DOPAMINE RECEPTORS

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OUTLINE

• Functions of Dopamine
• Dopamine Receptors structure
• Dopamine Receptors
  – D1 & D2 Family
• Regulation of Dopamine
Roles of Dopamine

• Role in movement
• Role in pleasure and motivation
• Controls the flow of information from other areas of the brain
Structure of Dopamine Receptors

- Oligosaccharide
- Extracellular
- Palmitoyl group
- Membrane-spanning α-helix
- Intracellular
Dopamine Receptors

• There are five types of dopamine receptors. D1, D2, D3, D4, D5.
• We can categorize dopamine receptors in two main subtypes:
  • **D1 like receptor family**: the Gs protein is involved and adenylyl cyclase would be activated. The action of the enzyme causes the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP).
  • **D2 like receptor family**: which is the receptor combining with the Gi protein and its activated alpha-subunit then inhibits adenylyl cyclase so that the concentration of cAMP is reduced.
Dopamine Receptors

- Five subtypes of dopamine receptor have been cloned. The D1 and D5 receptors are closely related, and couple to Gs alpha and stimulate adenylyl cyclase activity. In contrast, the D2, D3 and D4 receptors couple to Gi alpha and inhibit the formation of cAMP.
Distribution of Dopamine Receptors

cortex
$D_1, D_2, D_3, D_4, D_5$

striatum
$D_1, D_2$

limbic
$D_1, D_2, D_3, D_4, D_5$

pituitary $D_2$

cardiovascular
$D_1, D_2$
D1 receptors

- Most abundant receptor in the central nervous system
- Lack of intrones
- 446 aa
- Highly expressed in basal ganglia
- Chromosome 5
- Stimulate AC
D5

- Intronless
- 477aa
- 50% homology with D1
- Chromosome 4
- Very striking gene control pseudogene that %90 homology with D5
- Expression in nucleus of thalamus ;suggesting that role in pain stimuli
- Stimulate AC
D2

- 7 intrones
- Third cytoplasmic domain is long and the carboxyl terminus is short
- Chromosome 11
- Inhibitit AC, phosphoinositide turnover
- Activation of potassium channel, potentiation of arachidonic acid release
- Two isoforms; D2L and D2s by alternative splicing.
- Similar profiles in terms of affinity but different in regulation.
- Highly expressed in basal ganglia, nucleus accumbes septi, ventral tegmental area.
D3

- Five intrones
- 446aa
- Chromosome 3
- As a functional receptor remains uncertain
- Similarity to D2 and the expression areas may give clue
- Recent study shows it might mediate positive regulatory influences of Da on production of neurotension.
D4

- 4 introns
- 387 aa
- Homology with D2 and D3 41% and 39%
- Chromosome 11
- Hippocampus and frontal cerebral cortex
Dopamine 1 (DA1) Receptor agonists

- Fenoldopam
- Piribedil
- Ibopamine
- SKF 3893
- Apomorphine
Therapeutic uses of DA1 Receptor Agonists

• Decreases peripheral resistance
• Inducing lowering of arterial blood pressure-increases in heart rate and increases in sympathetic tone
• Increases in activity of the renin aldosterone system
Dopamine 2 (DA 2) Receptor Agonists

- Bromocriptine
- Pergolid
- Lisuride
- Guinpirole
- Carmoxirole
Therapeutic uses of DA2 receptor agonists

- Used for treating Parkinson’s disease
- Inhibits protactin release (which decreases tumor size)
DA 1 Receptor Antagonists

• SCH23390

• Clozapine (used for treating schizophrenia)
DA 2 Receptor Antagonists

• Metoclopramid

• Domperidone

• Sulpiride

• Haloperidol

• Gastric Motility Disorders