Dopamine receptor D2

Dopamine receptor D_2, also known as **D2R**, is a protein that, in humans, is encoded by the *DRD2* gene.The dopamine D2 receptor was discovered in 1975 by Philip Seeman who had named it as the antipsychotic/dopamine receptor [1] The dopamine D2 receptor is the main receptor for all antipsychotic drugs. Any drug that does not interfere with dopamine action at the D2 receptor does not have an antipsychotic action.

1 Function

This gene encodes the D_2 subtype of the dopamine receptor, which is coupled to G_i subtype of G protein-coupled receptor. This G protein-coupled receptor inhibits adenylyl cyclase activity.[2]

In mice, regulation of D2R surface expression by the calcium sensor NCS-1 in the dentate gyrus is involved in exploration, synaptic plasticity and memory formation.[3]

In flies, activation of the D2 autoreceptor protected dopamine neurons from cell death induced by a toxin mimicking Parkinson's disease pathology.[4]

2 Isoforms

Alternative splicing of this gene results in three transcript variants encoding different isoforms.[5]

The long form (**D2Lh**) has the "canonical" sequence and functions as a classic post-synaptic receptor.[6] The short form (**D2Sh**) is pre-synaptic and functions as an autoreceptor and regulates the levels of dopamine in the synaptic cleft.[6] Agonism of D2sh receptors inhibits dopamine release; antagonism increases dopaminergic release.[6] A third D2(Longer) form differs from the canonical sequence where 270V is replaced by VVQ.[7]

3 Genetics

Allelic variants:

- A-241G
- C132T, G423A, T765C, C939T, C957T, and G1101A[8]
- Cys311Ser
- −141C insertion/deletion[9] The polymorphisms have been investigated with respect to association with schizophrenia.[10]

Some researchers have previously associated the polymorphism Taq 1A (rs1800497) to the *DRD2* gene. However, the polymorphism resides in exon 8 of the *ANKK1* gene.[11] DRD2 TaqIA polymorphism has been reported to be associated with an increased risk for developing motor fluctuations but not hallucinations in Parkinson's disease.[12][13]

4 Ligands

Most of the older antipsychotic drugs such as chlorpromazine and haloperidol are antagonists for the dopamine D_2 receptor, but are, in general, very unselective, at best selective only for the "D_2-like family" receptors and so binding to D_2, D_3 and D_4, and often also to many other receptors such as those for serotonin and histamine, resulting in a range of side-effects and making them poor agents for scientific research. In similar manner, older dopamine agonists used for Parkinson's disease such as bromocriptine and cabergoline are poorly selective for one dopamine receptor over another, and, although most of these agents do act as D_2 agonists, they affect other subtypes as well. Several selective D_2 ligands are, however, now available, and this number is likely to increase as further research progresses.

4.1 Agonists

- N,N-Propyldihydrexidine - analogue of the D_1/D_5 agonist dihydrexidine; Selective for postsynaptic D_2 receptor over the presynaptic D_2 autoreceptor.
- Cabergoline (Caberl)
- Talipexole - selective for D_2 over other dopamine receptors, but also acts as α_2-adrenoceptor agonist and 5-HT_3 antagonist.
- Piribedil - also D_3 receptor agonist and α_2-adrenergic antagonist
- Pramipexole - also D_3, D_4 receptor agonist
- Quinpirole - also D_3 receptor agonist

- Quinelorane - affinity for $D_2 > D_3$
- Bromocriptine - full agonist
- Ropinirole - full agonist
- Sumanirole - full agonist; highly selective

4.2 Partial agonists

- Aplindore
- Aripiprazole (Abilify in USA)[14]
- Brexpiprazole/OPC-34712
- Cariprazine
- RP5063
- GSK-789,472 - Also D_3 antagonist, with good selectivity over other receptors [15]
- Ketamine (also NMDA antagonist)
- LSD - in vitro, LSD was found to be a partial agonist and potentiates dopamine-mediated prolactin secretion in lactotrophs.[16] LSD is also a 5-HT_2A agonist.
- Roxindole (only at the D2 autoreceptors)
- OSU-6162 - Also 5-HT_2A partial agonist, acts as "dopamine stabilizer"
- Salvinorin A - Also κ-opioid agonist.

4.3 Antagonists

- Atypical antipsychotics
- Domperidone - D_2 and D_3 antagonist; does not cross the blood-brain barrier
- Eticlopride
- Fallypride
- Desmethoxyfallypride
- L-741,626 (3-[4-(4-Chlorophenyl)−4-hydroxypiperidin-l-yl]methyl-1H-indole) - highly selective D_2 antagonist
- Raclopride - Radiolabled C^{11} Raclopride is commonly employed in Positron emission tomography studies[17]
- Hydroxyzine (Vistaril, Atarax)
- Itopride
- SV 293[18]
- Typical antipsychotics
- Yohimbine

D_2Sh selective (presynaptic autoreceptors)

- Amisulpride (low doses)
- UH-232

4.4 Allosteric modulators

- Homocysteine - allosteric antagonist[19]
- PAOPA[20]
- SB-269,652 [21][22][23]

4.5 Functionally selective ligands

- See reference[24]

5 Protein-protein interactions

The dopamine receptor D_2 has been shown to interact with EPB41L1,[25] PPP1R9B[26] and NCS-1.[27]

5.1 Receptor oligomers

The D_2 receptor forms receptor heterodimers *in vivo* (in living animals) with other G protein-coupled receptors; these include:[28]

- D_1–D_2 dopamine receptor heteromer
- D_2–adenosine A_2A
- D_2–ghrelin receptor
- D_{2sh}–TAAR1 (a presynaptic heterodimer)

The D_2 receptor has been shown to form hetorodimers *in vitro* (and possibly *in vivo*) with DRD_3,[29] DRD_5,[30] and 5-HT_2A.[31]

6 See also

- Dopamine receptor

7 References

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8 External links

- Receptors, Dopamine D2 at the US National Library of Medicine Medical Subject Headings (MeSH)
- Pappas, Stephanie. "Study: Genes Influence Who Your Friends Are". *Imaginova Corp.* LiveScience. Retrieved 20 January 2011.

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