All Psychotic Roads Lead to Increased Dopamine D2High Receptors: A Perspective

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Abstract

Objective: Brain dopamine supersensitivity is an established feature of schizophrenia. Animal models of schizophrenia also show dopamine supersensitivity, but surprisingly, no increase in dopamine D2 receptors. The objective is to determine the basis of dopamine supersensitivity in the animal models of schizophrenia, because this will be relevant to the clinical aspects. **Method:** This perspective reviews recent evidence from the animal and human literature. Because brain dopamine supersensitivity is known to be a feature of schizophrenia and related psychoses, and because antipsychotics have a dopamine-blocking action, we examined proposed animal models of psychosis and their dopaminergic abnormalities. **Results:** All the animal models reveal elevations in D2High (D2 receptors with functional high-affinity for dopamine). The models reviewed include lesions, sensitization by drugs (amphetamine, phencyclidine, cocaine, corticosterone), birth injury, social isolation, and gene deletions in pathways for NMDA, dopamine, GABA, acetylcholine, and norepinephrine. **Conclusion:** Multiple abnormal pathways converge to a final common pathway of dopamine supersensitivity and elevated D2High dopamine receptors, perhaps responsible for clinical psychosis and amenable to antipsychotic treatment. Measurement of D2High in humans has not yet been clearly achieved, but will, in time, assist in the diagnosis and treatment of psychosis.

Key Words: Schizophrenia, Psychosis, Dopamine D2 Receptor, D2High, PHNO, Dopamine Supersensitivity, Pergolide

Introduction

This neuroscience perspective on translational research on psychosis summarizes recent data showing that a common feature of the many animal models of psychosis is dopamine supersensitivity associated with an elevation of dopamine D2High receptors. This finding is an impetus to devising a method for measuring D2High in individuals in various stages of psychosis.

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The D2High dopamine receptor is the functionally active state of the dopamine D2 receptor (1). Dopamine has markedly different affinities for the two states of D2, binding at 1-100 nM to D2High, and at 100-10,000 nM to D2Low. Antipsychotic drugs, however, for which the dopamine D2 receptor is the main common target (2), have identical affinity for the high- and low-affinity states of D2.

Considering the many interconnecting pathways in the brain, it is not surprising that various types of brain injury by lesions, drugs, or by gene mutations in specific neurotransmitter pathways can result in major biochemical alterations in another different pathway. As summarized here, many brain injuries or treatments related or unrelated to dopamine transmission can result in biochemical and behavioral dopamine supersensitivity, the latter being an established feature of schizophrenia (3, 4). Dopamine supersensitivity in animals is measured by behavioral tests after challenges

with a single dose of amphetamine, apomorphine, cocaine or methylphenidate.

The psychotic symptoms in schizophrenia increase or intensify when the individual is challenged with psychostimulants at doses that have little effect in control subjects. As reviewed by Lieberman et al. (3), 74 to 78% of patients with schizophrenia become worse, with new or intensified psychotic symptoms, after being given amphetamine or methylphenidate. Psychotic symptoms can also be elicited in this way in control subjects, but only in 0 to 26%. In addition, the worsening of symptoms caused by the psychostimulants occurs to the same degree even when patients are taking antipsychotics. Altogether, psychotogens elicit or enhance psychotic symptoms in 40% of schizophrenia patients compared to ~2% of control individuals. The data thus indicate that, compared to control subjects, dopamine supersensitivity is prevalent in patients with schizophrenia, whether or not they are medicated with antipsychotics.

Psychotic symptoms occur not only in schizophrenia but in many brain diseases, and also as a result of the use of steroids, amphetamine, cocaine, phencyclidine or ethanol. Although each of these conditions shows unique features in addition to psychosis, no common basis or target has ever been identified to explain the psychotic signs and symptoms that are a common feature of these various states.

D1 and D2 Receptors in Schizophrenia

While the increase in behavioral dopamine sensitivity in animals has been at least two- or three-fold after denervation or after long-term antipsychotics, the total density of D2 receptors increases by only 10 to 40%. Moreover, even though most patients with schizophrenia are supersensitive to dopamine, the density of the total population of D2 receptors is elevated by 20 to 50% in postmortem human schizophrenia striatal tissues, a finding that has not been confirmed in never-treated schizophrenia volunteers when using [11C]raclopride positron emission tomography (PET).

In first-episode patients who have never been treated with antipsychotics, the concentration of D2 receptors (as monitored by PET) is generally elevated by only 8 to 30% in the frontal cortex and striatum, but reduced by 12 to 30% in the cingulate cortex, the right medial thalamic nucleus, and the midbrain. Considering the significant clinical increase in dopamine supersensitivity, the alterations in D2 receptors appear to be modest.

However, never-medicated schizophrenia patients may reveal either a decrease of ~15 to 40% or an increase (5) in the concentration of dopamine D1 receptors in the frontal cortex, the cingulate gyrus, the temporal cortex, and the striatum. Any reduction in D1 may contribute to an overactivity of D2, considering that D1 has been found to convert the functional D2High receptors into the less active or non-functional D2Low receptors. It should be kept in mind, however, that findings differ as to whether D1 and D2 are co-localized in the same neuron, and, therefore, able to influence one another directly.

It may be that D2 receptors in some regions increase in response to a reduction in dopamine release from presynaptic terminals, reflecting a hypodopamine state in psychosis. A second interpretation is that D2 in some regions becomes elevated by an increased synthesis of postsynaptic D2 during psychosis, reflecting a hyperdopamine state.

The observation that antipsychotic drugs alleviate psychosis by inhibiting D2 receptors supports the hypothesis that psychosis is associated with a hyperdopamine state. This conclusion also applies to dopamine partial agonists such as aripiprazole and bifeprunox, which antagonize D2 with dissociation constants (Ki values) of 1.8 nM and 3.8 nM, respectively, closely fitting the general relation between the clinical doses and the Ki values for all antipsychotics.

Despite the modest elevations in D2 receptors in schizophrenia, they may explain the hyperdopamine state. A more relevant question, however, is whether the functional state of D2, or D2High, is elevated in dopamine supersensitive animal models on one hand, and in clinical schizophrenia on the other.

Elevation of D2High in Dopamine-Sensitive Animals

Of the many animal models of psychosis that have been proposed, the model of amphetamine sensitization has received the most support. Although the amphetamine-sensitized animal is supersensitive to amphetamine and other dopamine-like drugs, the density of D2 receptors in the brain striatum is normal (2). Surprisingly, however, D2High receptors in the striatum were found to be markedly elevated, by 250% (see Table 1). Therefore, a series of collaborative studies investigated whether this elevation in D2High occurred in other animal models of psychosis.

The first group of animal models examined was the brain lesion models. Many types of brain lesions have been proposed as models for schizophrenia, including lesions of the neonatal hippocampus and the entorhinal cortex, and cholinergic lesions of the cerebral cortex. For example, the striata from dopamine-supersensitive adult rats with neonatal hippocampal lesions do not show any elevations in the total population of D2 receptors, but do reveal a two-fold to four-fold elevation in the proportion of D2High receptors.

After the brain lesion models of psychosis revealed that D2High receptors were consistently elevated, mice with specific gene deletions were examined. Table 1 summarizes

the markedly enhanced levels of D2High receptors in the brain striata of gene-deleted mice (gene knockout mice) that showed behavioral dopamine supersensitivity. Gene knockouts with no increase in behavioral dopamine sensitivity did not reveal any elevation in the proportion of D2High receptors.

In contrast to the elevation of D2High in the supersensitive animals, the striata from D1 knockout mice did not show any increase in the density of D1 receptors or in the proportion of D1High receptors.

Deletions of GABA, Glutamate, and Non-Dopamine Genes Increase D2High

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 D2High receptors. These genes include those for the GABAB1 receptor, RIIβ protein kinase A, PSD95 (Post-Synaptic Density protein 95), GPRK6 (G-Protein Receptor Kinase 6), the trace amine-1 receptor, and RGS9-2 (Regulator of G protein Signaling 9-2).

Considering the hypoglutamate hypothesis of schizophrenia, the deletion of the PSD95 gene is of interest (see Table 1). This protein serves to anchor the NMDA (N-methyl-D-aspartic acid) receptor to the cell membrane, and it is known that the dopamine D1 receptor forms a dimer with the NMDA receptor as well as a dimer with D2. Therefore, interference or deletion of PSD95 could cause receptor rearrangement leading to increased D2High and dopamine supersensitivity.

Many gene knockouts, of course, do not result in dopamine supersensitivity, because knockouts of some genes, such as those for adenosine A2A receptors, lead to dopamine *subsensitivity*. Indeed, in keeping with this reduction in dopamine sensitivity, the D2High receptors are reduced by 75% in the striata of adenosine A2A knockout mice. Similarly, knockouts of the metabotropic glutamate receptor 5 (mGluR5) are not supersensitive, and the proportion of D2High receptors does not increase.

Other Psychosis Models: Caesarian Birth with Anoxia; Psychostimulants; Social Isolation; Steroids

An important animal model for schizophrenia is that of birth hypoxia during Caesarian section (Table 1). Adult rats born by Caesarian section (with or without added anoxia) exhibit dopamine supersensitivity. Striata from these rats reveal a two-fold to five-fold elevation in the proportion of

Table 1 Increase in D2High Receptors in Dopamine-Supersensitive Animal Models for Psychosis

Treatment*	% Increase in Proportion of D2High
Sensitization by:	
Amphetamine	250%
Phencyclidine	180%
Cocaine	160%
Caffeine	125%
Quinpirole	50%
Corticosterone	210%
Lesions of:	
Neonatal hippocampus	270%
Neonatal hippocampus	160%
Cholinergic lesion in cortex	130%
Entorhinal hippocampus	100%
Knockout of gene for:	
Dopamine D4 receptor	200-900%
GPKR6	60-340%
Alpha-Adrenoceptor-1b	232%
GABAB1	225%
Dopamine-beta-hydroxylase	200%
Trace amine-1 receptor	160%
RGS9-2	135%
Nurr77	133%
Postsynaptic density 95	129%
Tyrosine hydroxylase (no dopamine)	120%
COMT	90%
Vesicular monoamine transporter	60-80%
RII beta (protein kinase A)	48%
Dopamine transporter	39%
Other:	
Caesarian birth with anoxia (rat)	130-460%
Rats socially isolated from birth	228%
Reserpine-treated rats	100%
Animals not showing dopamine supersensitivity:	
Dopamine D1 receptor knockout mice	-7%
Glycogen synthase kinase 3 knockout mice	19%
Adenosine A2A receptor knockout mice	-75%
mGluR5 knockout mice	20%

*Refs. in Ref. #2 and in preparation.

D2High receptors, but no increase in the total population of D1 or D2 receptors.

Rats that have been sensitized by amphetamine, phencyclidine, quinpirole, cocaine or caffeine become supersensitive to dopamine agonists. The striata from such supersensitive rats do not reveal any increase in dopamine D2 receptors, but do show a two-fold to four-fold elevation in the proportion of D2High receptors.

Social isolation is a risk factor for psychosis, and rats isolated from birth reveal dopamine supersensitivity and elevated D2High receptors (Table 1).

Steroid-induced psychosis in humans is a complication of glucocorticoid administration. Correspondingly, rats given high doses of corticosterone for five days become dopamine supersensitive and respond to amphetamine with increased locomotor activity. The striata from such corticosterone-treated rats show a 210% increase in D2High receptors.

Measurement of D2High Receptors in Humans

Because D2High receptors are consistently elevated in the animal models of the various human psychoses, and because the majority of psychotic episodes responds to D2 blockade, it appears reasonable to consider D2High a common target for the convergence of the various psychosis pathways. Moreover, it is reasonable to hypothesize that factors or altered genes that lead to dopamine supersensitivity can also increase the risk for psychosis or schizophrenia.

More specifically, dopamine supersensitivity and elevated D2High occurs in rats as a consequence of factors known to elicit psychosis in humans, including amphetamine, phencyclidine, cocaine, excessive caffeine, corticosterone, brain damage, birth trauma, social isolation and genetic alterations. In addition, the dopamine supersensitivity and elevation of D2High receptors elicited by antipsychotics may explain antipsychotic-induced supersensitivity psychosis.

Consistent with the hypothesis of D2High being the convergent target for various psychoses is the fact that most psychoses respond to treatment with D2 antagonists. This includes phencyclidine psychosis (6). The treatment of phencyclidine psychosis by haloperidol is significant, because haloperidol does not block NMDA receptors, indicating that the D2 target contributes to phencyclidine psychosis.

Because D2High is the functional state of the D2 receptor, the elevated D2High receptors may be related to some of the clinical signs and symptoms of psychosis. It is even possible that the fluctuations in the clinical intensity of psychotic signs and symptoms are related to the fluctuating proportions of D2High and D2Low. This relation will need to be tested when the selective imaging of D2High in patients becomes possible by radioactive D2High-selective agonists (7).

A reliable method for measuring D2High in humans is presently a major challenge. Although many ligands have been developed for this purpose ([11C]N-propylnorapomorphine; [11C]-(+)PHNO), no clear changes have yet been reported in psychotic subjects.

In fact, there are reports that the D2High state may not exist or is not detectable in intact cells (8). Although Sibley et al. (8) could not detect D2High receptors in intact anterior pituitary cells by means of [3H]spiperone, experiments with [3H]domperidone, a D2-selective label that clearly distinguishes between high- and low-affinity states for D2 receptors, have readily detected D2High receptors in these intact anterior pituitary cells and in thick slices of striatum containing mostly intact neurons (to be published).

Using [11C]NPA, Narendran et al. (9) found that the density of D2 sites was 79% of the density of [11C]raclopride sites (baboon striatum), suggesting that the D2High sites comprised 79% of the D2 population. However, such a comparison between the D2 densities of two ligands is not a reliable index of D2High, considering that D2 densities differ by 25 to 75% with different antagonist ligands on cloned D2-containing cells (see also 10).

Multiple Pathways, Multiple Genes, Multiple Causes

If there are multiple neural pathways that mediate psychosis by converging onto a similar set of brain D2High targets, it suggests that there can be multiple causes and multiple genes associated with psychosis in general and schizophrenia in particular. It is even likely that different families will probably have different sets of risk genes for schizophrenia.

Although the elevation of D2High receptors may be a necessary minimum for psychosis, it is not likely to be sufficient for full expression of psychotic features. For example, Hirvonen et al. (11) found a significant elevation of D2 receptors in healthy co-twins of schizophrenia individuals, suggesting that the elevation of D2 was necessary, but not sufficient, for psychosis to develop. At the same time, the elevation of D2 is becoming recognized as a valuable biomarker for prognosis and outcome in first-episode psychosis (12).

Future work may show that direct measurement of D2High receptors by means of a radioactive dopamine-like agonist can be an even more reliable biomarker for prognosis and outcome.

This perspective summarizes molecular dopamine supersensitivity as a possible basis for the *positive* signs and symptoms of psychosis. Less is known, however, about the biology underlying the *negative* aspects of psychosis, espe-

cially cognition, which is substantially impaired in schizophrenia. Recent work has implicated D2 here as well. Overexpression of D2 in the striatum (13) or overexpression of the human COMT-valine gene can lead to cognitive deficits in animals.

It is also important to point out that long-term administration of antipsychotic drugs can induce dopamine supersensitivity and antipsychotic tolerance in animals (2, 14). These effects presumably also occur in humans and may be part of the basis for supersensitivity psychosis (15, 16). Although the D2High receptors become elevated after long-term antipsychotics, these elevated D2High states readily reverse, unlike the permanently elevated D2High states in the other animal models of psychosis mentioned above. In fact, supersensitivity psychosis may sometimes be made manifest by rapid antipsychotic withdrawal or the rapid dissociation of clozapine or quetiapine from the D2 receptor (17).

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

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References

1. George SR, Watanabe M, Di Paolo T, Falardeau P, Labrie F, Seeman P. The functional state of the dopamine receptor in the anterior pituitary is in the high affinity form. Endocrinology 1985;117(2):690-697.

2. Seeman P, Schwarz J, Chen JF, Szechtman H, Perreault M, McKnight GS, et al. Psychosis pathways converge via D2high dopamine receptors. Synapse 2006;60(4):319-346.

3. Lieberman JA, Kane JM, Alvir J. Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology (Berl) 1987;91(4):415-433.

4. Curran C, Byrappa N, McBride A. Stimulant psychosis: systematic review. Br J Psychiatry 2004;185:196-204.

5. Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, et al. Prefrontal dopamine D1 receptors and working memory in schizophrenia. J Neurosci 2002;22(9):3708-3719.

6. Giannini AJ, Nageotte C, Loiselle RH, Malone DA, Price WA. Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. J Toxicol Clin Toxicol 1984-1985;22(6):573-579.

7. Willeit M, Ginovart N, Kapur S, Houle S, Hussey D, Seeman P, et al. High-affinity states of human brain dopamine D2/3 receptors imaged by the agonist [11C]-(+)-PHNO. Biol Psychiatry 2006;59(5):389-394.

8. Sibley DR, Mahan LC, Creese I. Dopamine receptor binding on intact cells. Absence of a high-affinity agonist-receptor binding state. Mol Pharmacol 1983;23(2):295-302.

9. Narendran R, Hwang DR, Slifstein M, Hwang Y, Huang Y, Ekelund J, et al. Measurement of the proportion of D2 receptors configured in state of high affinity for agonists in vivo: a positron emission tomography study using [11C]N-propyl-norapomorphine and [11C]raclopride in baboons. J Pharmacol Exp Ther 2005;315(1):80-90.

10. Sum CS, Pyo N, Wells JW. Apparent capacity of cardiac muscarinic receptors for different radiolabeled antagonists. Biochem Pharmacol 2001;62(7):829-851.

11. Hirvonen J, van Erp TG, Huttunen J, Aalto S, Nagren K, Huttunen M, et al. Increased caudate dopamine D2 receptor availability as a genetic marker for schizophrenia. Arch Gen Psychiatry 2005;62(4):371-378.

12. Corripio I, Perez V, Catafau AM, Mena E, Carrio I, Alvarez E. Striatal D2 receptor binding as a marker of prognosis and outcome in untreated first-episode psychosis. Neuroimage 2006;29(2):662-666.

13. Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V, et al. Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. Neuron 2006;49(4):603-615.

14. Samaha AN, Seeman P, Stewart J, Rajabi H, Kapur S. "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to failure over time. J Neurosci 2007;27(11):2979-2986.

15. Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry 1980;137(1):16-21.

16. Margolese HC, Chouinard G, Beauclair L, Belanger MC. Therapeutic tolerance and rebound psychosis during quetiapine maintenance monotherapy in patients with schizophrenia and schizoaffective disorder. J Clin Psychopharmacol 2002;22(4):347-352.

17. Seeman P. Atypical antipsychotics: mechanism of action. Can J Psychiatry 2002;47(1):27-38.