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"D-cell hypothesis of schizophrenia": Background theory of Novel non-D2 receptor medicinal chemistry

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Abstract

The latest psychopharmacological study showed effectiveness of a novel non-D2-receptor-binding drug, SEP-363856, for the treatment of schizophrenia. Characteristic receptor profile of the compound is shown to be trace amine-associated receptor 1 (TAAR1) full agonist and 5-hydroxytryptamin 1A (5-HT 1A) receptor partial agonist. I found the TAAR1 ligand neuron, D-neuron, in the striatum and nucleus accumbens (Acc), an antipsychotic acting site, of human brain, though failed to find in the homologous area of monkey. To study human D-neuron functions, total of 154 post-mortem brains, and a modified immunohistochemical method using high qualified antibodies against monoamine-related substances, was applied. Number of D-neurons in the caudate nucleus, putamen, and Acc was reduced in post-mortem brains with schizophrenia. The reduction was significant ($p<0.05$) in Acc. "D-cell hypothesis of schizophrenia", which I proposed based on this post-mortem brain study, that NSC dysfunction-induced D-neuron reduction as cellular and molecular basis of mesolimbic dopamine (DA) hyperactivity, showing progressive pathophysiology of schizophrenia, has been proved to be a predictive hypothesis for TAAR1 medicinal chemistry.

Keywords: Schizophrenia; TAAR1; D-neuron; β-phenylethylamine; Dopamine; Medicinal chemistry

1. Introduction

Schizophrenia is a mental illness, which afflicts approximately 1% of population, and manifests delusion, hallucination, disorganized thought, flattened affect, and impaired cognitive processes. The latest pharmacological research has demonstrated the effectiveness of a novel psychotropic agent, SEP-363856, with a unique, non-D_2 receptor mechanism of action.[1, 2] The compound is trace amine-associated receptor 1 (TAAR1) full agonist, and also 5-hydroxytryptamin 1A (5-HT 1A) receptor agonist. In the present article, I show the histochemically visualized TAAR1 ligand neuron, D-neuron in a post-mortem brain specimen, and how the D-neuron relate to pathogenesis of schizophrenia, that is called "D-cell hypothesis of schizophrenia".

Dopamine (DA) dysfunction,[3, 4] glutamate dysfunction,[5,6] neurodevelopmental deficits,[7,8] or neural stem cell (NSC) dysfunction,[9,10] 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.[3, 4] 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.[3, 4] Glutamate dysfunction theory was induced by the fact that intake of phencyclidine (PCP), an antagonist of N-methyl-D-aspartate (NMDA) receptor, produces equivalent to negative symptoms of schizophrenia, such as withdrawal or flattened affect, as well as positive symptoms.[5,6] The neurodevelopmental deficits hypothesis implicates that schizophrenia is the consequence of prenatal abnormalities resulting from the interaction of genetic and environmental factors.[7,8] NSC dysfunction has also been shown to be a cause of schizophrenia.[9,10] Although mesolimbic DA hyperactivity[3,4] has been well documented in pathogenesis of schizophrenia, the molecular basis of this mechanism has not yet been detailed. In the present article, I show the rational

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of reduction of D-neurons[11] (trace amine (TA) neurons, type 1), ligand neurons of TA-associated receptor 1 (TAAR1),[12] in the nucleus accumbens (Acc) in pathogenesis of mesolimbic DA hyperactivity of schizophrenia. The novel hypothesis, "D-cell hypothesis of schizophrenia", is a pivotal theory to link NSC dysfunction hypothesis with DA hypothesis in etiology of schizophrenia.

2. D-neuron

TA neuron in the rat central nervous system (CNS) was described by Jaeger et al. in 1983.[11] Initially, they defined "the non-monoaminergic aromatic L-amino acid decarboxylase (AADC)-containing cell", and called the "D-cell".[11] "D" means decarboxylation. AADC is an equivalent enzyme to dopa decarboxylase (DDC). The D-cell contains AADC but not dopaminergic nor serotonergic.[11] Then, it is natural that the D-cell is thought to produce TAs,[13,14] such as β-phenylethylamine (PEA), tyramine and tryptamine. AADC is the rate-limiting enzyme for TA synthesis. However, it is confusing that these TAs are also "monoamines", as each one has one amino residue. It would be better to use the nomenclature of "TA cells, type 1" for D-cells, and "TA neurons, type 1" for D-neurons. There are other types of TAs that are not synthesized by AADC. In the present article, I use the words, D-cell and D-neuron, signifying TA cell, type 1 and TA neuron, type 1, respectively.

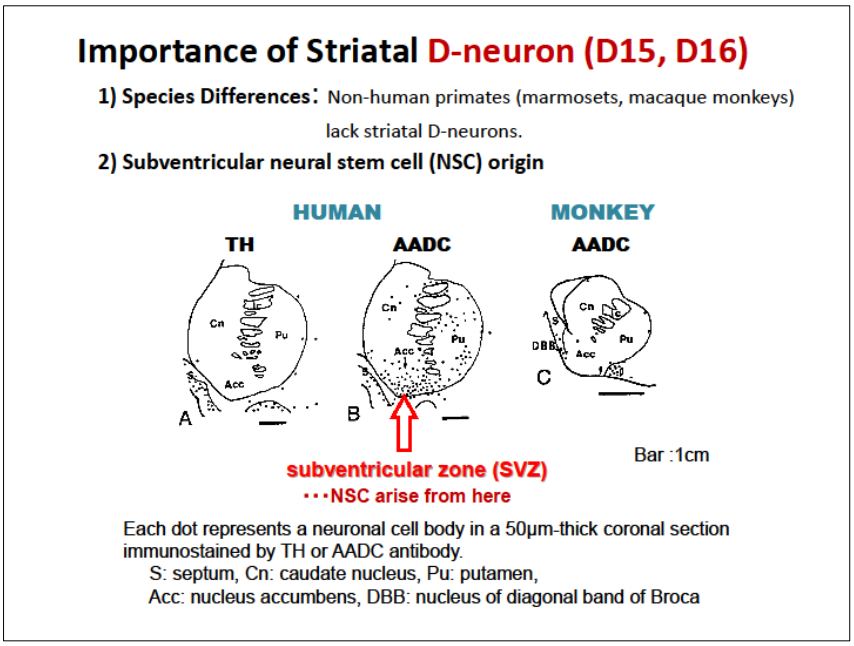

Figure 1 Importance of striatal D-neuron (D15, D16)

Non-human primates do not contain striatal D-neurons. Anatomical localization of the nucleus accummbens (Acc, D16) is overlapped with the subventricular zone (SVZ) of lateral ventricle, the region where NSC arise.[32]

In the human Acc (Fig. 1, Fig. 2A), caudate nucleus (Cn) and putamen (Pu), there are D-neurons, though monkey homologous area does not contain D-neurons (Fig. 1). By using pathological and legal autopsy brains of patients with schizophrenia, I showed lack of D-neurons in the Acc (D16), an antipsychotic acting site,[15,16] of patients with schizophrenia (Fig. 2B). D-neurons could not be identified in the cerebral cortices of brains with schizophrenia, though control cases contained D-neurons.[17]

Cloning of TA receptors in 2001,[18,19] elicited enormous efforts for exploring signal transduction of these G-protein coupled receptors whose genes are located on chromosome focus 6q23.1.[20] The receptors have been shown to co-localize with DA or adrenaline transporters in monoamine neurons and to modulate the functions of monoamines.[21, 22] The TAAR1 having a large number of ligands, including, PEA, tyramine, 3-iodothyronamine, 3-methoxytyramine, normetanephrine, and psychostimulants, for example methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA) and lysergic acid diethylamide (LSD),[18, 20, 23] has become a target receptor for exploring novel neuroleptics.[24, 25]

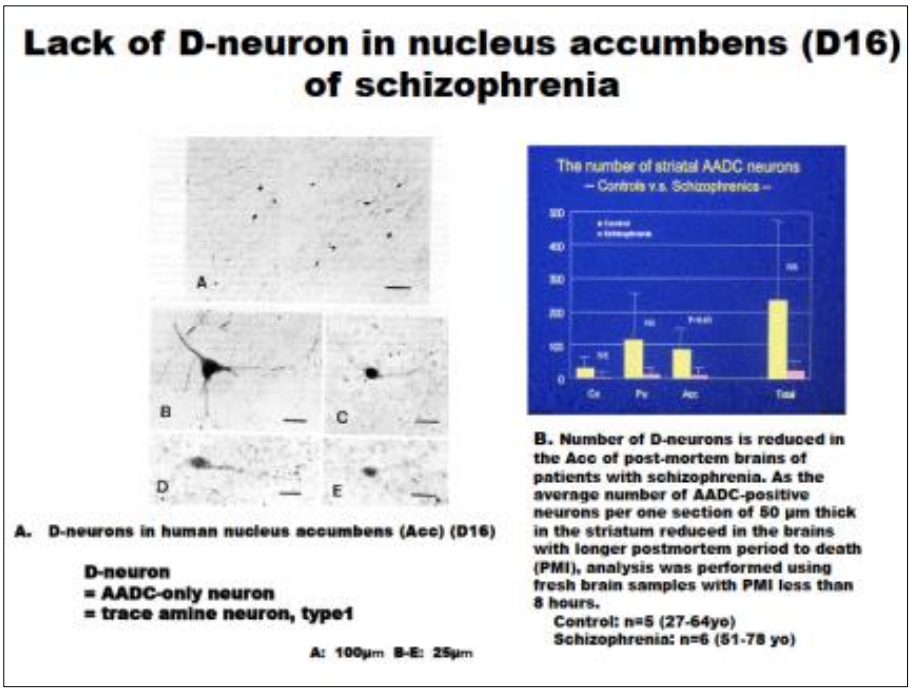

Figure 2A D-neuron in the nucleus accumbens (Acc, D16) of postmortem brain without any detectable neuropsychiatric diseases. The specimen was immunostained by using an antibody against aromatic L-amino acid decarboxylase (AADC).[42] ,**2B** Lack of striatal D-neuron in nucleus accumbens (Acc) of schizophrenia. The number of AADC-immunostained neurons (= D-neuron)42 is reduced in the striatum of schizophrenia. In the Acc, the reduction of D-neurons is significant (P<0.05). To detect the D-neuron lacking in Acc of patients with schizophrenia, total of 154 post-mortem brains were examined.

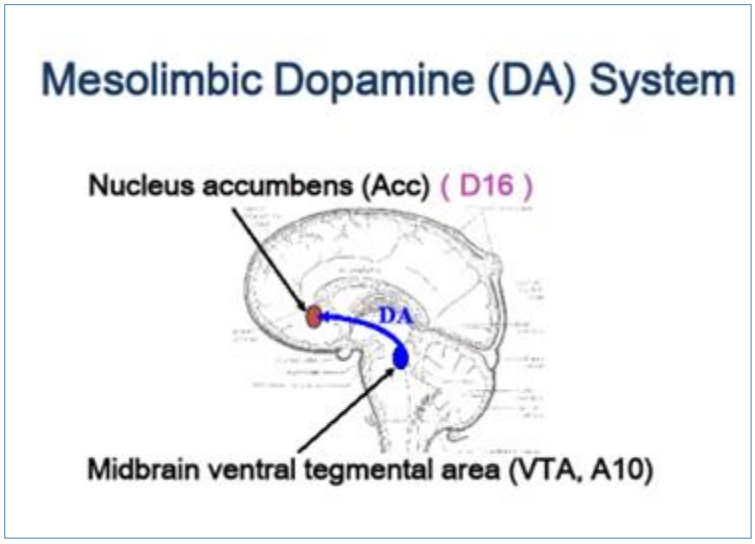

Figure 3 Scheme of human mesolimbic dopamine system

Reduced TAAR1 stimulation increases firing frequency of VTA DA neurons [20-24]. TAAR1 knockout mice show increase of spontaneous firing rate of VTA DA neurons, impaired prepulse inhibition, and are assumed to be a schizophrenia model animal [25, 26].

TAAR1 knockout mice showed schizophrenia-like behaviors with a deficit in prepulse inhibition (Fig. 3).[26,27] TAAR1 knockout mice showed greater locomotor response to amphetamine and released more DA (and noradrenaline) in response to amphetamine than wild type mice.[26] It has been shown that TAAR1 has a thermoregulatory function.[27] Interestingly, TAAR1 is the only human receptor that has been shown to bind endogenous TAs.[28]

As is the important fact, TAAR1 stimulation increase of DA neurons in the midbrain ventral tegmental area (VTA) reduced firing frequency of VTA DA neurons (Fig. 3).[24-28] This demonstrated critical role of TAAR1 stimulation decrease for mesolimbic DA hyperactivity in schizophrenia.

3. D-neuron = MAOB neuron in Acc: Study of MAOB, degrading enzyme of PEA

I examined ultrastructure of neurons enzymatically active to MAOB, trace amine degrading enzyme, by applying MAO enzyme histochemistry to mice lackinig MAOA .[29, 30] In MAOA (-) mice, type of MAO, visualized by MAO enzyme histochemistry, was only MAOB.[29] In the Acc shell, MAOB-active neuronal cell bodies were packed in dense MAOB-active fiber plexus, though MAOA-active structures could not be detected. Ultrastructural observation revealed that MAOB terminals contacted with unlabeled dendrites forming asymmetric synapses (not shown). Though amount is very low, a trace amine, that is PEA, in Acc, synthesized in D-neurons, intensely regulates TAAR1 signals in Acc via asymmetric synaptic contacts.

DNA methylation rate in promotor region of MAOB genes of postmortem brains with schizophrenia, examined by using bisulfite method, was higher in Acc and prefrontal cortex (PFC) in schizophrenia.[31] This may implicate epigenetic modification to compensate lack of trace amine in Acc and PFC, due to NSC dysfunction, by suppressing production of the degrading enzyme.

A new trace amine neuronal system, possessing AADC as a synthesizing enzyme, MAOB as a degrading enzyme and TAAR1 as a receptor, was identified. Transporter of trace amine, such as PEA, remains to be specified. Trace amine neurons, of which synthesizing enzyme is AADC, should be specified from those catalyzed by other enzymes, and be called type 1 trace amine.

4. D-cell hypothesis of schizophrenia (Fig. 4, Fig. 5)

"D-cell hypothesis" explains pathophysiology of mesolimbic DA hyperactivity of schizophrenia (Fig. 4). In brains of patients with schizophrenia, dysfunction of NSC in the subventricular zone of lateral ventricle (SVZ) causes D-neuron decrease in the striatum and Acc.[10, 29] This induces TA decrease in these nuclei. Lateral ventricle enlargement seen in schizophrenia brain imaging[30, 31] is also in part due to NSC dysfunction.[9,10]

TAAR1 stimulation decrease on DA terminals of VTA DA neurons, caused by TA decrease, increases firing frequency of VTA DA neurons.[25, 26] This increases DA release and DA turnover in the Acc,[4] resulting in mesolimbic DA hyperactivity (Fig. 4). D2 stimulation of NSC in the striatum is shown to inhibit forebrain NSC proliferation.[29,32] Striato-accumbal DA hyperactivity may accelerate D-neuron decrease, which accelerates hyperactivity of mesolimbic DA system. D2 blocking agents in pharmacotherapy of schizophrenia block inhibition to forebrain NSC proliferations,[32] and may also form TAAR1 ligands, such as 3-methoxytyramine and normetanephrine.[33] This is consistent with clinical evidences that initial pharmacotherapy using D2 antagonists is critical for preventing progressive pathognomonic procedures of schizophrenia.[34]

D-cell hypothesis not only links DA hypothesis with NSC dysfunction hypothesis, but also explains the mechanisms of disease progression of schizophrenia (Fig. 4, Fig. 5). To inhibit the cycle of pathological progression, following intervention is effective.

4.1. TAAR1 agonists (Fig. 5)

Early studies have shown formation of some TAAR1 ligands by administration of D2 antagonists including haloperidol and chlorpromazine.[33] In animal studies, effectiveness of TAAR1 ligands for schizophrenia-like symptoms of schizophrenia model animals has been shown.[25] Recent clinical trial studies have shown the efficacy of a novel agent, SEP-363856, TAAR1 full agonist and 5-hydroxytryptophan type 1A receptor partial agonist for treatment of schizophrenia.[1, 2] Efficacy of TAAR1 full agonist to schizophrenia seems to be equivalent to that of DA agonist for treatment of Parkinson's disease which lacks DA neurons in the midbrain substantia nigra.

4.2. D2 antagonists

Duration of untreated psychosis is a predictor of long-term outcome of schizophrenia. Importance of early intervention for first episode schizophrenia by using D2 antagonist has been emphasized.[34] Chronic D2 blocker administration has preventive effect for recurrence of psychoses. D2 antagonists block disease progression (Fig. 4). D2 antagonists may

have dual actions for inhibiting this cycle of disease progression by also forming some TAAR1 ligands (3-methoxytyramine, normetanephrine)[33] which increase TAAR1 stimulation (Fig. 5).

4.3. Neurotrophic substances

Disease progression is inhibited by neurotrophic substances (Fig. 5), for example, brain-derived neurotrophic factor (BDNF), lithium, anticonvulsants, or antidepressants. Neurotrophic effects of these substances activate NSC functions,[35] and inhibit striato-accumbal D-neuron decrease. Stress, aging, and alcohol intake suppresses NSC functions, which causes vulnerability to psychotic state.

Although it has not yet been detailed which type of TA in the human central nervous system is related to psychiatric symptoms, clinical and/or pharmacological observations enables us to determine a pivotal type of TA.

Early in 1994, Sabelli and Mosnaim proposed "Phenylethylamine hypothesis of affective behavior", indicating involvement of PEA in animal behaviours.[36] PEA, having similar chemical structure of methamphetamine, is the most probable TA which affects on psychiatric symptoms. One of the initial clinical symptoms frequently observed in first episode schizophrenia is disturbance of sleep-wake-rhythm, that is, insomnia and daytime hypersomnia. As PEA is the specific substrate for monoamine oxidase, type B (MAOB), MAOB knockout mice contained elevated level of PEA in the striatum by 8-10 times of that of controls.[37] Clinically, MAOB inhibitor, selegiline ameliorates daytime sleepiness of narcolepsy or other neuropsychiatric diseases, which is explained by PEA increase via inhibition of PEA degradation. Subventricular NSC dysfunction leads to D-neuron decrease and consequent TA decrease in Acc and striatum of schizophrenia.[11]

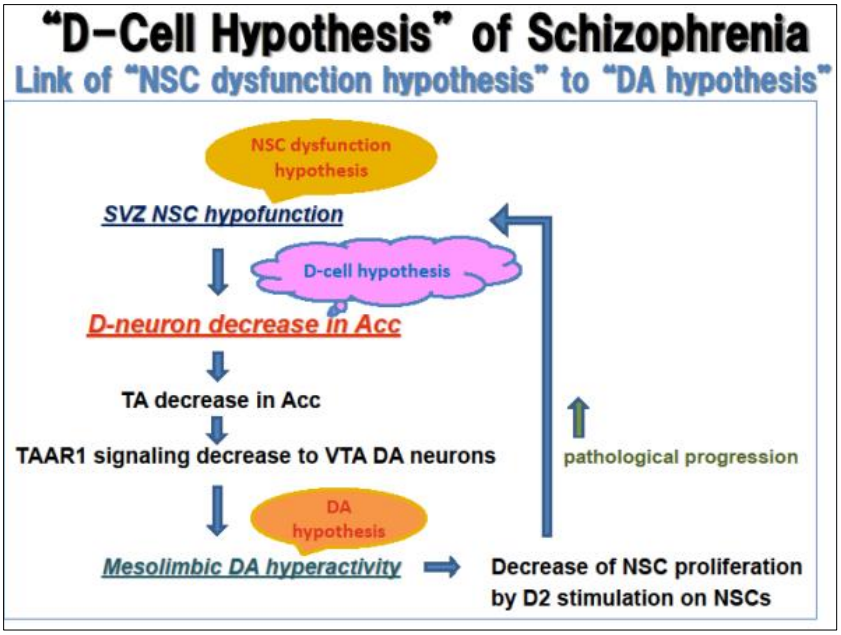

Figure 4 Scheme of "D-cell hypothesis of schizophrenia".

In schizophrenia brain, dysfunction of neural stem cells (NSC) in the subventricular zone (SVZ) of lateral ventricle causes D-neuron decrease in the striatum and nucleus accumbens (Acc). This induces TA decrease in these nuclei and TAAR1 stimulation decrease onto DA terminals of VTA DA neurons, causing firing frequency increase in VTA DA neurons.[25, 26] This increases DA release and DA turnover in the Acc, being the molecular basis of mesolimbic DA hyperactivity of schizophrenia. Striatal DA hyperactivity causes excessive D2 stimulation of NSC in the striatum and inhibits forebrain NSC proliferation,[35] which accelerates D-neuron decrease and accelerates mesolimbic DA hyperactivity. The rational is that lack of striato-accumbal D-neuron, due to SVZ NSC dysfunction, is pivotal in explaining mesolimbic DA hyperactivity of schizophrenia.

From aspect of food intake, PEA is included in chocolate. High incidence of chocolate habit of Novel Prizewinners, that is, eating chocolate more than twice a week, has been reported.[38] PEA is closely related to higher mental functions. Too much chocolate intake of children is generally restricted, possibly aimed at preventing D-neuron down regulation.

Based on recent progress in medicinal chemistry, there are various TAAR1 ligands. The 1st chemical compound proceeded to phase III clinical trial was SEP-363856,[1, 2] of which successful results have recent been shown. SEP-363856, TAAR1 full agonist, did not show extrapyramidal symptoms, implicating an improved antipsychotic agent[1, 2].

"D-cell hypothesis" proposed by a postmortem brain study of schizophrenia shows D-cell-involved etiological dynamism in also wide spectrum of psychotic state in neurological as well as psychiatric illnesses. NSC functions affect not only on D-neuron activity, but also clinical course and prognoses of neuropsychiatric illnesses (Fig. 4, Fig. 5). NSC protection as well as NSC activation is supposed to be critical for prevention and for improving prognoses of neuropsychiatric illnesses.

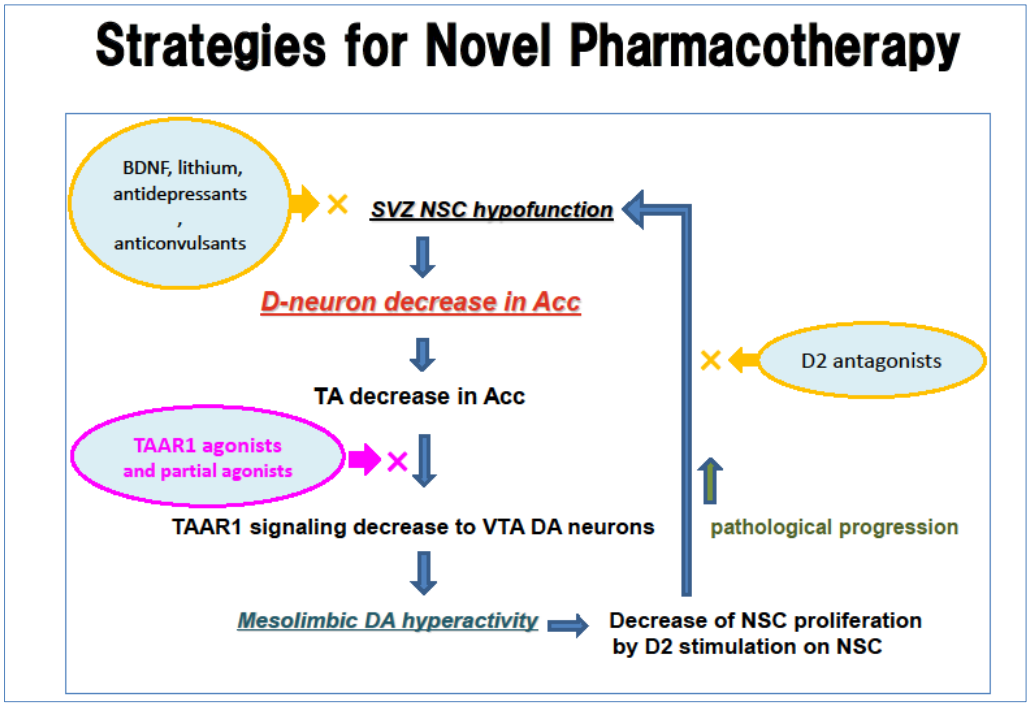

Figure 5 Novel strategies of treatment of schizophrenia, indicated by "D-cell hypothesis". Intervention By 1. TAAR1 agonists, 2. D2 antagonists, 3. Neurotrophic substances (shown by ×) to inhibit the cycle of pathological progression in available. Disease progression is inhibited by neurotrophic substances, for example, brain-derived neurotrophic factor (BDNF), lithium, anticonvulsants, or antidepressants. Neurotrophic effects of these substances activate NSC functions, and inhibit striato-accumbal D-neuron decrease. Stress, aging, and alcohol intake suppresses NSC functions, which also causes psychotic state.

5. Conclusion

The D-neuron, i.e., the TA neuron, type 1, is a clue for pathogenesis of neuropsychiatric illnesses, and key to TAAR1 medicinal chemistry. The rational is that D-cell hypothesis of schizophrenia is a pivotal theory to link NSC dysfunction hypothesis with DA hypothesis, which explains molecular basis of mesolimbic DA hyperactivity of schizophrenia. Further exploration of NSC- and D-neuron-mediated signal transduction of normal and/or disease state(s) is critical for future direction of neuropsychiatric research.

Compliance with ethical standards

Acknowledgments

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