

History of the dopamine hypothesis of antipsychotic action

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Abstract

The dopamine hypothesis of how antipsychotic drugs exert their beneficial effect in psychotic illness has an interesting history that dates back to 1950. This hypothesis is not to be confused with the dopamine hypothesis of schizophrenia; the aim of the latter is to explain the etiology of schizophrenia. The present review does not deal with schizophrenia but, rather, with the historical development of our current understanding of the dopamine-associated actions of the drugs that reduce the symptoms of psychosis. This historical review begins with the serendipitous discovery of chlorpromazine, a drug synthesized around a chemical core that initially served to produce man-made dyes. This molecular core subsequently contributed to the chemistry of antihistamines. It was with the aim of producing a superior antihistamine that chlorpromazine was synthesized; instead, it revolutionized the treatment of psychosis. The first hypothesis of how this drug worked was that it induced hypothermia, a cooling of the body that led to a tranquilization of the mind. The new, at the time, discoveries of the presence of chemical transmitters in the brain soon steered investigations away from a temperature-related hypothesis toward questioning how this drug, and other drugs with similar properties and effects, modulated endogenous neurotransmission. As a result, over the years, researchers from around the world have begun to progressively learn what antipsychotic drugs do in the brain.

Key Words: Chlorpromazine; Haloperidol; G-Protein coupled receptors; Binding assays; Receptor imaging; High affinity states

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Core Tip: This history starts with the synthesis of chlorpromazine in 1950 and traces the steps taken to discover how this drug, and related drugs, work to reduce, sometimes to reverse, the delusions and hallucinations associated with psychosis. The task to understand how these drugs work in the brain continues, as many unknowns remain.

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INTRODUCTION

The synthesis of chlorpromazine in 1950 marks the beginning of modern psychopharmacology. While the clinical usefulness of this drug was almost immediately recognized, it took another 20 years to begin to uncover its mode of action. This review covers the history of these years and the steps that were taken to arrive at the dopamine hypothesis of antipsychotic drug action. It more briefly also outlines how this hypothesis has fared over the ensuing years (Table 1).

HISTORY

Prior to the availability of chlorpromazine, many drugs had been used in psychiatry to tranquilize agitated patients, but this was the first psychoactive agent to not only calm patients, but also to decrease the intensity of their psychotic symptoms. Synthesized by Paul Charpentier of the French pharmaceutical company Rhône-Poulenc, chlorpromazine was the product of a long process that began in the mid-1800s, starting out as a search for a method to synthesize dyes. This search led, in 1883, to the identification by August Bernthsen of a molecular structure, which he called a phenothiazine nucleus, around which later generations of chemists began to make antihistamine drugs for the treatment of allergies. In 1947, the pharmaceutical company, Rhône-Poulenc, produced promethazine, a first generation antihistamine[1] (Figure 1).

Promethazine induced hypothermia in laboratory animals so, in 1949, French military surgeon, Laborit[2] tried giving it to soldiers in order to lower their body temperature and prevent shock before, during, and after surgical operations. He noted that promethazine induced a “euphoric quietude” in his soldiers[2].

Hoping to increase the potency of promethazine, on December 11, 1950, Charpentier *et al*[3] introduced a chlorine atom into one of the rings of promethazine (Figure 2).

The new drug was called RP (for Rhône-Poulenc) 4560. It was tested on rats and produced “detachment, slow reaction to stimuli, and a decrease in initiative.” The compound was again sent for human trials to Laborit, now at the Val de-Grâce Hospital in Paris, and, because of its psychological effects in animals, to a variety of French psychiatrists as well.

The first published report of its effect in humans was by Laborit and his team in February 1952. They reported that the drug calmed anxious patients without producing oversedation[4]. Three psychiatrists reported on the effect of the drug one month later[5]. This team concluded that 50-100 mg of RP4560, diluted in a glucose solution and given intravenously to patients with mania, kept them calm for 3 to 18 h, as long as an analgesic or a barbiturate was administered concurrently.

In May 1952, psychiatrists Delay and Deniker[6] published their observation on the soothing effect of the drug in patients with psychosis[6]. In June, this team once again reported positive results[7]. Going on the theory that the drug worked by cooling the body, a therapeutic intervention commonly used by psychiatrists at the time[8-10], in July, Delay *et al*[11] published more detailed results of 8 cases treated with RP4560 [11]. They diagnosed six of these patients as suffering from acute mania, one was said to show “excited delirium.” One patient showed “recurrent excitement” and was described as having “trouble thinking” and using “over rationalization.” In today’s classification systems, this patient might be diagnosed with schizophrenia. In this clinical group’s hands, RP4560 was administered without adjuncts, by injection, with oral tablets substituted for injections usually by the 10th treatment day. The results were remarkable—calm was induced in all patients, with minimum sedation. This created such a sensation in psychiatric circles that, by November 1952, the drug had become available by prescription in France[12].

The pharmaceutical firm Smith Klein and French bought the American rights to the drug and, in 1954, received Food and Drug Administration approval to market it in the United States under the name, Thorazine. The advertisement in the May 1954 issue of the American Journal of Psychiatry read: “Thorazine is useful in controlling anxiety,

Table 1 Major steps in the dopamine hypothesis of antipsychotic drug action

Year	Major Advances
1950	Synthesis of chlorpromazine[3]
1952	Preliminary evidence of antipsychotic effect of chlorpromazine[6,7,11]
1958	Synthesis of haloperidol[16]
1960	Parkinson basal ganglia are deficient in dopamine[19]
1963	Neuroleptics raise level of monoamine metabolites[18]
1966	Neuroleptics may antagonize dopamine receptors[26]
1971	2 nmol haloperidol in plasma effective in psychosis[34]
1974	Synthesis of (+-) butaclamol[36]
1975	Tritiated haloperidol binds DA receptors[38]
1975	Effective neuroleptic dose correlates with D2 block[39]
1979	Multiple dopamine receptors[54]
1984	Bimodal D2 distribution in schizophrenia[45]
1984	High and low affinity states for D2[58]
1988	Cloning of the D2 receptor[63]
1988	<i>In vivo</i> imaging of D2 occupancy[47]
1990	Cloning of D3[67]
1999	Fast-off theory[71]
2000	Multiple genetic variants of D2 receptor[73-75]
2000	Impact of the D3 receptor[81]
2005	Impact of other neurotransmitter receptors[83]
2010	Impact of receptor heterodimers[85]
2017	Impact of D2 high affinity state[77]
2021	Structure and specificities of D1, D2 signaling complexes[79]

tension, agitation, confusion, delirium, or hostility, whether occurring in schizophrenic, manic-depressive, toxic, or functional states." [1]. In France and also in Canada[13-15], the drug was called Largactil. Since it was mainly used in hospitalized patients who, for the most part, suffered from psychotic disorders, it swiftly gained a worldwide reputation for being able to reverse the symptoms of psychosis.

The phenothiazine core molecule was malleable and comparably easy to copy so that compounds with very similar efficacy were readily produced. By 1964, a variety of pharmaceutical companies had synthesized and marketed their own phenothiazines: promazine, trifluorpromazine, methoxypropazine, trifluoperazine, fluphenazine, thioridazine, and prochlorperazine. In 1958, haloperidol, a non-phenothiazine drug [a butyrophenone synthesized on the base of an opioid analgesic, meperidine (Demerol)] was created by pharmaceutical genius, Paul Janssen. This compound proved to be more potent against delusions and hallucinations than the phenothiazines[16].

Both phenothiazines and butyrophenones were initially called 'major tranquilizers' to distinguish them from the 'minor tranquilizer,' meprobamate[17], which was being widely marketed at the time for anxiety.

Searching for the mode of action of major tranquilizers, in 1963, Carlsson and Londqvist[18] reported that this category of drugs increased the level of metabolites of catecholamines. They suggested "... that chlorpromazine and haloperidol block monoaminergic receptors in brain" It was not possible at the time to selectively distinguish among alpha-adrenoceptors, beta-adrenoceptors, and dopamine receptors.

There were, nevertheless, several reasons to believe that it was the dopamine pathway that was involved. Firstly, the clinical side effects of chlorpromazine and haloperidol were tremor, rigidity, and akinesia -e.g. Parkinsonian signs and, by then, Parkinson's disease had been linked to a deficiency of dopamine[19]. Secondly, it had already been suggested that dopamine-mimetic drugs such as amphetamine acted *via*

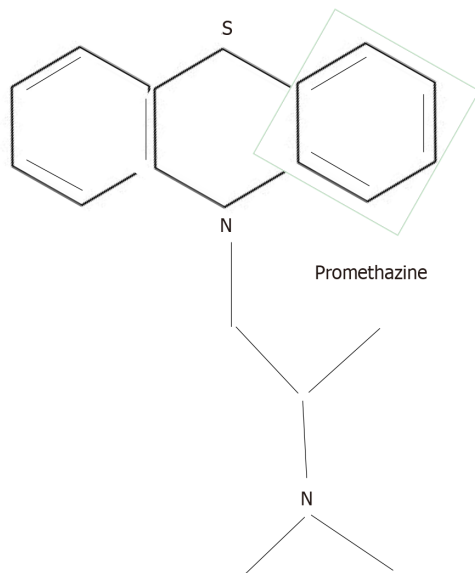


Figure 1 Promethazine.

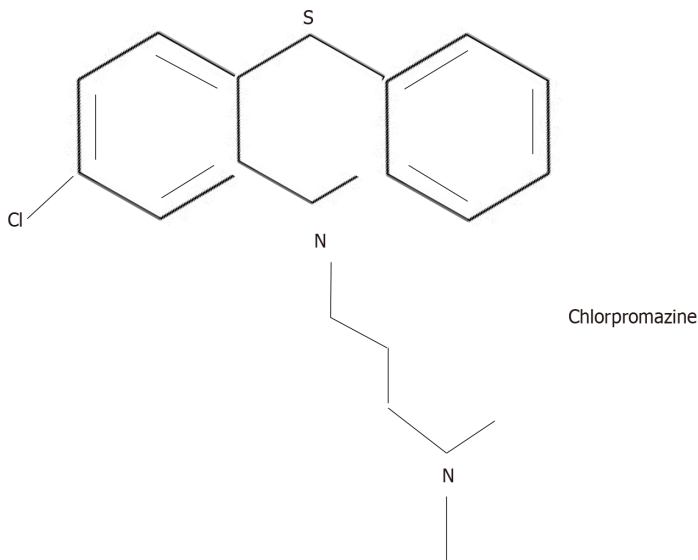


Figure 2 Chlorpromazine.

dopamine receptors[20] and that amphetamines could induce schizophrenia-like psychotic symptoms in patients[21,22]. Disulfiram (Antabuse), in clinical use to prevent alcohol addiction, was known to inhibit dopamine beta-hydroxylase, the enzyme that converts dopamine to noradrenaline, and this drug, too, was capable of inducing psychosis[23].

There were also reports of chlorpromazine accelerating the turnover of dopamine [24]. Van Rossum[25] had noticed in 1965 that major tranquilizers (or neuroleptics as they were called by this time), though not, as was first thought, particularly antiadrenergic, were, instead, potent amphetamine antagonists[25].

The significance of dopamine for the action of antipsychotic drugs, a breakthrough often attributed to Arvid Carlsson (who did not seriously consider dopamine in the context of the action of these drugs until much later) was first formulated by Jacques van Rossum. In 1966, van Rossum[26] hypothesized that dopamine receptor blockade was a likely explanation for the mechanism of action of this group of drugs. He referred to neuroleptics as the first available dopamine antagonists. In 1967, van Rossum[27] wrote: "When the hypothesis of dopamine blockade by neuroleptic agents can be further substantiated, it may have far going consequences for the pathophysiology of schizophrenia. Overstimulation of dopamine receptors could then

be part of the aetiology. Obviously such an overstimulation might be caused by overproduction of dopamine, production of substances with dopamine actions (methoxy derivatives), abnormal susceptibility of the receptors, etc.” [27].

Van Rossum, thus, formulated *two* dopamine hypotheses (1) The hypothesis that dopamine receptor blockade was responsible for the antipsychotic effects of drugs like chlorpromazine, haloperidol, and similar drugs; and (2) The hypothesis that an excess of dopamine might be part of the etiology of schizophrenia. These two distinct hypotheses are often conflated [28].

They are conflated because, in the 1970s, it was hoped that the discovery of how neuroleptics work could lead to understanding the nature of schizophrenia itself. Based on the fact that amphetamine releases dopamine and amphetamine-induced psychosis is clinically very similar to an acute episode of schizophrenia [29], van Rossum [27] thought that schizophrenia might be due to an overproduction of dopamine [27].

From today’s standpoint, overactivity of dopamine, while possibly explaining the hallucinations and delusions of schizophrenia, does not shed light on the more fundamental negative and cognitive symptoms of schizophrenia. Over the years, many attempts have been made to elaborate and expand on van Rossum’s dopamine hypothesis of schizophrenia to account for symptoms other than delusions and hallucinations [30,31]. It remains the case, however, that schizophrenia is too multifaceted and heterogeneous a disorder to be fully explained by dopamine overactivity alone. That being said, it is still possible that the secretion and transmission of dopamine serves as a final common pathway to the expression of specific schizophrenia symptoms [32].

Van Rossum’s first hypothesis—that neuroleptics (today referred to as antipsychotics) exert their effect through dopamine receptors—has enjoyed a longer life than his second. In 2020, Kaar *et al* [33], in their review of mechanisms underlying clinical response to antipsychotics, conclude that “all currently licensed antipsychotic drugs show appreciable binding to dopamine D2 receptors at therapeutic doses, and this action is core to their therapeutic action.”

Van Rossum [25-27] had pointed out that overstimulation by dopamine could result from a number of potential causes, from overproduction by the secreting cell to oversensitivity of receptors on the post-synaptic cell. By extension, antipsychotic drugs could theoretically act by blocking dopamine synthesis or secretion or by interfering with its transport across the synapse or by blocking membrane receptors.

In 1971, Zingales [34] reported that the concentration of haloperidol in the plasma of treated patients was approximately 3 nanograms *per* millilitre of plasma (3 nmol) [34]. Because over 90% of haloperidol in plasma is bound to plasma proteins, the actual free concentration that enters the brain would then have to be approximately 1 nmol. This was a problem for the radioactive tagging needed in the search for specific targets of haloperidol action. The classical way to find a drug target was to tag the drug with a radioactive marker. In this case, however, because the drug needed to be diluted down to 1 nmol and still have enough radioactivity left for the experiment to succeed, the radioactive label had to be extra powerful. No such label existed at the time.

In November 1971, Philip Seeman, a Toronto physician/pharmacologist, asked Paul Janssen to persuade the company, I.R.E. Belgique, to prepare radioactive haloperidol at a high specificity of 10.5 Curies *per* millimole, which the company succeeded in doing in 1974.

True drug receptor targets have to take up the radioactively labelled ligand; a second important criterion in identifying a specific site of action is stereoselectivity—the configuration of the relevant molecule must fit the configuration of the target [35]. Seeman obtained mirror image antipsychotic molecules (+butaclamol and -butaclamol), the first one active, the second inactive [36,37]. A specific antipsychotic target was confirmed when the site was blocked by +butaclamol to a significantly greater degree than it was by -butaclamol. This more or less settled the identity of the antipsychotic receptor. A further step was to see which of the endogenous neurotransmitters had the most affinity for this location. When tested against noradrenaline, acetylcholine, serotonin, and dopamine, dopamine proved to be the most potent. This meant that the antipsychotic receptor was a dopamine receptor [38].

Soon after discovering the receptor, Seeman *et al* [39,40] showed that the published clinical doses of all antipsychotic drugs available at the time, regardless of their molecular structure, directly correlated with their ability to displace radioactive haloperidol [39,40]. This graph has recently been called “the most famous graph in schizophrenia therapeutics.” [41]. The findings from the Seeman laboratory were soon confirmed by binding studies from other labs [42-44]. A further confirmatory finding was that treatment with antipsychotic drugs increased the density of dopamine

receptors in post mortem brain tissue of individuals with schizophrenia[45].

In vivo molecular imaging studies were not initially available but, when they were, they were eventually able to confirm striatal dopamine D2 receptor blockade at clinically effective doses of all antipsychotic drugs, including first and second-generation agents and dopamine partial agonists[46-52]. The initial molecular imaging studies in patients with treated schizophrenia suggested a therapeutic window (relatively good response without unacceptable extrapyramidal adverse effects) of between 60% and 80% D2 receptor occupancy. The definition of 'response,' of course, varies and non-response did not necessarily correlate with low occupancy rates[53].

Since then, the field of dopamine receptors has considerably expanded[54]. The receptor labeled by [3H] haloperidol was called D2[55,56], because, by the mid 1980s, five dopamine receptors, all belonging to a G-protein coupled set of receptors, had been isolated. Today, D1 and D5 are known to stimulate the cyclic adenosine monophosphate signaling pathway through G_s G-proteins, whereas D2R, D3, and D4 inhibit this signal *via* G_{i/o} G-proteins[57]. Moreover, each of these receptors can exist, as can all G-protein linked receptors, in a state of high or low affinity for their ligand [58,59]. Of the 5 known dopamine receptors, D1, D4, and D5 were cloned in the Seeman laboratory[60-62].

The dopamine D2 receptor was cloned in 1988 in the Civelli lab[63,64]. In 1989, Grandy *et al*[65] used *in situ* hybridization to map the gene to the 11q22-q23 junction.

Because of the excellent correlation between the affinity for striatal D2 receptors and the average clinical dose of antipsychotic drugs given to patients with schizophrenia, there was at first general agreement that all effective antipsychotic drugs must act by not only blocking dopamine D2 receptors in the striatum, but also blocking them in the mesolimbic system, where symptoms of psychosis are thought to originate[66].

In 1990, the D3 receptor (closely related to D2) was cloned in the laboratory of Jean-Claude Schwartz[67].

Soon after, the 2nd generation antipsychotic drugs were brought to market, and they appeared to have much lower affinity for the D2/D3 receptors (they induced far fewer extrapyramidal symptoms) but to be just as potent against psychotic symptoms (delusions and hallucinations) as the older drugs. Clozapine, in particular, the best antipsychotic in that patients resistant to all other drugs often respond when prescribed clozapine, attached to many neurotransmitter receptors besides D2/D3 [68]. Many of the new drugs[69], including clozapine[70] had affinity for serotonin 2AR, which was thought explain their much lower relative rate of extrapyramidal effects.

Another explanation was that the antipsychotics drugs that do not elicit extrapyramidal symptoms, such as clozapine and quetiapine, bind to the D2 receptor more loosely than dopamine itself so that endogenous dopamine displaces them very quickly from the target receptor. Drugs that bind most tightly to the D2 receptor (chlorpromazine, trifluoperazine, fluphenazine, haloperidol, risperidone) stay on the receptor for 20-30 min and it is this long continuous occupation that may be responsible for parkinsonism[71,72]. This explanation suggests that, though a certain threshold percentage of D2 receptors still need to be bound in order to obtain an antipsychotic effect, the binding need not be of long duration. 'Hit and run' or 'fast-off' binding is able to prevent some of the adverse effects while still maintaining efficacy against psychosis.

An unresolved continuing problem with respect to antipsychotic drug action is that at least one third of patients with schizophrenia do not respond to drugs that block D2, whether transiently or for long periods, whether with or without serotonin 2A binding. One possible explanation is that individuals inherit different genetic variants of the D2 receptor[73-76], and that these variants determine response. Since the functional state of the dopamine receptor in the anterior pituitary[58], and perhaps everywhere in the brain[77], is its high affinity form, it is perhaps the relative duration of time that these receptors spend in their various affinity states that determines the extent of clinical response. It has been hypothesized that an interaction between D1 and D2 receptors influences the time spent in the high affinity functional state[78]. Every year, more knowledge accumulates about the signaling complexes of D1 and D2 receptors[79] and new radioactive ligands are available that bind specifically to high affinity sites[80].

Although binding to the D2 receptor continues to be considered as the cornerstone of antipsychotic action, the original hypothesis has undergone several refinements, such as the acknowledgement that other dopamine receptors as well as other neurotransmitter receptors play a part[81-84]. There now exist effective antipsychotic drugs that defy the earlier established D2 receptor occupancy threshold, which makes it difficult to attribute antipsychotic effect to any single neurotransmitter receptor[85-

87].

CONCLUSION

Dopamine D2 receptor blockade remains necessary in order to obtain antipsychotic response in most patients. Individuals differ, however, and it remains possible, even probable, that specific subgroups of patients showing psychotic symptoms may respond most robustly to pharmaceutical agents that mainly affect brain chemical transmitters other than dopamine. Pimavanserin, for instance, a serotonin 2A receptor antagonist, has had some success in treating the psychosis associated with Parkinson's disease, a condition of dopamine deficiency[88], but the Food and Drug Administration in the United States has recently found it insufficiently effective for the psychosis associated with Alzheimer's dementia. Differently caused psychoses may respond to differently configured drugs. Looking for the mechanism of action of drugs for psychosis continues, and, as new mechanisms are found, the secrets of the multiple causes of psychotic disorders may be decoded.

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