

Perspective of D-Neuron (Trace Amine Neuron) Research: From Novel Therapeutic Strategies

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Perspective

Recent pharmacological studies have shown the importance of trace amine-associated receptor, type 1 (TAAR1), a subtype of trace amine receptors, to be a prospective target receptor for novel neuroleptics. So-called D-neuron (trace amine (TA) neuron) is the ligand neuron of TAAR1. In 1984, Jaeger et al. specified D-neuron groups from D1 (the spinal cord) to D14 (the bed nucleus of stria terminalis) in the rat central nervous system (CNS). Later, the author and her colleagues reported D15 (striatum), D16 (the nucleus accumbens, Acc), D17 (basal forebrain) and D18 (cerebral cortex), rostrally to D14, in human brains by using a PTC (Patent Cooperation Treaty)-patent-requiring method. The forebrain D-neuron system was far developed in the human. We also found lack of D-neurons in D16 (Acc) of post-mortem brains of patients with schizophrenia [1-3].

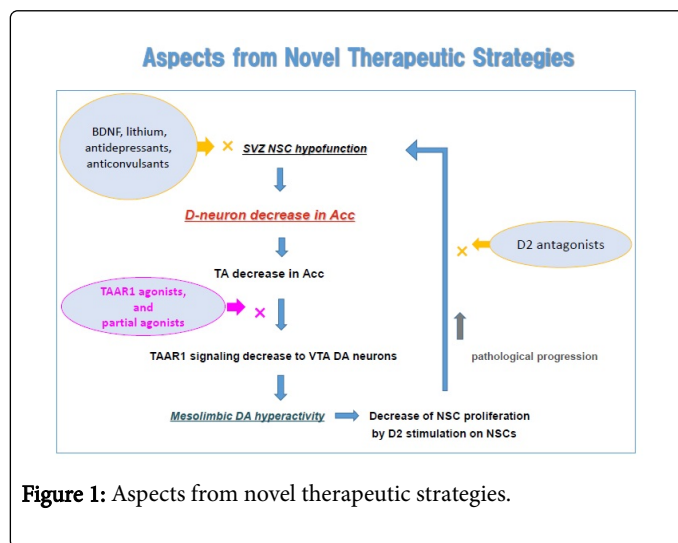


Figure 1: Aspects from novel therapeutic strategies.

TAAR1 has a large number of ligands, including tyramine, β -phenylethylamine, tryptamine and methamphetamine, which may effect on human mental states. Reduced TAAR1 stimulation of dopamine (DA) neurons in the midbrain ventral tegmental area (VTA) has been revealed to increase firing frequency of VTA DA neurons. TA decrease caused by D-neuron decrease, and consequent TAAR1 stimulation decrease of terminals of midbrain VTA DA neurons leads to mesolimbic DA hyperactivity in schizophrenia [4].

Neural stem cell (NSC) dysfunction in the sub-ventricular zone of lateral ventricle (SVZ), which overlaps with D16, is supposed to be a cause of lack of D-neurons in D16 of schizophrenia. The rational is that the "D-cell hypothesis (TA hypothesis)" is pivotal to link DA hypothesis with NSC dysfunction hypothesis of schizophrenia (Figure

1). This hypothesis may also explain pathogenesis of paranoid-hallucinatory state of other psychoses, including dementia. From a therapeutic direction, (1) TAAR1 agonists, and/or TAAR1 partial agonists, (2) DA-D2 antagonists, and (3) neurotropic substances which act on sub-ventricular NSC, may have potential to normalize mesolimbic DA hyperactivity (Figure 2).

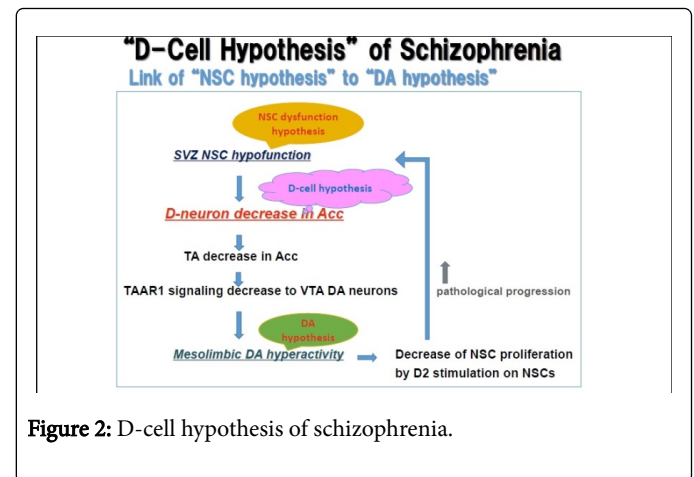


Figure 2: D-cell hypothesis of schizophrenia.

Importance of Striatal D-neuron (D15, D16)

- 1) Species Differences: Non-human primates (marmosets, macaque monkeys) lack striatal D-neurons.
- 2) Subventricular neural stem cell (NSC) origin

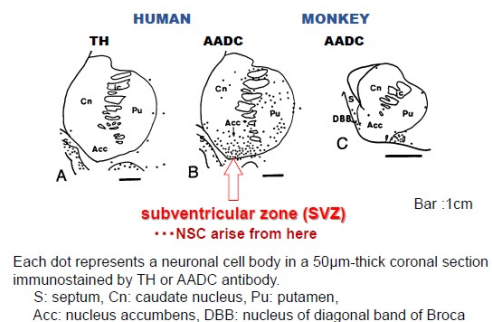


Figure 3: Importance of striatal D-neuron (D15, D16).

The sub-ventricular-accumbal region (SVAc), where NSC and D-neuron interact with each other, would be an important anatomical area in pathogenesis of mental disorders (Figure 3). Intranasal administration of neuroactive substances and/or their precursors to

reach the neuroleptic acting site(s), such as SVAc, by using nanotechnology is a possible prospective therapeutic strategy, being devoid of gastrointestinal side effects [5,6].

Further, transplantation of iPSC-induced D-neurons into SVAc would also be a future research focus of the treatment of CNS disorders.

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