Dopamine Receptors in the Human Brain

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Dopamine plays an important role in controlling movement, emotion and cognition. Dopaminergic dysfunction has been implicated in the pathophysiology of schizophrenia, mood disorders, attention-deficit disorder, Tourette's syndrome, substance dependency, tardive dyskinesia, Parkinson's disease and other disorders.

In 1952, Delay and Deniker reported the use of chlorpromazine (Thorazine) to treat psychosis. They initiated an important advance in the treatment of schizophrenia without a clear understanding of the mechanisms underlying the drug's therapeutic effect. In 1963, Carlsson first postulated that the effects of neuroleptics were secondary to dopamine receptor blockade. Also at this time researchers discovered that dopamine depletion in the striatum played a role in Parkinson's disease. In 1979, Kebabian and Calne determined that at least two dopamine receptors mediated this system, and for the next decade the actions of dopamine were viewed as being mediated by two dopamine receptors, D1 and D2.

There has been an explosion of interest and information regarding dopamine receptors in the human brain. Recent advances in molecular genetics have revealed the two-receptor model to be a gross oversimplification. In the last three years, seven distinct dopamine receptors have been identified. For clinicians to make effective use of the new drugs that will emerge from this active research area, they will need to understand how dopamine affects behavior and keep abreast of the developments in dopamine pharmacology. This article is intended as the clinician's practical guide to the current understanding of dopamine receptors and their role in neuropsychiatric illness. (For a comprehensive review of dopamine receptors, see Niznik and Van Tol, and Gingrich and Caron.)

The Dopaminergic System

In the brain, the principal dopamine systems arise from cells in the midbrain and the hypothalamus. The cells in the midbrain can be divided into three groups: A8 in the retro-rubral field, A9 in the substantia nigra, and A10 in the ventral tegmental area. The neurons arising from A8 and A9 ascend to the striatum, forming part of the extrapyramidal system, and are involved in initiating and coordinating movement. The neurons of the A10 area project to the limbic and cortical areas and are referred to as the mesolimbic and mesocortical tracts, respectively. Researchers believe that these neurons are involved in emotional expression and cognitive function, and this system may be involved in the pathophysiology of mood disorders, schizophrenia and substance abuse.

The dopamine cells of the hypothalamus project via the tuberoinfundibular tract to the infundibulum and anterior pituitary. In this area, dopamine acts directly to inhibit the release of prolactin. When a neurotransmitter binds to a receptor, an extracellular signal is transduced into an intracellular one, causing a functional change inside target neurons. The nervous system contains two basic types of receptors. Fast receptor systems, such as the GABAA receptor and the nicotinic receptor at the neuromuscular junction, involve the direct binding of a neurotransmitter to a ligand-gated channel, which opens or closes the channel. Slower G-protein-linked receptor systems, as seen in the dopaminergic system, work through second-messenger systems, such as cyclic adenosine monophosphate (cAMP), and have a longer duration of action. (G-proteins derive their name from the conformational change induced in guanine nucleotides by the neurotransmitter-receptor complex.)

All of the dopamine receptors are similar in structure, and they mediate their effects through G-proteins. The prototypic makeup of all dopamine receptors consists of a protein composed of approximately 400 amino acids. These receptor proteins span the cell membrane and have extracellular, intramembrane and intracellular components. Each receptor contains seven...
hydrophobic, membrane-spanning segments. Small changes in the primary amino acid sequence of the protein-receptors results in secondary structural changes that differentiate the dopamine subtypes. Intracellularly, dopamine receptors interact with either stimulatory or inhibitory G-proteins. This interaction stimulates or inhibits adenylate cyclase, an enzyme that can catalyze the production of cAMP, one of the most important second messengers in the cell. The cAMP then exerts several biochemical changes such as activating genes and influencing the opening and closing of calcium and potassium channels.

**D1-Like Receptors**

**D1** or **D1A.** The D1 receptor is the most abundant dopamine receptor in the brain. This receptor is linked to stimulatory G-proteins that activate adenylate cyclase. The D1 receptors are found in high concentration in the substantia nigra pars reticulata, caudate, putamen, nucleus accumbens, olfactory tubercle, and frontal and temporal cortex. To date, the role of the D1-like receptors in psychiatric disorders is unclear. Some evidence suggests that these receptors affect behavior indirectly through their regulatory effects on the D2-like receptors. Recent research suggests that the stimulation of D1 receptors has a synergistic effect on the D2 receptor motor response to dopamine. This information has led to the development of D1 and D2 agonists, such as pergolide (Permax) for the treatment of Parkinson's disease.

The unique pharmacological profile of clozapine (Clozaril) may, in part, be secondary to clozapine's mild affinity for the D1 receptor, which is not found in many of the classical neuroleptics.

**D1B or D5.** The D5 receptors also are linked to stimulatory G-proteins and activate the enzyme adenylate cyclase. Their agonist/antagonist profile is similar to that of D1 receptors, except that D5 receptors have been found to have a 10-fold higher affinity for dopamine D1 receptors. The higher affinity for dopamine suggests that D5 receptors may be involved in maintaining dopaminergic tone and arousal. The D5 receptor has been anatomically localized to the cortex, hippocampus and limbic system.

**D2-Like Receptors**

**D2.** The dopamine D2 receptors are linked to inhibitory G-proteins and initiate their action by inhibiting the enzyme adenylate cyclase. The D2 receptors are localized both presynaptically and postsynaptically. Researchers have identified two molecular forms of the D2 receptor, referred to as D2-long and D2-short because of their differing size. The two isomers of D2 are pharmacologically identical except for minor differences in their affinity for specific G-proteins. These receptors exhibit high affinity for a number of drugs, such as apomorphine, bromocriptine (Parlodel) and dopamine (Intropin), that act as agonists. Their anatomical distribution includes the striatum, substantia nigra and the pituitary gland. Antipsychotic action and extrapyramidal side effects of classical neuroleptics are a function of dopamine D2-like receptor blockade. The potency of a neuroleptic is defined by its ability to block D2 receptors. This ability to block the D2 receptor is not uniform throughout the dopaminergic system. For example, clozapine has a moderate affinity for the D2 receptor in the striatum but a much higher affinity for the D2 receptor in the olfactory tubercle, a structure closely tied to the limbic system.

**D3.** The dopamine D3 receptor appears to be pharmacologically very similar but distinct from the D2 receptor. The D3 receptor may have a two- to five-times lower affinity for classical neuroleptics, making it unlikely to be the main site of neuroleptic action. The D3 receptor has not been found to affect adenylate cyclase and appears to be a presynaptic receptor. Its anatomical distribution includes the olfactory tubercle, nucleus accumbens, striatum, substantia nigra and hypothalamus. The presynaptic location and high affinity for dopamine exhibited by these receptors suggests that they may play an autoreceptor role, monitoring the amount of synaptic dopamine.

**D4.** The dopamine D4 receptor appears pharmacologically similar to D2 and D3 receptors but has a 10-times-greater affinity for the atypical antipsychotic clozapine, suggesting that D4 receptors may be the main site of clozapine's antipsychotic action. The anatomical distribution of this receptor includes the frontal cortex, medulla, hypothalamus and lower levels located in the basal ganglia. Clinicians are beginning to realize the possible benefits from gaining a more complete understanding of the dopaminergic system. Advances in molecular genetics, combined with positron emission tomography (PET) and single photon emission computed tomography (SPECT) scanning capable of performing receptor-ligand imaging, have provided a new, more direct access into brain functioning. Schizophrenia. There has been considerable debate over what role the dopamine receptors play in the pathophysiology of schizophrenia. In 1986, Wong and coworkers reported a significant increase in D2 receptors in the caudate of drug-naive schizophrenic patients compared with controls.
Subsequently, Farde and associates, using a different ligand, found no difference in the D2 receptor density. In 1993, Seeman and colleagues reported that the discrepancy in the findings noted above was not secondary to an increase in D2 receptors, as initially reported by Wong, but actually may be secondary to a six-fold increase in the density of D4 receptors in schizophrenic patients versus controls.

Recently, a modified dopamine hypothesis of schizophrenia has been introduced. It suggests some schizophrenic patients have a hypodopaminergic state in the prefrontal cortex, resulting in negative symptoms, which could lead to hyperdopaminergia in the mesolimbic system and striatum, resulting in positive symptoms.

High-level dopamine receptor blockade occurs within 24 hours after initiation of neuroleptic treatment, yet the antipsychotic effects take days to achieve. This delay suggests that the initial blockade of dopamine receptors eventually leads to a secondary change that ameliorates the symptoms. Current theories on these secondary changes include electrophysiological adaptations, such as a depolarization of dopamine neurons and changes in gene expression of dopaminergic and dopaminoreceptive neurons.

Clinically, a lag exists between the discontinuation of a neuroleptic and the resolution of extrapyramidal symptoms. Using PET, Baron and colleagues found that normal receptor availability may take five to 15 days to resume after discontinuation of neuroleptic treatment and lags significantly behind plasma levels of the neuroleptic, as illustrated in Figure 4.

Farde has proposed that striatal D2 receptors have to be blocked more than 75 to 80 percent before extrapyramidal symptoms appear. PET and SPECT studies have revealed a D2 occupancy rate of 65 percent to 85 percent with the classic neuroleptics but a lower occupancy rate of 40 percent to 60 percent for the atypical neuroleptic clozapine. Atypical neuroleptics have been shown to cause fewer extrapyramidal symptoms, which, in the case of clozapine, may be secondary to decreased blockade of D2 receptors in the striatum compared with classical neuroleptics (See Figure 5).

Much attention has focused recently on the interaction between dopamine and serotonin neurons in mediating psychosis, negative symptoms and the extrapyramidal side effects of neuroleptics. Serotonin can inhibit the firing of dopaminergic neurons that project to the striatum. Serotonin reuptake inhibitors used to treat depression occasionally can produce extrapyramidal side effects, and the lesioning of serotonergic neurons in the dorsal raphe can diminish haloperidol-induced catalepsy. Serotonin also can inhibit the firing of dopaminergic neurons in limbic structures such as the nucleus accumbens. Serotonin's effects on dopamine can be mediated by 5-HT2, 5-HT1A and 5-HT3-receptor systems. Ondansetron (Zofran), the only clinically approved 5-HT3 receptor antagonist (for chemotherapy-induced nausea), is being tested for its antipsychotic properties. Meltzer has suggested that a high 5-HT2/D2 affinity ratio may be critical for producing antipsychotic effects without extrapyramidal symptoms. Clozapine has been found to be effective in nearly half of treatment-resistant schizophrenic patients. Its efficacy in this population may, in part, be due to its increased affinity for D4 or other limbic dopaminergic receptors and/or its serotonin-5-HT2 antagonist properties. The new antipsychotic medication risperidone (Risperdal) also has been found to improve negative symptoms and cause fewer acute and chronic motor side effects compared with classical neuroleptics. This superior profile is believed to be secondary to its serotonin 5-HT2 antagonist properties, which may ameliorate the negative symptoms and affect the dopamine receptors in such a way as to reduce the incidence of extrapyramidal symptoms.

**Cocaine.** Many researchers are investigating the role that dopamine receptors may play in substance abuse. Acute cocaine use results in an increase in synaptic dopamine as the cocaine blocks presynaptic dopamine reuptake. Chronic cocaine use appears to down-regulate the D2 receptors in response to overstimulation.

Abrupt discontinuation of cocaine leads to a state of dopamine depletion, which can cause the intense depression and agitation experienced during the crash phase as well as the subsequent anhedonia, dysphoria, lethargy, somnolence and apathy that can be present for six to 18 weeks after discontinuation of cocaine (See Figure 6).

Dopamine agonists, such as amantadine (Symmetrel), bromocriptine and other amines currently are being investigated as potential relapse-prevention treatments.

**Future Endeavors**

Scientists are embarking on an exciting period in understanding the dopaminergic system. The next challenges will be: to determine the function of each receptor; to better understand the regulatory interaction between the dopamine receptors and other neuromodulators; and to use this knowledge to develop psychopharmacological treatments that target specific symptoms and cause minimal side effects.
References:

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