

Importance of D-neuron research in neuropsychiatry

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Definition of “D-Neuron”

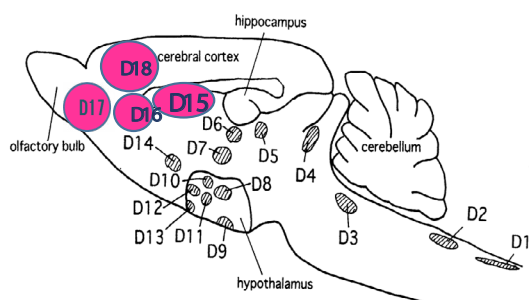
The D-neuron in the rat central nervous system (CNS) was described by Jaeger *et al.* [1]. Initially, they defined as “the non-monoaminergic aromatic L-amino acid decarboxylase (AADC)-containing cell”, and called the “D-cell”. AADC is an equivalent enzyme to dopa decarboxylase (DDC). The D-cell contains AADC but neither dopaminergic nor serotonergic. Then, it is natural that the D-cell is thought to produce the trace amine (TA), 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 TA has one amino residue.

D-cells which Jaeger *et al.* reported were proved to be neurons by electro-microscopic observation, and they are also called D-neurons. The latter is much more accurate nomenclature [2].

Since 2001, when the trace amine receptor was cloned, D-neurons have come to be recognized as ligand-producing neurons of the trace amine-associated receptor (TAAR).

Anatomy and species differences

The localizations of D-neurons 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 CNS using AADC immunohistochemistry. In this usage, the classification term “D” means decarboxylation. In rodents, a small number of D-neurons in the striatum have been rostrally described. The author reported in 1997, “dopa-decarboxylating neurons specific to the human striatum”, that is, “D-neurons” in the human striatum (classified to be D15) and the nucleus accumbens (Acc, D16) (Figure 1), though monkey



- D1: in the spinal cord, along the spinal canal
- D2: nucleus tractus solitarius
- D3: parabrachial complex (PBC) (rostral medulla and pons)
- D4: midbrain (nuclei associated with the posterior commissure)
- D5: pretectal nuclei
- D6: lateral habenular nucleus
- D7: paracentral nucleus of the dorsal thalamus
- D8: nucleus preammillaris of the hypothalamus
- D9: arcuate nucleus
- D10: zona incerta
- D11: lateral hypothalamic region
- D12: dorsomedial hypothalamic nucleus
- D13: suprachiasmatic nucleus (SCN)
- D14: bed nucleus of stria terminalis

Localization of D-neuron (=trace amine neuron)

AADC neuron

non-serotonergic, non dopaminergic

=AADC (+) / TH (-) / TPH(-) neuron

AADC : aromatic L -amino acid decarboxylase

TH : tyrosine hydroxylase

TPH : tryptophan hydroxylase

Forebrain D-neuron system is far developed
in humans compared to non-human primates.

D15 : striatum

D16: nucleus accumbens (Acc)

D17: basal forebrain

D18: cerebral cortex

Figure 1. Localization of D-neuron in mammalian

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AADC neurons in human N. Accumbens (D16)

D- neuron
= trace amine neuron

A: 100 μ m
B- E: 25 μ m

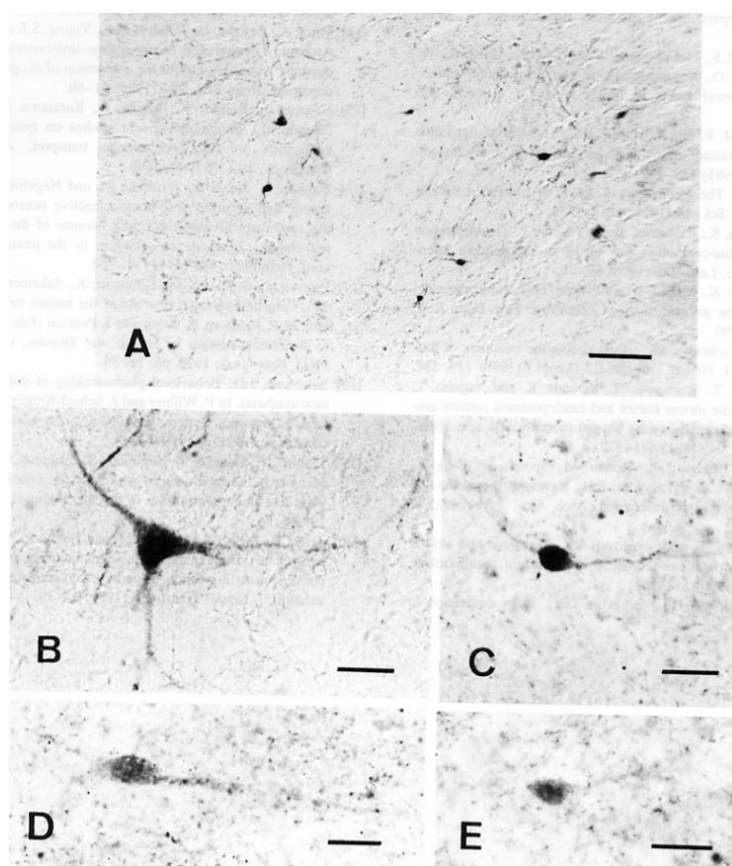


Figure 2. Photomicrographs of D-neurons in the human nucleus accumbens (D16).

striatum did not contain D-neurons in these areas [3]. By using human post-mortem brain materials, D-neurons have been also described in the basal forebrain (D17) and the cerebral cortex (D18). In humans, D-neuron system is far developed in the forebrain (Figure 2).

Corresponding to anatomical nomenclature of amine neurons, that is, A group for catecholamine neurons (A1 - A16), B group for serotonergic neurons (B1 - B14), and C group for epinephrine (adrenergic) neurons (C1-C3), D group is used as the classification term for TA neurons (D1-D18) [4].

Lack of D-neurons in striatum (D15) and nucleus accumbens (D16) of post-mortem brains with schizophrenia, and D-cell (D-neuron) hypothesis

In 2003, by using pathological and legal autopsy brains of patients with schizophrenia, reduction of D-neurons in the striatum (D15) and Acc (D16) of patients with schizophrenia was also shown. This finding lead to establish D-cell hypothesis of schizophrenia, that links dopamine hypothesis to neural stem cell (NSC) dysfunction hypothesis, explaining molecular mechanisms of mesolimbic dopamine hyperactivity [2, 4].

Medicinal chemistry related to D-neuron

The human D-neuron is the ligand neuron of trace amine-associated receptor 1 (TAAR1). TAAR1 is now assumed to be a prospective target receptor of neuroleptics, including antipsychotics, antidepressants and hypnotics. Animal studies have shown the effectiveness of TAAR1 agonists and partial agonists for schizophrenia symptoms and addiction [4]. Nevertheless, D-neuron signal is yet unclear. Further

studies should be conducted to elucidate detailed signals between NSC, D-neuron, trace amines, TAAR1 and dopamine.

References

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