Dopamine and schizophrenia

From Scholarpedia


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Estimates of the prevalence of schizophrenia vary between 0.4% and 1.7%. Schizophrenia is the most common of the many psychotic disorders, which include schizoaffective disorder (~0.3%), major depressive disorder with psychotic features (~0.4%), substance-induced psychotic disorders (~0.4%) and psychotic disorders due to a general medical condition (~0.2%).

Although the abnormalities in brain development associated with schizophrenia may begin in utero, childhood-onset schizophrenia is relatively uncommon. Typically, the symptoms of schizophrenia emerge gradually during the teenage years, with affected individuals meeting the criteria for diagnosis in the late teenage years or early twenties. The protective effect of estrogen may delay its onset in women (M.V. Seeman and Lang, 1990). However, there are some patients who will have their first episode of illness in the fourth or fifth decade of life. The signs and symptoms of schizophrenia generally include the so-called negative signs such as self-isolation and withdrawal from family and friends, and the positive symptoms such as apparently bizarre and unexplainable behaviour, and hallucinations and delusions.

The currently used antipsychotics alleviate most of the symptoms, but approximately 20% of symptoms such as apathy, lack of ambition, memory and interpersonal difficulties, are often resistant to antipsychotics.

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The dopamine hypothesis of schizophrenia

The role of dopamine receptors in schizophrenia is intertwined with the pharmacology of antipsychotics. The first antipsychotic, chlorpromazine (RP 4560), emerged as a potent antihistamine that enhanced analgesia and caused surgical patients to be “calm and somnolent, with a relaxed and detached expression”. A 1952 report by Delay et al. showed that within three days chlorpromazine alleviated hallucinations and stopped internal “voices” in eight psychotically disturbed patients. The rapid onset of antipsychotic action within days is consistent with a brain receptor target for the antipsychotics (Kapur et al., 2005; Agid et al., 2006).

Soon after the clinical introduction of chlorpromazine and haloperidol for psychosis, the Parkinsonian side-effect (akinesia, tremor, rigidity) of these medications became obvious. Because these side-effects mimicked Parkinson’s disease, and because Ehringer and Hornykiewicz (1960) found that dopamine was low in the brains of patients who died with Parkinson’s disease, it was widely speculated that antipsychotics interfered with dopamine neurotransmission.

The earliest outline of the dopamine hypothesis of schizophrenia is from J. Van Rossum (1967; Baumeister and Francis, 2002) who wrote:

“…When the hypothesis of dopamine blockade by neuroleptic agents [now called antipsychotic drugs] can be further substantiated it may have fargoing consequences for the pathophysiology of schizophrenia. Overstimulation of dopamine receptors could then be part of the aetiology….”

Early speculation by Carlsson and Lindqvist (1963) was that antipsychotics might block the monoamine receptors for noradrenaline, dopamine and serotonin, because they found that chlorpromazine and haloperidol increased the production of metabolites of adrenaline and dopamine, and they stated that these antipsychotics also blocked serotonin. Such experiments, however, did not identify which receptor was selectively blocked. For example, although Andén et al. (1970) reported that antipsychotics increased the turnover of dopamine and noradrenaline, they could not show that the antipsychotics were selective in blocking dopamine; that is, chlorpromazine enhanced the turnover of noradrenaline and dopamine equally.

The dopamine D2 receptor is the main target for antipsychotics

In searching for the “antipsychotic receptor”, it was first essential to know the therapeutic aqueous concentration of a typical antipsychotic such as haloperidol in the plasma water or the spinal fluid of haloperidol-treated patients (Seeman, 1980). This was calculated to be ~1-2 nM (Seeman, 1992, 2002). Second, because antagonists have nanomolar dissociation constants for their receptors, it required a specific activity higher than 10 Ci/m mole to label the antipsychotic receptor in vitro with [3H]haloperidol (Seeman et al., 1974, 1975).

The correlation between the daily clinical doses of antipsychotics and the antipsychotic dissociation constants (Ki values to inhibit the binding of [3H]haloperidol) indicated that the “antipsychotic receptor” had finally been successfully identified and directly labeled (Seeman et al., 1975). This relation is in 1. Although chlorpromazine and thioridazine do not fit the correlation shown on the left, these fit along the correlation on the right (data from Seeman, 1992, 2006)] , using [3H]raclopride and human cloned dopamine D2 receptors.
The name “antipsychotic/dopamine receptor” was re-named the dopamine D2 receptor to distinguish it from the dopamine D1 receptor, to which many antipsychotics did not bind, as shown in 2.

Because dopamine was the most potent endogenous compound to inhibit the binding of 

$[^3]H$haloperidol, the antipsychotic receptor was a dopamine receptor (Seeman et al., 1975, 1976; Burt et al., 1976).

**The dopamine D2 receptor and schizophrenia**

The dopamine D2 receptor was cloned in 1988 (Bunzow et al.) (3 While many studies have not found an association between schizophrenia and D2 polymorphisms, there are two significant polymorphisms of D2 (3) associated with schizophrenia, including serine311cysteine which occurs in 3.6% of 5,363 control individuals, compared to 7.1% of 3,707 individuals with schizophrenia (Glatt and Jönsson, 2006).

In vitro
The in vitro densities of D2 receptors in post-mortem schizophrenia striata fall into two groups with values of ~13 (4 and 5) and ~26 pmol/g (5), with an overall average of about 20 pmol/g, an increase of about 50% compared to control (Seeman, 1987). Many of the tissues came from non-medicated individuals.

High- and Low-affinity states of the D2 receptor; the D1-D2 link

At least half the neurons in the striatum that have D2 receptors also have D1 receptors, and these receptors interact. An example is in 6, where very low concentrations of dopamine, 1
to 10 nM, inhibited the binding of $[^3H]$raclopride to rat striatal homogenate to the D$_{2}^{\text{High}}$ receptors in the presence of a D1-blocking drug.

Moreover, each of these receptors has a state of high affinity, D$_{2}^{\text{High}}$, and a state of low affinity for dopamine, D$_{2}^{\text{Low}}$, with D$_{2}^{\text{High}}$ being the functional state in the anterior pituitary (George et al., 1985; McDonald et al., 1984) and in nigral dopamine terminals.

The example of the D1-D2 link in 6 suggests that a reduction in the density of D1 receptors or a reduction in the strength of the link can lead to an overactive D2 or D$_{2}^{\text{High}}$ receptor.

Moreover, as diagrammed in 7 (top right), the high-affinity state of the D2 receptor, D$_{2}^{\text{High}}$, is constantly and quickly interconverting with the low-affinity state, D$_{2}^{\text{Low}}$ (right). The D1 receptor (left), when stimulated by an agonist, accelerates the shift of D$_{2}^{\text{High}}$ into D$_{2}^{\text{Low}}$. The D1-D2 link (7 middle) would cause more of the D2 receptors to reside in the active functional state of D$_{2}^{\text{High}}$.

Any reduction in the D1-D2 link (7 middle) would cause more D$_{2}^{\text{High}}$, an overactive D2 and hyperactive behaviour or psychosis (see later).
An example of the D1-D2 link in post-mortem human striatal tissue is shown in 8. High concentrations of dopamine, 400 nM, inhibited the binding of $[^3]H$raclopride to all D2 receptors, including $D_2^{\text{High}}$ and $D_2^{\text{Low}}$, an effect that was reversed by the presence of the D1-blocking drug SCH23390.

In post-mortem schizophrenia tissue, however, the D1-blocking drug is not able to reverse the action of such high concentrations of dopamine (400 nM) (9; Seeman et al., 1989).

In vivo measurement of D2 receptors in schizophrenia brain

In first-episode patients who have never been treated with antipsychotics, the concentration or density of D2 is elevated by ~10% to 30% in the frontal cortex (Kessler et al., 2006) and striatum (see Wong et al., 1997; Farde et al., 1990; Talvik et al., 2006; Nordström et al., 1995; Abi-Dargham et al., 2004; Laruelle et al., 2005; Corripio et al., 2006; Perez et al., 2003; Hirvonen et al., 2005), but reduced by 12-30% in the cingulate cortex (Suhara et al., 2002; Buchsbaum et al., 2006), the right medial thalamic nucleus (Buchsbaum et al., 2006; Yasuno et al., 2004; Talvik et al., 2003), and the midbrain (Tuppurainen et al., 2003, 2006) (10 (Kessler et al., 2006; Suhara et al., 2002; Buchsbaum et al., 2006; Seeman and Kapur, 2000).

However, never-medicated schizophrenia patients also reveal a reduced binding of $[^3]H$raclopride to all D2 receptors, including $D_2^{\text{High}}$ and $D_2^{\text{Low}}$, in post-mortem Parkinson’s diseased tissue (from 10 to 3 pmol/g), an effect that is reversed by the presence of the D1-blocking drug SCH23390 (from Seeman et al., 1989, with permission).
general decrease in the concentration of dopamine D1 receptors in the frontal cortex (Hirvonen et al., 2006; Karlsson et al., 2002), the cingulate gyrus (Hirvonen et al., 2006), the temporal cortex (Abi-Dargham, 2003), and the striatum (Hirvonen et al., 2006) (10). This reduction in D1 may contribute to an overactive D2, as in 7.

**Dopamine supersensitivity in psychosis**

Because antipsychotics, including aripiprazole and bifeprunox, alleviate psychosis by inhibiting D2, it indicates that psychosis is associated with a hyper-dopamine state (1).

Psychotic symptoms in schizophrenia increase or intensify when the individual is administered a psychostimulant at doses that have little effect on control subjects. As reviewed by Lieberman et al. (1987) and by Curran et al. (2004), 74-78% of patients with schizophrenia have new or intensified psychotic symptoms after being given amphetamine or methylphenidate even when patients are taking antipsychotics. This compares to 0-26% in control subjects. The data indicate that dopamine supersensitivity is prevalent in patients with schizophrenia.

Psychotic symptoms occur not only in schizophrenia but in many brain diseases, and also as a result of the use of steroids, amphetamine, cocaine, or phencyclidine.

**Which of the three D2-type dopamine receptors is hyperactive in schizophrenia?**

After the human D2 receptor was cloned and sequenced, two additional D2-like receptors were identified, D3 and D4, as shown in 11 and 12, with

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**Figure 10:** Dopamine receptor alterations in brain regions of non-medicated schizophrenia subjects, as detected by brain imaging of radioligands. None of the subjects had ever been treated with antipsychotics (patients of Kessler et al. were off medication). D2 receptors were increased in the frontal cortex, decreased in the cingulate gyrus, increased by up to 18% in the striatum, and decreased by 16-29% in the thalamus, the temporal cortex and the mid-brain (substantia nigra). D1 receptors were generally decreased. Although $[^{11}\text{C}]\text{NNC112}$ revealed an increase in D1, this radioligand is not selective. The superscripts 18, 11, and 12 before each radioligand indicate $[^{18}\text{F}]$, $[^{11}\text{C}]$, and $[^{123}\text{I}]$, respectively. Background image adapted from Okubo et al., 1999, with permission.

**Figure 11:** The amino acid sequence of the human dopamine D3 receptor (Sokoloff et al., 1990). A polymorphism occurs in the ninth amino acid, and a frame shift has been reported. Standard amino acid code. (© Philip Seeman, 2007. Published by Elsevier Ltd. All rights reserved.)

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**Figure 12:** The amino acid sequence of the human
Dopamine D4 receptor. This receptor has many variants of the number and amino acid composition of the 16-amino acid segment shown, of which the most common is 4 segments in the D4.4 receptor. The D4.7 receptor is also shown. Standard amino acid code. © Philip Seeman, 2007. Published by Elsevier Ltd. All rights reserved.

anatomical localizations shown in 13.

The D3 receptor has been extensively investigated for linkage and association to schizophrenia (Sokoloff et al., 1990), but the results remain controversial. The only D3-selective drug that has been tested against schizophrenia is BP897 at 10 mg per day for 4 weeks, a dose that did not attain a significant antipsychotic effect.

Likewise, the D4 receptor, although earlier thought to be elevated in schizophrenia, has not been found to be a main target for schizophrenia treatment.

While all the antipsychotic therapeutic concentrations occupy approximately 70% of the D2 receptors, the D3 and D4 receptors are occupied by some antipsychotics but not by all, as shown in 14 (Seeman, 2002).

An example of D2

Figure 13: Localization of dopamine D2-type receptors in the human brain. Shaded and darkened regions express relatively higher amounts of D2, D3 and D4 receptors. (Adapted from Seeman, 1992, with permission.) 3: Third ventricle; AC: nucleus accumbens; AM: amygdala; C: caudate nucleus; Cx: cerebral cortex; G: globus pallidus; Hipp: hypothalamus; H: hippocampus; ICJ: Island of Calleja; L: lateral ventricle; O: olfactory tubercle; P: putamen; SN: substantia nigra; VTA: ventral tegmental area

Figure 14: Fraction of D2, D3 and D4 dopamine receptors that are calculated to be occupied in human brain at observed clinical concentrations of antipsychotics in the spinal fluid or the plasma water. While all the antipsychotic therapeutic concentrations occupy approximately 70% of the D2 receptors, the D3 and D4 receptors are occupied by some antipsychotics but not by all. See text for method of deriving occupancies. Cloz.: clozapine; CPZ: chlorpromazine; Flupen.: flupenthixol; Halo.: haloperidol; Molin.: molindone; Olan.: olanzapine; Per.: perphenazine; Raclo: raclopride; Remox.: remoxipride; Sulp.: S-sulpiride; Thior.: thioridazine. From Seeman, 2002,
occupancy is given in 15, where the % of D2 receptors occupied by risperidone is approximately 70% at the average therapeutic daily dose of 2 to 6 mg. The data in 14 and 15 are consistent with the point of 1 that the main target for antipsychotic action is the D2 receptor.

What aspects of antipsychotic action provide an insight to the psychotic process?

First, because all antipsychotics have antagonist or partial agonist action on D2, this convergence suggests that the psychotic process entails an abnormality in the regulation of D2, either pre- or post-synaptically.

Second, the onset of antipsychotic action occurs within days (Delay et al., 1952; Agid et al., 2006), suggesting a receptor-based action. The continued improvement over weeks and months may be dependent on the slower processes involved in the extinction of the psychotic memories.

Third, several antipsychotics, notably clozapine and quetiapine, are termed atypical insofar as they do not elicit Parkinsonism. While there are many hypotheses explaining this lack of Parkinsonism (Seeman, 2002), a unique feature of clozapine and quetiapine is that they rapidly dissociate from D2, including both the cloned D2 in vitro (16 as well as in the patient’s D2 (17). This “fast-off D2” property may account for the atypical nature of clozapine and quetiapine in avoiding the side-effect of Parkinsonism. Adapted from Seeman, 2002, with permission.

Because the “fast-off D2” nature of clozapine and quetiapine yields a low D2 occupancy for at least 12 hours or more (17), it indicates that D2 in patients need not be continuously occupied for much of the 24 hour day. This observation

Figure 15: Representative data showing that the occupancy of D2 receptors is approximately 70% at the usual daily dose of 2-6 mg risperidone per day. Data re-graphed from Kapur et al. Refs in Seeman, 2002

Figure 16: Several atypical antipsychotics, especially clozapine and quetiapine, rapidly dissociate from the human cloned D2 receptor in vitro. This “fast-off D2” property may account for the atypical nature of clozapine and quetiapine in avoiding the side-effect of Parkinsonism. Adapted from Seeman, 2002, with permission

Figure 17: Clozapine and quetiapine rapidly dissociate from striatal D2 dopamine receptors in patients, in contrast to traditional antipsychotics such as haloperidol that remain attached to D2 for several days. Adapted from Seeman, 2002, with permission.
suggests that the psychotic process may not be continuous but may be pulsatile or may have a considerable time delay until psychotic brain regions have time to recruit sufficient neuronal or biochemical activity for psychotic symptoms.

Antipsychotic drugs themselves can occasionally induce an increase in the high-affinity state of dopamine D2 receptors and the associated state of behavioural dopamine supersensitivity. Therefore, withdrawal of an antipsychotic can unmask the dopamine supersensitivity and precipitate an episode of supersensitivity psychosis (see Chouinard et al., 1978; Chouinard and Jones, 1980; Chouinard, 1991).

It should also be mentioned that Parkinson's diseased patients are supersensitive to dopamine-like drugs as a result of their loss of dopamine neurons. Such individuals, therefore, may readily develop a psychosis when taking L-DOPA or related dopamine agonists. Clozapine or quetiapine are best used to alleviate such a psychosis, because these two antipsychotics occupy D2 receptors for a much shorter time than haloperidol or olanzapine, thus minimizing Parkinsonian side-effects. Although most dopamine agonists act on D2, L-DOPA produces endogenous dopamine which acts on D1 and D2. D1, therefore, may contribute to a psychotic episode, despite the fact that D1 antagonists have not been found to have any significant antipsychotic action.

Animal models of psychosis

Many animal models for psychosis and schizophrenia have been proposed. The majority of these models show behavioural dopamine supersensitivity and an elevation of D2\textsuperscript{High}.

Various brain injuries or treatments related or unrelated to dopamine can result in dopamine supersensitivity, the latter being an aspect of schizophrenia, as already noted.

Considering the many interconnecting pathways in the brain, it is not surprising that various types of injury to the brain by drugs, brain lesions, or by gene mutations in specific neurotransmitter pathways can result in major biochemical alterations in another completely different pathway.

Measurement of D2\textsuperscript{High} dopamine receptors

An advance in measuring D2\textsuperscript{High} receptors was using \[^{3}\mathrm{H}]\text{domperidone} for this purpose instead of \[^{3}\mathrm{H}]\text{spiperone} or \[^{3}\mathrm{H}]\text{raclopride}. The latter two ligands, for example, do not readily reveal a clear distinction between D2\textsuperscript{High} and D2\textsuperscript{Low} (18) and 19.
[^3]H]domperidone, however, demonstrates a sharp demarcation between the two states of the D2 receptor (19 right) and provides an accurate measurement of the proportion of D2 receptors in the high-affinity state.

### Elevation of D2\textsubscript{High} in dopamine-supersensitive animals

The factors that cause behavioural dopamine supersensitivity are listed in 20, all of which influence the proportion of D2\textsubscript{High}.

Of the many animal models of psychosis that have been proposed, the model of...
amphetamine sensitization has received much support. Although the amphetamine-sensitized animal is supersensitive to amphetamine, the density of D2 in the brain striatum is normal. The D2\textsuperscript{High} receptors in the striatum, however, were elevated by 250% (21). Another example, using a different method, is in 22 (Seeman et al., 2002).

Many types of brain lesions have been proposed as models for schizophrenia, including lesions of the neonatal hippocampus (Lipska et al., 1993), cholinergic lesions of the cerebral cortex, the entorhinal cortex (Sumiyoshi et al., 2004, 2005), and the medial pre-frontal cortex.
Dopamine behavioral supersensitivity also occurs after many types of drug treatment and in mice with specific gene deletions. 22(bottom) and 23 summarize the enhanced levels of D2\textsuperscript{High} receptors in the brain striata of such gene-deleted mice with behavioral dopamine supersensitivity.

While dopamine supersensitive knockout mice do not reveal elevation in the density of D2, an elevation occurs in D2\textsuperscript{High} (but not D1 or D1\textsuperscript{High}) in all the brain striata of knockout mice that had previously shown behavioral dopamine supersensitivity.

Deletions of genes that are not related to the dopamine system also yield animal models of behavioral dopamine supersensitivity and at the same time reveal marked elevations in D2\textsuperscript{High} receptors. These genes are listed in 23.

Knockouts of some genes (adenosine A2A receptors) lead to dopamine subsensitivity, where the D2\textsuperscript{High} receptors are reduced by 75% (23).

An important animal model for schizophrenia is that of birth hypoxia during Caesarian section (Boksa and El-Khodor, 2003) where the adult striata also have elevated D2\textsuperscript{High} receptors (23).

The psychostimulant animal models for human psychosis include phencyclidine (23), amphetamine, cocaine, and tetrahydrocannabinol.

Steroid-induced psychosis has its correlate in rats given high doses of corticosterone; they become dopamine supersensitive. The striata from such rats show a 210% increase in D2\textsuperscript{High} receptors (23)(Refs in Seeman et al., 2005, 2006).

Although long-term haloperidol causes supersensitivity (Chouinard, 1991) THIS REFERENCE IS MISSING IN THE REFERENCES LIST. AUTHOR NEEDS TO ADD and increases the proportion of D2\textsuperscript{High} receptors, this increase dissipates within days after withdrawal (24). SOME DATA ARE NOT IN AGREEMENT WITH THIS: This rapid dissipation is in contrast to the permanent elevation of D2\textsuperscript{High} in the amphetamine-sensitized rat striatum or in the gene knockout mice.

D2\textsuperscript{High} dopamine receptors were also elevated after repeated administration of amphetamine, phencyclidine, corticosterone, reserpine, and quinpirole. Adapted from Seeman et al., 2006, with permission.
Biochemical factors controlling the D2\textsuperscript{High} state

The rate of interconversion between the high- and low-affinity states of a G protein-linked receptor may be minutes or seconds. There are many factors that increase the prevalence of the high-affinity state and, therefore, the sensitivity of the tissue to the agonist.

RGS9 co-localizes with D2 in the striatum and accelerates the termination of D2-triggered events. A reduction in RGS9, as occurs in RGS9 knockout mice, leads to behavioral dopamine supersensitivity and a marked increase in the proportions of D2\textsuperscript{High} receptors in the striatum (23).

The reduced expression of RGS9-2 in schizophrenia hippocampus (25) is consistent with supersensitivity and increased D2\textsuperscript{High} levels.
Because D2\textsuperscript{High} receptors are consistently elevated in all the animal models of the various human psychoses, and because the majority of psychotic episodes respond to D2 blockade, D2\textsuperscript{High} may be a common target for the convergence of the various psychosis pathways. Consistent with this hypothesis of D2\textsuperscript{High} is the fact that most psychoses respond to treatment with D2 antagonists, including phencyclidine psychosis (Giannini et al., 1984; 1984-85). The treatment of phencyclidine psychosis by haloperidol is significant, because haloperidol does not block NMDA receptors, indicating that the D2 target is critically active in phencyclidine psychosis (Refs in Seeman et al., 2005b, 2006).

Because D2\textsuperscript{High} is the functional state of D2, the elevated D2\textsuperscript{High} receptors and their fluctuations may be related to some of the clinical signs and symptoms of psychosis. This relation will need to be tested when the selective imaging of D2\textsuperscript{High} in patients becomes possible by radioactive D2\textsuperscript{High}-selective agonists (Willeit et al., 2006).

If there are multiple neural pathways that mediate psychosis by converging onto a similar set of brain D2\textsuperscript{High} targets, it suggests that there can be multiple causes and multiple genes associated with psychosis in general and schizophrenia in particular.

The negative aspects of psychosis, especially cognition, which is impaired in schizophrenia, may arise from overexpression of D2 in the striatum (Kellendonk et al., 2006).

Dopamine supersensitivity is likely to be a compensatory mechanism, the brain’s response to many different primary neural defects. The primary defects probably lead to other secondary effects as well, thus accounting for the wide variation of clinical signs and symptoms, not only in schizophrenia but in psychosis in general.

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Internal references


External links

- Philip Seeman's website (http://www.utoronto.ca/seeman/)

See Also

Basal Ganglia, Dopamine, Dopamine Anatomy, Dopamine Modulation, Reward, Reward Signals

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