Introducción

La disfunción del dopamina (DA) [1,2], la disfunción del glutamato [3,4], los déficits neuropsicológicos [5,6], o la disfunción de los células estelares (NSC) [7,8] son hipótesis bien conocidas para la etiología de la esquizofrenia. La disfunción de dopamina (DA) se ha citado como una posible explicación para el comportamiento paranoido-hiperactivo en la esquizofrenia [1,2] (Tabla 1A). También se ha explicado por la eficacia de los bloqueadores D2 de la dopamina en el tratamiento de los síntomas paranoido-hiperactivos, y por el efecto de los estimulantes de la dopamina como la metanfetamina o la amfetamina [1,2].

Resumen

Recientemente, los estudios farmacológicos han demostrado la importancia del receptor asociado con las aminas trazas, tipo 1 (TAAR1), como un objetivo potencial para los nuevos neurolepticos. El autor presenta la investigación de los tanulos D-neuron (neuronas que producen aminas trazas) en el campo psiquiátrico. Aunque la disfunción del dopamina (DA) es una hipótesis bien conocida para la etiología de la esquizofrenia, su base molecular todavía no ha sido clara. Para explicarlo, se ha notado la modulación de la función de las aminas trazas (TAs) en la neurotransmisión de la dopamina (DA). El receptor TAAR1 tiene un gran número de ligandos, incluyendo la tiaramina, la β-feniletileamina y la metanfetamina, que influyen en el estado mental humano. La disminución significativa de la actividad de los tanulos en el área tegmental ventral (VTA) ha sido revelada para aumentar la frecuencia de disparo de las neuronas de dopamina (DA) de VTA. La disminución de los tanulos D-neuron en el núcleo acumbens (Acc) de pacientes con esquizofrenia ha sido reportada. La disminución de los tanulos D-neuron en el Acc de pacientes con esquizofrenia, debido a la disfunción de las células estelares (NSC) en la zona subventricular de la venticula lateral, podría ser crucial para la etiología de la esquizofrenia. La nueva hipótesis "D-cell hypothesis (TA hypothesis)" (en la que se involucran los tanulos D-neuron y el receptor TAAR1), está en coincidencia con los reportes recientes sobre la eficacia de los ligandos de TAAR1 en modelos animales de esquizofrenia.

Palabras clave: Dopamina; D-neuron; Amino de Trazas; Esquizofrenia; TAAR1; Dopa Decarboxilase (DDC)
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-methylenedioxyamphetamine (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

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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 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-methylenedioxyamphetamine (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].

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 hyperactivity 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

<table>
<thead>
<tr>
<th>MAOB and PEA</th>
<th>MAOB degrades TAs including β-phenylethylamine (PEA).</th>
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<tr>
<td>1. MAOB knockout mice contained elevated level of PEA in the striatum by 10 times of that of controls [38].</td>
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<td>2. Clinically, MAOB inhibitor, selegiline ameliorates daytime sleepiness of narcolepsy or other neuropsychiatric diseases. (Due to PEA increase?)</td>
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<tr>
<td>3. In schizophrenia, insomnia and daytime sleepiness are frequently observed as initial symptoms. •••by PEA decrease due to D-neuron decrease?</td>
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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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