Dopamine Receptor Pharmacology: What We Clinicians Need to Know

Rakesh Jain, MD, MPH
Clinical Professor
Department of Psychiatry
Texas Tech Health Sciences Center
School of Medicine
Midland, Texas

Why Does Dopamine Matter and Why Devote Time to Understanding it Better?


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Dopamine Sits at the Junction of Reward and Addiction (and So Much More)


Through its Main 4 Pathways, Dopamine Exerts Vast Control over Brain/Body Functioning

• Mesolimbic dopamine pathway
  - Involved in pleasurable sensations, reward, euphoria of drugs of abuse, and psychosis
  - Hyperactivity of dopamine neurons may mediate positive symptoms
  - 
• Mesocortical dopamine pathway
  - Involved in cognition, executive function, and regulation of emotion/affect
  - Hypoactivity in the mesocortical pathway may mediate cognitive, negative, and affective symptoms
• Nigrostriatal pathway
  - Involved in control of motor movements
  - Plays significant role in EPS
  - 
• Tuberoinfundibular pathway
  - Involved in neuroendocrine regulation
  - Plays significant role in neuroendocrine adverse effects (hyperprolactinemia)

Dopamine and Other Neurotransmitter Pathways


A Quick Primer on Dopamine and Other Neurotransmitter Pathways


Dopamine – A Life Story
Macro and Micro Understanding of Dopamine, Its Pathways, and Receptors

The signaling pathways in the postsynaptic neuron are only representative of D1-like receptor signaling (which increases cAMP). D2-like receptors are known to have opposite effects on cAMP activity, and thus slightly different downstream signaling cascades. Dopaminergic signaling affects on ion channels and membrane permeability.


Dopamine Neurons Fire in Both Tonic and Phasic Fashion

1. Tonic DA release is dependent on slow, irregular spike activity of VTA DA neurons
2. Is modulated by glutamatergic afferents from the PFC
3. Tonic DA releases low levels of DA (5–20 nM concentrations) into the extracellular space
4. Where it is subject to a limited degree of catabolism by COMT
5. Phasic DA transmission is evoked by behaviorally salient stimuli, and is triggered by burst firing of VTA neurons
6. Which release very high levels of DA into the synaptic cleft, where it stimulates postsynaptic D2-like DA receptors
7. Phasic DA is inactivated by removal from the synaptic cleft via rapid uptake by DAT
8. Although tonic DA occurs in too low a concentration to stimulate intrasynaptic D2-like DA receptors, it stimulates presynaptic D2-like DA autoreceptors
9. Which then inhibit phasic DA release


Dopamine Along with Other Monoamines is Involved in Various Mood Disorders

• One hypothesis of mood disorders is that it may arise from a deficit or underactivity in the brain of monoamine signaling (DA, 5-HT, and/or NE)
• Deficiency in monoaminergic neurotransmission may be in the monoamine levels themselves, or through disrupted receptor signaling
• Evidence supporting this hypothesis is that antidepressant therapies have been shown to raise neurotransmission tone of these neurotransmitters (5-HT, NE, and/or DA) and reduce depressive symptoms


Monoamine Pathways Overlap in Several Areas of the Brain

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Dopamine, Through its Receptors, Modulates Multiple Other Neurotransmitters

Dopamine interacts with the following Systems through its multiple Receptors (DR1-5)

- GABA
- Glutamate
- Acetylcholine
- Histamine
- Serotonin
- Norepinephrine


Dopamine Serves as a Great Regulator/Communicator in the Neural Circuitry of Monoamines

Dopamine May Be Particularly Important in Addressing Residual Symptoms of Depression

Many Symptoms Appear to be Influenced by Monoamine Signaling

Most Common DSM-IV Residual Symptoms Of MDD

- Dopamine: Pleasure, reward, motivation/drive
- Norepinephrine: Alertness, concentration, energy
- Serotonin: Obsessions, compulsions, memory

Attention
- Mood, cognitive function
- Appetite, sex, aggression
- Anxiety, impulse, irritability

Brain Region PFC S NA Hy SC

Concentration, interest, fatigue (mental)
Fatigue (physical)
Insomnia
Fatigue, energy

Monoamine pathways implicated
- NE/DA NE/DA NE/DA 5-HT/NE NE/DA

Dopamine Pathways: Clinical Implications

Nigrostriatal pathway: where DA cells within pars compacta (A9) and neighboring area (group A9) from SN project to striatum, this projection is involved in mostly the control of voluntary movement.

Mesolimbic & Mesocortical pathway: which is the projection from VTA, cell group A10, to the NAc, PFC, and other limbic areas. These neurons play a crucial role in reward-related behaviors.

Tuberoinfundibular pathways: which are the cells from arcuate nucleus (cell group A12) and paraventricular nucleus (cell group A14) of the hypothalamus, projecting to the pituitary. This pathway is known to control the release and synthesis of pituitary hormone, mostly prolactin.

Functional Pharmacology of Dopamine

Dopamine and Nucleus Accumbens: Deep Connections to Cognition, Emotion, and Pain Modulating Regions of the Brain

Dopamine Impacts the Pain / Insomnia / Mood Triad

Vulnerability model of tonic/phasic DA dysregulation. Solid arrows represent putative bidirectional pathways through which abnormalities in the homeostatic regulation of tonic and phasic DA contribute to the combind triad of insomnia, chronic pain, and depression. Dashed arrows represent putative moderators of DA function in this model.

Dopamine – Impacts Multiple Issues (Cognition, Affect, and Pain)
Food and Food Cravings

Interactions with Dopamine and Its Receptors

Food reward circuit involving DA system and D2 receptors. As the drug addiction, it appears that food stimuli activate VTA/NAc DA mesolimbic circuit with phenotypic importance of feeding behaviors translated through signaling in midbrain DA system for connection between homeostatic and hedonic system of food intake.

DS = dorsal striatum.


How Dopamine and Its Various Receptors Affect Exercise Motivation

Physical activity (ie, intensity and duration of exercise) can cause changes in neuronal signaling as well.


Dopamine and Music

“Music has existed in human societies since prehistory, perhaps because it allows expression and regulation of emotion and evokes pleasure.”

Dopamine, NAc, and Mesolimbic striatal systems are all activated by Familiar and Novel music and its involvement in reward, motivation, and pleasure.


Dopamine and Music

Dopamine and Music

Dopamine Receptor Classification and Its Diverse Pharmacology

Dopamine Receptor Classification

Individual Receptors are Diverse and We Clinicians Need to Know the Differences

- **D1 Like Family**
  - Members are
    - D1 (coded by the DRD1 gene)
    - D5 (coded by DRD5 gene)
  - Stimulation of these leads to increased cAMP

- **D2 Like Family**
  - Members are
    - D2 receptor (coded by DRD2 gene)
    - D3 receptor (coded by DRD3 gene)
    - D4 receptor (coded by DRD4 gene)
  - Stimulation of these leads to decreased cAMP

The Dopamine Receptor Family

- Mediated by G protein-coupled receptors in 2 major groups
  - D1-class (D1 and D5)
    - Found primarily postsynaptically
  - D2-class (D2, D3, D4)
    - Expressed pre- and postsynaptically
    - D2 is the high affinity binding site for virtually all antipsychotic agents

Location, Location, Location...
Significant Differences in Dopamine Receptor Distribution

Basic Genetic, Structural, and Pharmacologic Properties of Dopamine Receptor Subtypes

Dopamine D1 Family

- D1 dopamine receptors are expressed at a high level of density in the nigrostriatal, mesolimbic, and mesocortical areas, such as the caudate-putamen (striatum), NAc, SN, olfactory bulb, amygdala, and frontal cortex, as well as at lower levels in the hippocampus, cerebellum, and thalamic areas
- D5 dopamine receptors are expressed at low levels in multiple brain regions, including pyramidal neurons of the PFC, the premotor cortex, the cingulate cortex, the entorhinal cortex, SN, hypothalamus, the hippocampus, and the dentate gyrus

Dopamine D2 Family

- The highest levels of D2 dopamine receptors are found in the striatum, the NAc, and the olfactory tubercle. D2 receptors are also expressed at significant levels in the SN, VTA, hypothalamus, cortical areas, septum, amygdala, and hippocampus
- The D3 dopamine receptor has a more limited pattern of distribution, the highest level of expression being observed in the limbic areas, such as in the shell of the NAc
- The D4 dopamine receptor has the lowest level of expression in the brain, with documented expression in the frontal cortex, amygdala, hippocampus, hypothalamus, globus pallidus, substantia nigra pars reticulata, and thalamus

Dopamine D2 Family (cont’d)

- Activation of brain dopamine receptors. D1, D2, and, to a lesser degree, D3 dopamine receptors are critically involved in reward and reinforcement mechanisms
- Both D1 and D2 dopamine receptors seem to be critical for learning and memory mechanisms, such as working memory, that are mediated primarily by the PFC
- D2, D3, and, potentially, D5 dopamine receptors seem to have a minor modulatory influence on some specific aspects of cognitive functions that are mediated by hippocampal areas
- D3 dopamine receptors exert some relatively minor modulatory influences on many of the functions generally attributed to D2 dopamine receptors
**Update on D2 Receptor:**

Emergence of D2 Subtypes – D2L and D2S

- The D2 receptor exists in 2 isoforms: the long form (D2L) and the short form (D2S). The 2 isoforms are generated from the same gene by alternative splicing. D2L differs from D2S by the addition of 29 amino acids in the third intracellular loop of its protein structure.
- D2L and D2S may differentially contribute to the therapeutic actions and adverse effects of antipsychotic agents, and may have implications for developing better antipsychotic agents.
- In animal knock out mouse model, deletion of D2L diminishes drug-induced parkinsonism.
- D2S has been shown to be mostly expressed presynaptically and to be mostly involved in autoreceptor functions, whereas D2L seems to be predominantly a postsynaptic isoform.

**D3 Receptor Details**

- In high DA areas of the brain, D3R partial agonism has the net effect of dampening DA neuronal firing, thus lowering psychosis or mania.
- There may also be an association with increased cortical static tone for alertness and wakefulness if the D3R is agonized.
- Evidence amassed so far includes statistically and clinically significant improvements in positive symptoms of schizophrenia among subjects found to possess DRD3 polymorphisms for the D3R gene, and this D3 property may be implicated as a risk to developing schizophrenia symptoms.
- Animal models have demonstrated that negative symptoms improve, including cognition and social behavior, with D3R agonism.
- Notably, D3 receptors possess a high affinity for DA (420-fold higher than that of D2 receptors) and, unlike D2 receptors, small changes in their number or function may lead to dramatic effects on synaptic transmission, suggesting that D3 receptors could be critical modulators of normal dopaminergic function and despite their localization, also of cognition.
- Dopamine D3 receptor expression and function are both down-regulated in stress and depression.

**3 Major Functions of Dopamine Receptors:**

**Locomotion, Reward, Cognition**

<table>
<thead>
<tr>
<th>Locomotion</th>
<th>Reward</th>
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<tbody>
<tr>
<td>Locomotion represents a well-characterized function of DAergic receptors. DA in the dorsal striatum modulates basal ganglia activity, by DAergic receptors mainly expressed on GABAergic medium spiny neurons.</td>
<td>The mesolimbic DAergic pathway plays a central role in the processing of reward-related stimuli, which mainly increase extracellular DA levels in the NAc.</td>
</tr>
<tr>
<td>D1 and D2 are main dopamine receptors involved.</td>
<td>D1R, D2R, and D3R are dopamine receptors involved.</td>
</tr>
</tbody>
</table>

**Focus on the 3rd Major Function of Dopamine Receptors:**

**Cognition**

**Regulation of Cognitive Functions – DA regulates essential cognitive functions through Dopamine receptors expressed in the PFC, striatum, and hippocampus.**

- **D1R**
  - D1 family control working memory, behavioral flexibility, decision-making, and goal-directed behaviors.
- **D2R**
  - D2 are highly expressed in striatum and hippocampus and moderately in layer 5 of PFC and regulate behavioral flexibility, goal-directed behaviors, and decision-making, also affecting working- and long-term memory.
- **D3R**
  - D3R indirectly modulate PFC-dependent cognitive functions, by inhibiting mesocortical DAergic activity and/or adjusting cortical ACh levels. Thus, D3R inhibition improves attention, learning, memory and executive functions, whereas stimulated D3R modulates behavioral flexibility.
- **D4R**
  - In PFC and hippocampus affect different cognitive tasks, including inhibitory avoidance and object recognition memory being also involved in attention and exploratory behavior.

**Dopamine and Its Various Roles in Health and Illness**

**Dopamine and Its Complex Role in Cognition (Learning)**

- **A. Reference scenario**
- **B. Effect of phasic dopamine burst on learning**
- **C. Effect of phasic dopamine dip on learning**
- **D. Effect of dopamine increase during choice**

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Dopamine: Glutamate Interactions in the Development of Psychosis


Dopamine and Its Receptors, Deeply Involved in Inflammation (Macrophage Cell Interactions)


Dopamine Receptors and Cytokines: Deep Interactions


D3 Dopamine Receptor and Its Role in Modulating Inflammation


D3 Receptor – Emerging Details in Cognition and Reward


Dopamine Release Triggered by Just Visualizing Cues (eg, Cocaine in Recreational Users)

Dopamine and Marijuana (and its individual ingredients – THC and CBD) Interactions

Dopamine and Marijuana: A Multiple Targeted Approach May Be Needed to Treat Mood Disorders – Dopamine’s Importance (especially in Treatment-Resistant Depression)

*ADHD = attention-deficit/hyperactivity disorder, MAO = monoamine oxidase inhibitor, NA = neuropeptide Y, NPY = neuropeptide Y, NTS = nucleus tractus solitarii, PFC = prefrontal cortex, SERT = serotonin transporter, SN = substantia nigra, VTA = ventral tegmental area*


Agonism, Partial Agonism, and Antagonism
Appreciating the Differences in these 3 Separate Receptor Activities

Drugs

<table>
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<tr>
<th>Receptors</th>
<th>( D_1 )</th>
<th>( D_2 )</th>
<th>( 5-HT_{1A} )</th>
<th>( 5-HT_{2A} )</th>
<th>( 5-HT_{2C} )</th>
<th>( 5-HT_{7} )</th>
<th>( H_1 )</th>
<th>( M_1 )</th>
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<tr>
<td>Aripiprazole</td>
<td>0.34</td>
<td>0.8</td>
<td>1.7</td>
<td>3.6</td>
<td>15</td>
<td>93</td>
<td>37</td>
<td>1000</td>
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<tr>
<td>Brexiprazole</td>
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<td>1.1</td>
<td>0.085</td>
<td>2.6</td>
<td>34</td>
<td>134</td>
<td>3.7</td>
<td>11</td>
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<td>Cariprazine</td>
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<td>0.12</td>
<td>0.47</td>
<td>18.8</td>
<td>61</td>
<td>19</td>
<td>23.2</td>
<td>1000</td>
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<tr>
<td>Clozapine</td>
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<tr>
<td>Ziprasidone</td>
<td>57</td>
<td>3.8</td>
<td>155</td>
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Various Atypicals and Their Effect on the \( D_2 \) Receptor

Select Atypicals and Their Effect on the \( D_3 \) Receptor

Examining Similarities and Dissimilarities Among the 3 Partial Agonists at the Dopamine Receptor

Dopamine Depletion: The Birth of a New Mechanism to Treat Tardive Dyskinesia

VMAT2 Inhibitor

VMAT1 is not widely distributed in the human brain

VMAT2 is extensively distributed in the human cortex, striatum, and basal ganglia

It is found in pre-synaptic neurons


Dopamine and “Hyperkinetic” Disorders: Tardive Dyskinesia, Tourette’s, Huntington’s Disease

Dopamine “depletion” – a new approach to modulating Dopamine (through VMAT2 inhibition)

Selective VMAT2 Inhibitors
- Tetrabenazine
- Valbenazine
- Deutetrabenazine

Dopamine and Nucleus Accumbens: Deep Brain Stimulation
Targeting both Refractory Anxiety and Mood Disorders

Targeting NAc – A Central player in HEDONIC DRIVE

NAc contains a larger proportion of small cells with high concentrations of D_1 and D_2 receptors

Dopamine in the Body
It’s a Central Player in Multiple Bodily Functions

Functions mediated by dopamine receptors that are localized outside the CNS include:
- Olfaction, vision, and hormonal regulation (such as the pituitary D_2 dopamine receptor-mediated regulation of prolactin secretion)
- Kidney D_1 dopamine receptor-mediated renin secretion
- Adrenal gland D_2 dopamine receptor-mediated regulation of aldosterone secretion
- Sympathetic tone regulation
- D_1, D_2, and D_4 receptor mediated regulation of renal function
- Blood pressure regulation and vasodilation
- Gastrointestinal motility

In Conclusion:
- Dopamine is a central neurotransmitter in health and illness
- It serves diverse roles in “brain/mind” and “body” functioning
- Dopamine receptor pharmacology is quite well understood
- We clinicians would benefit from better understanding its physiological tasks, and its role in illnesses
- There are diverse means to pharmacologically manipulate dopamine and its receptors
- It behooves us to know dopamine and its receptor pharmacology well in order to serve our patient’s needs better