forebrain NSC proliferations. It is consistent with clinical evidence that initial pharmacotherapy using D2 blockers is proved to be critical for preventing progressive pathognomonic procedures of schizophrenia.

Some evidence supporting “D-cell hypothesis (TA hypothesis”) is shown in Table 2.

Table 2.

Some evidence supporting “D-cell hypothesis (TA hypothesis)” of schizophrenia

MAOB and PEA MAOB degrades TAs including β-phenylethylamine (PEA).

1. MAOB knockout mice contained elevated level of PEA in the striatum by 10 times of that of controls [38].
2. Clinically, MAOB inhibitor, selegiline ameliorates daytime sleepiness of narcolepsy or other neuropsychiaric diseases. (Due to PEA increase?)
3. In schizophrenia, insomnia and daytime sleepiness are frequently observed as initial symptoms . ‥by PEA decrease due to D-neuron decrease?

Neural stem cell (NSC)

1. NSC dysfunction hypothesis of schizophrenia
2. Ventricular enlargement in brain imaging of patients with schizophrenia [7, 8]
3. Decrease of D-neurons in the nucleus accumbens (Acc) of patients with schizophrenia [9].
4. Decreased level of plasma brain-derived neurotrophic factor (BDNF) in patients with schizophrenia

Trace amine (TA)

1. Disturbance of sleep-wake-rhythm of patients with schizophrenia. (insomnia and daytime hypersomnia)
2. Decrease of TA neurons (=D-neurons) in post-mortem brains of schizophrenia [9].
3. Chocolate habit of Novel Prizewinners [39] ?

Conclusion

1. So-called D-neuron, i.e., the TA neuron, and TAAR1 is a clue for pathogenesis of DA hyperactivity of schizophrenia. Further exploration of D-neuron signal transduction is essential.
2. “D-cell hypothesis (TA hypothesis) of schizophrenia” links NSC dysfunction hypothesis with DA hypothesis.
3. TAAR1 is involved in many neuropsychiatric diseases including substance abuse, such as alcohol dependence, and parkinsonism.
4. Drug designing by TAAR1 ligand searching studies is essential for novel neuroleptic discovery.

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