Journal of Neurological Disorders
ISSN: 2329-6895

Ikemoto, J Neurol Disord 2016, 4:5
DOI: 10.4172/2329-6895.1000286

Perspective Open Access

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

Keiko Ikemoto*

Department of Psychiatry, Iwaki Kyoritsu General Hospital, Iwaki, 973-8555, Japan

***Corresponding author:** Keiko Ikemoto, Department of Psychiatry, Iwaki Kyoritsu General Hospital, Iwaki, 973-8555, Japan, Tel: +81-246-26-3151; Fax: +81-246-27-2148; E-mail: ikemoto@iwaki kyoritsu.iwaki.fukushima.jp

Rec date: Jul 25, 2016; **Acc date:** Aug 04, 2016; **Pub date:** Aug 06, 2016

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].

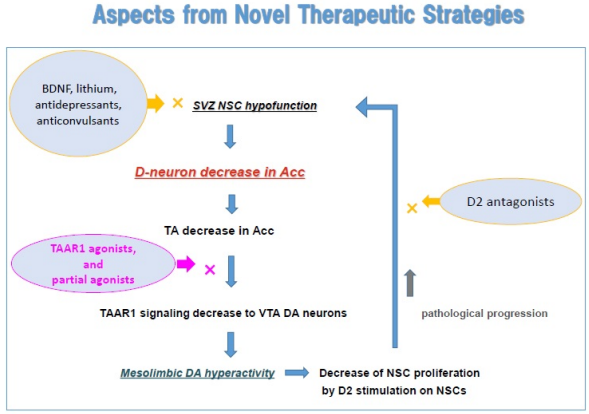

Figure 1: Aspects from novel therapeutic strategies.

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).

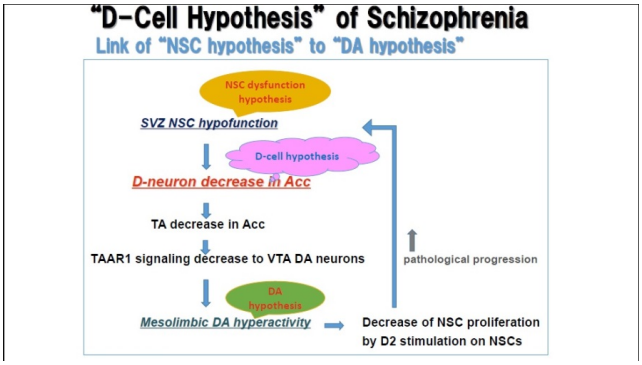

Figure 2: D-cell hypothesis of schizophrenia.

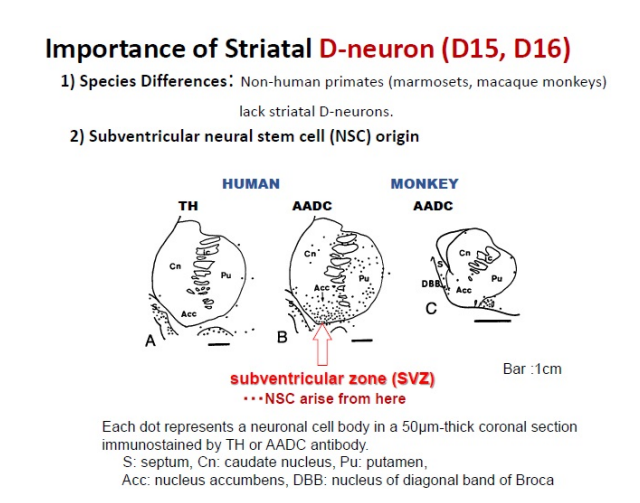

Figure 3: Importance of striatal D-neuron (D15, D16).

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.

References

1. Jaeger CB, Ruggiero DA, Albert VR, Park DH, Joh TH, et al. (1984) Aromatic L-amino acid decarboxylase in the rat brain: Immunocytochemical localization in neurons of the brain stem. Neuroscience 11: 691-713.
2. Ikemoto K, Satoh K, Maeda T, Fibiger HC (1995) Neurochemical heterogeneity of the primate nucleus accumbens. Exp Brain Res 104: 177-190.
3. Zucchi R, Chiellini G, Scanlan TS, Grandy DK (2006) Trace amine-associated receptors and their ligands. Br J Pharmacol 149: 967-978.
4. Bradaia A, Trube G, Stalder H, Norcross RD, Ozmen L, et al. (2009) The selective antagonist EPPTB reveals TAAR1-mediated regulatory mechanisms in dopaminergic neurons of the mesolimbic system. Proc Natl Acad Sci USA 106: 20081-20086.
5. Ikemoto K (2015) TAAR1 ligands as prospective neuroleptics: From research of so-called D-neuron (trace amine neuron). JJ Medicinal Chem 1: 1-7.
6. Ikemoto K (2016) Involvement of so-called D-neuron trace amine neuron in pathogenesis of schizophrenia: D-cell hypothesis, In: Farooqui & Farooqui, (eds.) Trace amines and neurological disorders. Potential mechanisms and risk factors. Chapter 20, Elsevier (in press).