Dopamine Receptors and Psychosis

by Philip Seeman

Five different receptors for the neurotransmitter dopamine are known to exist in human brain. Dopamine receptors are found in regions that influence thinking, emotion, decision making and body movement. Some mechanisms have been partially revealed. For instance, certain receptors cooperate to control physical mobility and to form links that maintain mental health. Others increase in number in schizophrenia.

As integral elements in disorders such as Parkinson's disease, prolactinoma tumors, Huntington's chorea, Tourette's syndrome, and shock, in addition to schizophrenia, dopamine receptors offer primary targets for selective pharmacologic intervention.

Clarification of the therapeutic actions of antipsychotic drugs has increased understanding of the biochemical processes underlying mental activity. The story of dopamine receptors is intertwined with the history of antipsychotic drugs. When schizophrenic delusions and hallucinations were blocked by chlorpromazine in 1952, researchers around the world turned their attention to target sites of drug action. Once the link between psychosis and dopamine was established, the search for dopamine receptors accelerated. There are currently five known dopamine receptors and examination of their attributes is permitting the discovery of more selective drugs.

The research path started with antihistamines after the second world war. Henri Laborit, a French navy surgeon, used them to combat shock after surgery. He noticed a “euphoric quietude” in these patients and wrote that they were “...calm and somnolent, with a relaxed and detached expression.” In 1950, aware of Laborit’s work, the Rhone-Poulenc drug company began to synthesize antihistamines with a more sedative action to enhance anesthesia during surgery. Compound 4560, now known as chlorpromazine, emerged as the most potent compound in this series.

Chlorpromazine was tested by many French physicians in various medical situations. J. Sigwald and D. Bouthier were the first to use it as the sole medication for a psychotic patient. However, because their work was not reported until 1953, it was the 1952 report by Jean Delay and Pierre Deniker at St. Anne’s Hospital in Paris that captured attention. Delay and Deniker wrote that they were encouraged by Laborit’s belief that such a calming drug could provide “hibernation therapy.” This therapy, an idea started in Russia at the time of Ivan Pavlov, was based on the premise that a disturbed nervous system could be stabilized by “hibernating” or slowing down the brain’s activity.

Delay and Deniker’s work with eight psychotic patients showed that within three days, chlorpromazine alleviated hallucinations and stopped internal “voices.” Nurses saw their ward transformed overnight from noisy turmoil or “Bedlam” (a term that arose to describe conditions at Bethlehem Hospital in England) to peace and quiet.

In addition to chlorpromazine, many other antipsychotic drugs of the same chemical class, the phenothiazines, were later synthesized, and at least ten are in common clinical practice today. Another type of antipsychotic from a different chemical class was developed in 1957. Paul Janssen’s discovery of haloperidol as an effective antipsychotic was surprising, because its chemical structure (a butyrophenone) was very different from the phenothiazine three-ring structure of chlorpromazine. Over time, haloperidol has become more popular because it is less sedating.
The antipsychotic actions of chlorpromazine and haloperidol led to an important strategy in the search for brain abnormalities in schizophrenia. In the 1960's and 1970's, scientists looked for target sites where these drugs acted and then determined whether the sites were aberrant in schizophrenia.

An early clue detected by clinicians was that antipsychotic drugs caused patients to develop side effects, such as tremor and rigidity, that were similar to the clinical signs of Parkinson's disease. An absence or marked reduction of brain dopamine had been discovered in patients with Parkinson's disease in 1960. Therefore, these Parkinsonian side effects suggested that antipsychotic drugs might selectively interrupt dopamine transmission in the brain, as proposed in 1967 by J. M. Van Rossum at the University of Nijmegen in the Netherlands. There was no agreement on this point, however, because Swedish workers reported that antipsychotic drugs affected the transmission of both noradrenaline and dopamine in animals.

Antipsychotic Research Focused on Dopamine

Dopamine belongs to the ever-growing number of compounds in the brain that are known to serve as transmitters between nerve cells. Depending on the criteria used to define them, there may be as many as 40 to 50 neurotransmitters. The first endogenous compound to be established as a neurotransmitter was acetylcholine. In the 1950's and 1960's, many amines and simple amino acids joined the list, including epinephrine (usually referred to as adrenaline outside the United States), norepinephrine, serotonin, glutamic acid, glycine, gamma-aminobutyric acid, and dopamine.

Dopamine was found to exist in brain in 1958. It required another 15 years or so before it could be established that dopamine was a neurotransmitter. The name dopamine is actually an acronym, derived from its chemical name dihydroxyphenylethylamine. This compound, first synthesized in 1923, is also a precursor in the synthesis of norepinephrin.

Serotonin, norepinephrin, and dopamine are among the most abundant neurotransmitters in brain. Dopamine attaches to the D2 dopamine receptor by two hydrogen bonds, one with serine and one between aspartic acid and the lone pair of electrons in the -NH2 group of dopamine.
Dopamine and dopamine receptors occur in highest concentration in the putamen, the caudate nucleus, and the nucleus accumbens. Lower concentrations exist in the amygdala, the median eminence (to control the release of prolactin from the anterior pituitary gland), and in certain regions of the cerebral cortex. Small quantities of dopamine are also found, together with norepinephrine, in the autonomic nervous system.

The major dopamine pathway of the brain (orange, left) has its cell bodies in the substantia nigra area of the brainstem. Long axons rise from this area and terminate with greatest density in the corpus striatum, which controls movement. It is this dopamine pathway that degenerates in Parkinson’s disease.

A second major pathway (orange, right) has its cell bodies in the ventral tegmental area of the brainstem. Dopamine cells here send ascending projections to the limbic system, which regulates emotional behavior.

The search for a selective action shared by all antipsychotic drugs focused on the dopamine-rich regions of the brain, particularly the caudate nucleus, the putamen, and the nucleus accumbens. Between 1964 and 1974, my colleagues and I at the University of Toronto tested the action of antipsychotic drugs systematically on the various steps involved in dopamine transmission. We found that the drugs interfered at every step in the transmission process. That is, the drugs blocked nerve action potentials and the entry of calcium ions into the neuron, and they affected the release and uptake of dopamine into the nerve tissue.

In addition, other workers at Yale University found that antipsychotic drugs blocked the dopamine-stimulating action of adenylyl cyclase. This enzyme was associated with a receptor now known as the dopamine D1 receptor: “D” for dopamine and “1” because it evidenced the first biochemical response known to be specifically sensitive to dopamine.

Much to our dismay, all of these blocking actions occurred at concentrations much too high to be of clinical relevance. For example, although haloperidol, one of the most potent antipsychotics, exerted blocking effects at concentrations between 50 and 1000 nanomoles per liter (nM), the concentration of haloperidol in patients receiving it under therapeutic conditions was known to be approximately 1 nM in spinal fluid.

The goal, therefore, was to find a target in the brain that was sensitive to 1 nM haloperidol. In order to do this, we decided to work with tritiated haloperidol. This approach was immediately successful, and we readily found a binding site in the dopamine-rich tissue for radioactive haloperidol. Dopamine was more potent than noradrenaline or any other neurotransmitter in inhibiting the binding of radioactive haloperidol, thus defining the binding site as a dopamine receptor. The elusive 1 nM binding site had finally been found, and other labs soon provided confirmation. Identical
results were achieved with radioactive dopamine.

We named this haloperidol binding site the “antipsychotic/dopamine receptor,” an awkward term that was later replaced by a simpler name proposed by Drs. Pier-Franco Spano, John Kebabian, and Donald Calne: the “dopamine D2 receptor.” The number two was used to indicate that this binding site was the second one found to be specifically sensitive to dopamine and that it differed significantly from D1.

**Variable Binding Indicated Multiple Receptors**

A wide variety of antipsychotic drugs were tested on the antipsypsycho...
The five known dopamine receptors, with variations that exist in humans. The amino acid chain of each dopamine receptor passes through the cell membrane seven times. The third loop, between transmembrane regions 5 and 6 on the cytoplasmic side, is associated with the G proteins that mediate many of the post-receptor actions of the receptor. Dopamine (red) is shown attaching to aspartic acid and two of the serines in each receptor.

Five variants of D2 exist, three of which (A, S, C) occur in only 0.5% to 4% of the population. The other two variants are D2_short and D2_long, both of which are present together in different proportions (mostly the long form) in different cells. The short form is missing one exon corresponding to 29 amino acids. The response occurring after the action of dopamine on the receptor may differ in magnitude between the long and short versions of D2. No significant differences have reproducibly been found for the binding of dopamine agonists or antagonists to the different variants of D2.

The D1 and D5 receptors are often referred to collectively as “D1-like” because these two proteins have a very similar amino acid structure and because they both respond to dopamine by stimulating adenylate cyclase, which mediates the action of receptors. The D2, D3, and D4 receptors are often referred to as the “D2-like” group because they, too, share a similar structure and because they all inhibit adenylate cyclase. The D2-like receptors are also distinguished by their sensitivities to various antipsychotic drugs. For example, D2 is sensitive to raclopride, but D4 is not. Sometimes, therefore, the phrase “D4-like” is used when referring to the possible existence of other undiscovered dopamine receptors that may also be insensitive to raclopride.
There are no variants of D1. Human D3 has two variants, one of which is a nonfunctional protein where the shift in the DNA reading frame results in a different and shorter protein.

There are many variants of D4 in humans. The third cytoplasmic loop contains between 2 and 10 repeats of 16 amino acids in the different forms of D4. For simplicity, these forms are named D4.2, D4.3, up to D4.10. Deletions and frame shifts are also possible. Although no human variants of the D5 protein have yet been reported, there are two D5 "pseudogenes" which are present in all individuals (a pseudogene is a nonfunctional variant of another gene, and it produces an incomplete and nonfunctional protein).

The most complex dopamine receptor and, in fact, the most complex receptor in brain, is D4. The gene for the D4.4 form of this receptor is found in approximately two-thirds of the North American population. Because clozapine has a ten-fold higher affinity for D4 than for D2, it was tested on all the forms of D4. Clozapine was found to have the same dissociation constant on all D4 forms.

The DNA sequences of the repeat regions of D4 are not precisely the same. In fact, there are at least 25 types of DNA sequences which code for the 16 amino acid repeat. Tentatively, these different DNA sequences have been named with Greek letters. For example, one person might have a D4 gene which is D4.4alpha-beta-theta-zeta, while a second person might have a D4 gene which is D4.4alpha-beta-lamda-zeta. Curiously, the first, second, and last repeats (that is, the alpha, beta, and zeta repeats) are the same in all humans. The other types of repeats are randomly found at repeat positions three, four, five, six, seven, eight and nine. Hence, there are millions of genetic variations of the dopamine D4 receptor in the human population.

Approximately 10 to 13% of the African, Caribbean, and Afro-American population have a mutation in a single amino acid at position 194 in D4. Surprisingly, this mutation results in a D4 receptor that is not sensitive to either dopamine or clozapine. One teenager has been found to be homozygous for this mutation, but he is presently within normal limits clinically.

In addition, approximately 8% of the population have a deletion of ASAG in D4, and about 2% of the population have a shift in the DNA reading frame resulting in a short protein of 98 amino acids. The one individual who is homozygous for this latter mutation is obese, complains of excessive sweating, and has a son with Tourette's syndrome.

**Actions of Dopamine Receptors Affect Mental Health**

Messenger RNA for each of these receptors shows a unique distribution in the various regions of the brain. The location of D1 and D2 receptors in the motion-controlling regions of the caudate nucleus and the putamen is consistent with the
Brain region location of mRNA for the five known dopamine receptors.

A clinical example of synergism between D1 and D2 receptors in a patient with Parkinson's disease. The D2-stimulating action of intravenous lisuride alone was slow and not maintained (red). The D1-stimulating action of low doses of L-DOPA potentiated the lisuride action on D2 to elicit a more immediate and maintained improvement of the patient's mobility (yellow).

The notion that these two receptors play a major role in body motion. In contrast, D3 and D4 receptors in the frontal cortex, hippocampus, and nucleus accumbens are located in brain regions that influence thinking, emotions, and decision making. This pattern suggests that D3 and D4 have an important role in psychiatric disease.

In controlling body motion, dopamine D1 and D2 receptors cooperate and enhance each other's action, as demonstrated during attempts to alleviate a patient's immobility from Parkinson's disease. Lisuride was used to stimulate the dopamine D2 receptors. The clinical action of lisuride required 5 hours to peak and it could not maintain its maximum effect. However, when low doses of L-DOPA (a drug prescribed for Parkinson's disease that reduces symptoms) were added, the lisuride action was more immediate and maintained. Because the D1 receptor is more sensitive to dopamine than the D2 receptor, the low doses of L-DOPA used here may reasonably be considered to stimulate mainly dopamine D1 receptors.

One molecular basis for D1 and D2 cooperation is that these receptors use an identical protein in the post-receptor path of action. D1 normally maintains D2 in a partly desensitized state. This restraining influence of D1 on D2 is lost in psychosis, as measured in post-mortem tissues from patients who died with schizophrenia. With the "brakes" removed on D2, the D2 receptor may then become overactive, leading to hallucinations and delusions.

In addition to a disrupted link between D1 and D2 in psychosis, the density of the D2-like receptors, particularly the dopamine D4 or D4-like receptors, is elevated in brain tissues from schizophrenic patients. An elevation in dopamine D2-like receptors has also been found in living schizophrenic patients by Dr. Dean Wong at Johns Hopkins University, using radioactive spiperone. Using radioactive raclopride, however, Dr. Lars Farde in Stockholm did not find an elevation in D2 receptors in such patients. It turns out that raclopride binds to D2 and D3 receptors, while spiperone binds to D2, D3, and D4 receptors.

Although the dopamine content is found to be normal in the schizophrenic brain, an elevation in receptor density would simulate a "hyper-dopamine-like" state. This is in contrast to drug-induced psychosis, as occurs in the hallucinations and delusions brought on by cocaine or high doses of L-DOPA. In these cases, the density of dopamine receptors is normal, but more dopamine is released, creating a hyper-dopamine and psychotic state.
Highly Selective Pharmacologic Approaches Are Possible

Clinical concentrations of raclopride occupy D2 and D3 receptors, but not D1, D4 or D5, or receptors for acetylcholine and serotonin. This selectivity contrasts with a less selective antipsychotic, clozapine, although clozapine does favor D4 over the other dopamine receptors. These data were obtained from experiments using homogenized tissue in test tubes, but these numbers can also be applied clinically with surprising therapeutic value.

For example, Farde, Göran Sedvall, and their colleagues at the Karolinska Hospital in Stockholm have shown with brain imaging that a 75% blockade of D2 receptors is the therapeutic level for all of the antipsychotics except clozapine. That is, when 75% of the D2 receptors are occupied, hallucinations and delusions are essentially blocked, although it may take another two or three weeks for the thought-disturbing memories of the psychosis to dissipate.

In fact, the concentration of antipsychotic in the spinal fluid of the patient that effectively blocks 75% of the dopamine D2 receptors exactly matches the antipsychotic concentration that blocks the same number of dopamine D2 receptors in the test tube. This further supports the dopamine hypothesis of schizo-

D1 and D2 receptors affect each other’s action via the beta-gamma unit of the G protein. When coupled to its G protein (dark blue), each receptor is functional with a high affinity for dopamine (green). When uncoupling occurs, the receptor loses its affinity for dopamine. The beta-gamma unit (pink) shuttles between the G proteins of the two receptors, enabling D1 to keep D2 partly desensitized to dopamine. In psychosis, this restraining influence is lost and the D2 receptor becomes overactive, leading to hallucinations and delusions.

Right panel: Alternatively, an elevation in the density of dopamine D2-like or D4-like receptors results in a “hyperdopamine–like” state that also leads to psychosis.

Positron emission tomography shows that radioactive raclopride (red), which binds to D2 and D3 receptors, localizes to the caudate nucleus and putamen in an untreated patient’s brain (left). After treatment with a daily dose of the antipsychotic drug risperidone for one week (right), the amount of radioactive raclopride localized in the brain was reduced by 75%. This result is supportive of the general observation that 75% blockade of D2 receptors is the therapeutic level of D2 receptor blockade for all neuroleptics except clozapine.
The density of dopamine D4-like receptors is elevated in schizophrenia, as measured in post-mortem human brain tissues (caudate nucleus and putamen). The elevation is not a result of antipsychotic medication during lifetime, because patients with Alzheimer's and Huntington's disease also took antipsychotic drugs, and they have an almost normal density of these receptors. Here, yellow dots represent individual brains. Controls are humans who died of non-neurologic diseases.

Dopamine D2 receptors suppress cell division. A prolactin-secreting tumor of the anterior pituitary gland squeezes optic nerve fibers and causes limited vision in the lateral eye fields (left). Several months of stimulation of D2 receptors by bromocriptine reduced the tumor and resulted in an almost complete recovery in this patient (right).

increase the blood pressure, but rather to keep the blood vessels dilated and keep the body tissues well perfused with blood. D1 receptors on the arteriole muscle cells directly dilate the arteriole. D2 receptors at the nerve terminals also result in dilation of the vessel by inhibiting the release of noradrenaline (norepinephrine) which normally causes constriction of the vessel. Although the vascular dopamine receptors had originally been termed "DA1" and "DA2" by Dr. Leon Goldberg at the University of Chicago, they have virtually identical sensitivities to various drugs as
the dopamine D1 and D2 receptors, respectively.

What future findings may one expect of this research? Using the isolated and cloned dopamine receptors, more selective medications will be found, thus minimizing unwanted clinical side effects in the treatment of schizophrenia, Parkinson's disease and related psychomotor disorders. Additional dopamine receptors may be found in the human genome. Moreover, it is possible that the concentration level or molecular sequence of new receptors may be clinically diagnostic for certain psychiatric illnesses such as manic-depressive psychosis or schizophrenia.

Psychiatry and neurology have come far in the last twenty years, with a quantitative receptor basis now existing for drug therapy. The idea of one abnormal gene for one psychiatric disease is unrealistic. Each category of psychiatric illness may contain several biological variations, each possibly associated with a different set of genetic abnormalities. The dopamine system just happens to be a final common path for the expression of thoughts and emotion; it may be, therefore, only the smoke and not the fire. The dopamine system may not cause illness, but it can help guide us to the root of the problem.

Nevertheless, the antipsychotic strategy in studying schizophrenia has borne practical fruit. A therapeutic basis and new receptor targets for treating schizophrenia and Parkinson's disease have been found. Such helpful advances in basic and clinical science, however, will always require the clinical arts of psychiatry and neurology to optimize drug therapy for patients with these psychomotor diseases.

**RECENT REVIEWS**


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