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Psychosis Pathways Converge via $D2^{High}$ Dopamine Receptors

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KEY WORDS schizophrenia; psychosis biomarker; degenerative brain; amphetamine; phencyclidine; gene mutations; dopamine receptors; psychosis; $D2^{High}$ receptors; dopamine supersensitivity; gene knockouts

ABSTRACT The objective of this review is to identify a target or biomarker of altered neurochemical sensitivity that is common to the many animal models of human psychoses associated with street drugs, brain injury, steroid use, birth injury, and gene alterations. Psychosis in humans can be caused by amphetamine, phencyclidine, steroids, ethanol, and brain lesions such as hippocampal, cortical, and entorhinal lesions. Strikingly, all of these drugs and lesions in rats lead to dopamine supersensitivity and increase the high-affinity states of dopamine D2 receptors, or $D2^{High}$, by 200–400% in striata. Similar supersensitivity and $D2^{High}$ elevations occur in rats born by Caesarian section and in rats treated with corticosterone or antipsychotics such as reserpine, risperidone, haloperidol, olanzapine, quetiapine, and clozapine, with the latter two inducing elevated $D2^{High}$ states less than that caused by haloperidol or olanzapine. Mice born with gene knockouts of some possible schizophrenia susceptibility genes are dopamine supersensitive, and their striata reveal markedly elevated $D2^{High}$ states; such genes include dopamine-β-hydroxylase, dopamine D4 receptors, G protein receptor kinase 6, tyrosine hydroxylase, catechol-*O*-methyltransferase, the trace amine-1 receptor, regulator of G protein signaling RGS9, and the RIIβ form of cAMP-dependent protein kinase (PKA). Striata from mice that are not dopamine supersensitive did not reveal elevated $D2^{High}$ states; these include mice with knockouts of adenosine A_{2A} receptors, glycogen synthase kinase GSK3β, metabotropic glutamate receptor 5, dopamine D1 or D3 receptors, histamine H1, H2, or H3 receptors, and rats treated with ketanserin or a D1 antagonist. The evidence suggests that there are multiple pathways that converge to elevate the $D2^{High}$ state in brain regions and that this elevation may elicit psychosis. This proposition is supported by the dopamine supersensitivity that is a com-

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mon feature of schizophrenia and that also occurs in many types of genetically altered, drug-altered, and lesion-altered animals. Dopamine supersensitivity, in turn, correlates with $D2^{High}$ states. The finding that all antipsychotics, traditional and recent ones, act on $D2^{High}$ dopamine receptors further supports the proposition. **Synapse 60: 319–346, 2006.** © 2006 Wiley-Liss, Inc.

INTRODUCTION

Although many biological abnormalities have been found in various psychotic diseases, it is important to search for a target or biomarker that is common to these psychoses, including schizophrenia, so as to develop better treatment of these conditions. This overview considers the proposal that one such common biomarker is behavioral dopamine supersensitivity and its accompanying elevation of $D2^{High}$ dopamine receptors (Seeman et al., 2005a), $D2^{High}$ being the functional high-affinity state of the D2 receptor (George et al., 1985; McDonald et al., 1984).

Considering the many interconnecting pathways in the brain, it is not surprising that various types of insult to the brain by drugs, brain lesions, or gene alterations of a specific biochemical pathway can result in a major biochemical alteration in another completely different pathway. For example, as shown later, various treatments unrelated to dopamine transmission can result in biochemical and behavioral dopamine supersensitivity, the latter being a feature of schizophrenia (Curran et al., 2004; Lieberman et al., 1987). Therefore, while several genes (such as BDNF, neuregulin, dysbindin, D-amino acid oxidase, and calcineurin) are thought to be associated with schizophrenia and thought to be related to glutamate or NMDA neurotransmission (Collier and Li, 2003; Neves-Pereira et al., 2005), this review indicates that mutations in such genes may well lead to dopamine supersensitivity and to a common biochemical basis for this supersensitivity.

BIOMARKERS OF PSYCHOSIS AND SCHIZOPHRENIA

Psychotic symptoms can occur in many diseases, including schizophrenia, degenerative brain disease, and with the abuse of steroids, amphetamine, cocaine, phencyclidine, or ethanol. Although each of these diseases and conditions has its own specific characteristics, no common target has ever been identified to explain the basis of the psychotic signs and symptoms in these various conditions. Although there have been many biological findings proposed as biomarkers of psychosis, especially in schizophrenia (Tamminga and Holcomb, 2005; Wyatt et al., 1988), none have yet stood the test of time.

SUSCEPTIBILITY GENES FOR SCHIZOPHRENIA

In the case of schizophrenia, for example, an appropriate biomarker would be a mutation or a set of gene mutations that are consistently associated with the illness in many pedigrees. However, no such genes or gene regions have yet been found. Although between 10 and 20 chromosome regions harbor genes that are associated with schizophrenia (Lewis et al., 2003), these regions include a massive number of possible genes. In fact, these regions include many genes, ~20% of the human genome, and harboring ~6000 genes, as illustrated in Figure 1.

Among the gene regions identified by Lewis et al. (2003) are genes frequently mentioned in reviews on this topic. For example, schizophrenia has been associated with the genes for neuregulin (Stefansson et al., 2002, 2004; but not by Thiselton et al., 2004), dysbindin-1 (but not by Morris et al., 2003), D-amino acid oxidase, catechol-*O*-methyl transferase (COMT; Benson et al., 2004; Palmatier et al., 2004; Weinberger et al., 2001), proline dehydrogenase, calcineurin, metabotropic glutamate receptor 3 (Egan et al., 2004), disrupted-in-schizophrenia (DISC1; James et al., 2004), and brain-derived neurotrophic factor (see reviews by Craddock et al., 2005; Harrison and Owen, 2003; Harrison and Weinberger, 2005; McGuffin et al., 2003; Weinberger et al., 2001).

It has been noted that several of these genes are related to glutamate neurotransmission, potentially supporting a glutamate hypothesis of schizophrenia (Goff and Coyle, 2001; Hashimoto et al., 2004; Krystal et al., 2005; Mueller and Meador-Woodruff, 2004; Neves-Pereira et al., 2005; Owen et al., 2005). However, a review of 18 short-term trials of glutamatergic drugs for schizophrenia does not show significant clinical benefit (Tuominen et al., 2005). This situation may change as a result of the finding by Depoortère et al. (2005) that a highly selective blocker of the glycine transporter (see also Atkinson et al., 2001) inhibited amphetamine-induced locomotion in PCP-sensitized rats. Although this important finding by Depoortère et al. (2005) suggests that their compound is potentially antipsychotic, there are many drugs that inhibit amphetamine-induced behaviors but are not clinically effective as antipsychotic medications (Fritts et al., 1997; Itzhak and Martin, 2000; Kim and Vezina, 2002).

It is possible, therefore, that the activities of these genes are also readily related to behavioral dopamine supersensitivity. For example, knockouts of the gene

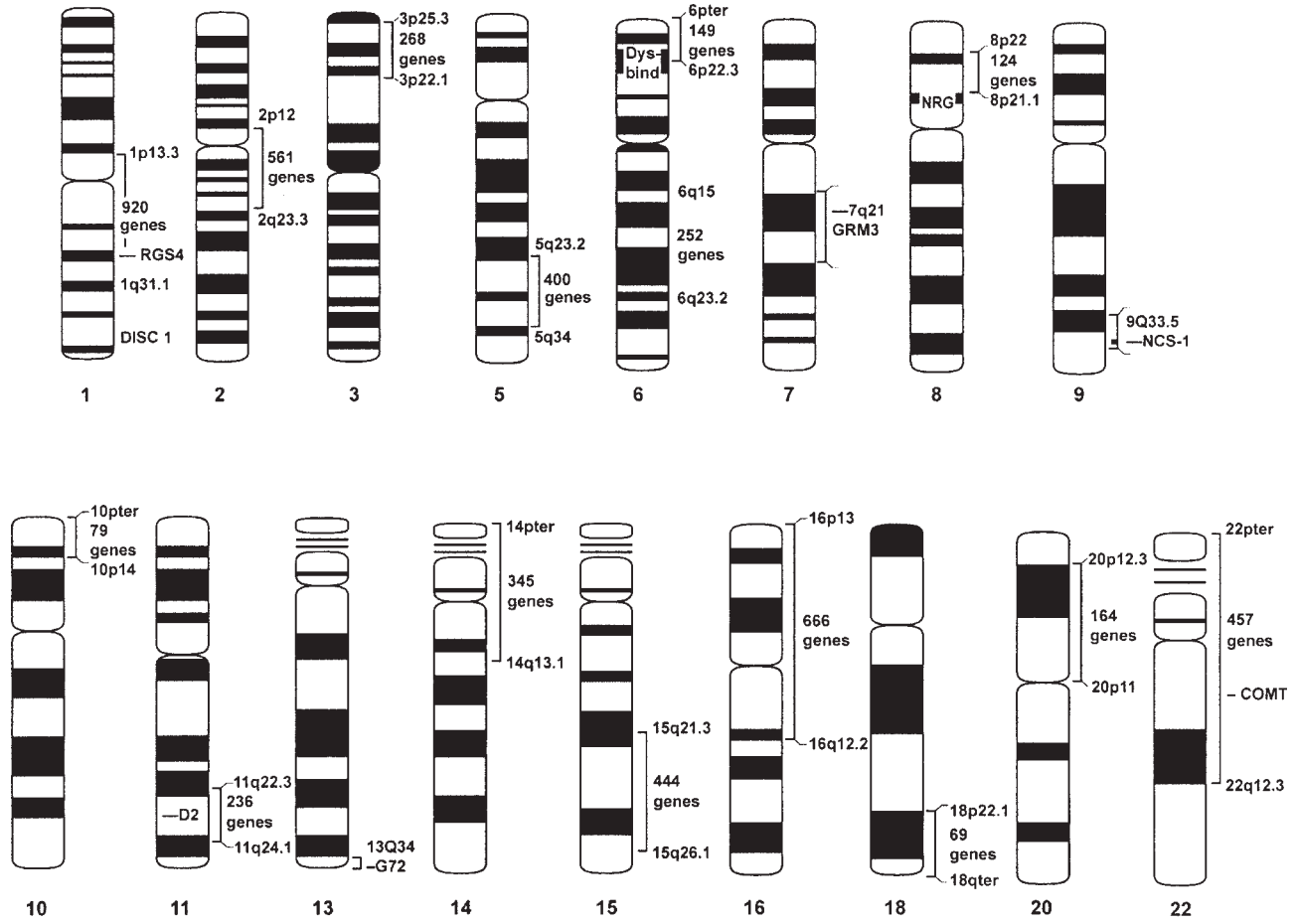

Fig. 1. Chromosome regions and genes associated with schizophrenia, as reported by Lewis et al. (2003). Abbreviations: RGS4, regulator of G protein signaling; DISC, disrupted-in-schizophrenia; Dysbin, dysbindin; GRM3, metabotropic glutamate receptor-3; NRG, neuroregulin; NCS-1, neuronal calcium sensor-1; G72, which interacts with D-amino acid oxidase; D2, dopamine D2 receptor; COMT, catechol-*O*-methyl transferase. The square brackets show the approximate numbers of genes within the regions associated with schizophrenia, the total number of genes being of the order of 6000 genes.

for calcineurin (Miyakawa et al., 2003) or proline dehydrogenase (Paterlini et al., 2005) cause dopamine supersensitivity. Furthermore, D-amino acid oxidase (which interacts with gene G72; Chumakov et al., 2002) can lead to inhibition of dopamine-β-hydroxylase (Naber et al., 1982) and consequent dopamine supersensitivity (Seeman et al., 2005a; Weinshenker et al., 2002). Moreover, neuregulin-1 causes dopamine release (Yurek et al., 2004), while reduction in dysbindin-1 interferes with innervation in the entorhinal hippocampal cortex (Talbot et al., 2004), injuries of which elicit dopamine supersensitivity and a marked elevation of D2^{High} dopamine receptors (Sumiyoshi et al., 2005). In addition, it is known that brain-derived neurotrophic factor induces behavioral dopamine sensitization (Guillin et al., 2001). As reviewed below, behavioral dopamine supersensitivity is invariably associated with an elevation in D2^{High}, that is, an elevation in the proportion of dopamine D2 receptors in the state of high affinity for dopamine (Seeman et al., 2005a).

In searching for schizophrenia risk genes, it has been especially difficult to replicate the genetic association or linkage of a particular gene or a particular chromosome region to schizophrenia in different pedigrees and different groups of patients. This is not particularly surprising, considering that the findings of such studies are highly dependent on the ethnic composition of the population under study. While no single gene of major effect has yet been identified, it is likely that several genes cooperate to lead to schizophrenia, as noted by many authors (e.g., Talbot et al., 2004).

NONGENE BIOMARKERS

The search for nongene biomarkers for schizophrenia has resulted in several biomarkers, although none are unique to psychosis or schizophrenia (Torrey et al., 2005). For example, the apparent elevation of dopamine D2 receptors in lymphocytes in schizophrenia or psychosis (Bondy and Ackenheil, 1987; Soyka et al., 1994) has not

TABLE I. Psychostimulant response rates

	Studies	Schizophrenia subjects	% Worse	Control subjects	% Worse with psychotic symptoms
Oral amphetamine[b]		38	74	39	0
Methylphenidate[a]	5	65	74	39	10
Methylphenidate i.v.[b]		54	78	34	26
d-Ephedrine[a]	9	127	43	307	0
Amphetamine (all routes)[a]	13	281	24	141	1
Patients on antipsychotics[a]	4	52	62		
Antipsychotic-free patients[a]	17	330	41	248	3

[a]Studies reviewed by Lieberman et al., 1987.
[b]Studies reviewed by Curran et al., 2004.

been pursued further because no saturable binding of a D2 radioligand was detected on human lymphocytes (Coccini et al., 1991; Rao et al., 1990; Vile and Strange, 1996).

Important biomarkers for schizophrenia are the eye-tracking abnormalities extensively studied by Holzman and others (Holzman et al., 1988; Kathmann et al., 2003; Matthysse et al., 2004; Sporn et al., 2005) and enlarged ventricles (Egan and Weinberger, 1997; Papiol et al., 2005). There is also a considerable literature on pathomorphology biomarkers in the temporal lobe and entorhinalcortex in schizophrenia (Arnold et al., 1991, 1995; Jacob and Beckmann, 1986, 1994; Ottersen and Storm-Mathisen, 1984).

An additional biomarker that has been extensively examined is that of prepulse inhibition or PPI, using the eye-blink component of the startle response. The PPI test involves measuring the eye blink, or contraction of the orbicularis oculi muscle, in response to a sudden loud sound (acoustic startle response). The eye-blink is attenuated or inhibited when a brief low-intensity stimulus is presented 30–500 ms before the startle-eliciting stimulus (thus, PPI). Deficits in the magnitude of the PPI have been found in schizophrenia patients (Braff et al., 2005; Duncan et al., 2003a,b; Kumari et al., 2004; Mackeprang et al., 2002; Meincke et al., 2004a,b; Oranje et al., 2002) and also in their unaffected siblings (Wynn et al., 2004). In measuring the deficit in patients, some studies find the optimal interval between the sound and the eye-blink to be 60 ms (Ludewig et al., 2003), while other studies can detect the deficit when using an interval of either 30, 60, 100, 120, or 140 ms (see also Cadenhead et al., 2000, who did not find a PPI deficit). Although men with schizophrenia showed less PPI than healthy men, women with schizophrenia did not differ in PPI from healthy women (Kumari et al., 2004). Braff et al. (2005), however, did find that schizophrenia women had a reduction in PPI.

Studies with patients on maintenance doses of antipsychotics show that there is no effect of haloperidol, olanzapine, risperidone, zuclopenthixol, perphenazine, mesoridazine, thiothixene, or M100907 on the PPI deficit (Duncan et al., 2003a,b; Graham et al., 2004; Kumari et al., 1998; Mackeprang et al., 2002), suggesting that the PPI deficit is a stable indicator of reduced sensorimotor gating in schizophrenia. However, studies by Oranje et al. (2002) and Meincke et al. (2004a,b) showed that clinically improved patients (who had taken various antipsychotics, including clozapine) did not reveal PPI deficits. Moreover, it is important to point out that PPI deficits have been reported in many other nonpsychotic psychiatric and neurological disorders, suggesting that PPI deficits may reflect cognitive deficits in general.

PPI is a convenient measurement in animals, and using gene knockout mice, it has been shown that the mGluR5 receptor (Brody et al., 2004a,b), the dopamine D1 and D2 receptors (Ralph et al., 1999; Ralph-Williams et al., 2002, 2003), the serotonin-1A and 1B receptors (Dulawa et al., 2000), and the GABA system (Heldt et al., 2004) may each contribute to the PPI effect. While the mGluR5 knockout mouse reveals a PPI deficit, the deficit was not altered by raclopride, clozapine, lamotrigine, or M100907 (Brody et al., 2004a,b). This is in contrast to the GAD65 knockout mouse (glutamic acid decarboxylase) where the PPI deficit was reversed by clozapine (Heldt et al., 2004). Some antipsychotics can reverse lesion-induced or drug-induced PPI deficits in animals (Anderson and Pouzet, 2001; Feifel and Priebe, 1999; Feifel et al., 2004; Le Pen and Moreau, 2002; Martinez et al., 2002; Russig et al., 2004), but not PPI induced by MK801- or NMDA-type drugs (Bast et al., 2000, 2001). In general, therefore, the antipsychotic action on PPI in animals differs from the general lack of reversal of PPI by antipsychotics in schizophrenia patients, suggesting basic differences in the underlying biology of PPI in humans and animals.

BIOMARKER OF DOPAMINE SUPERSENSITIVITY IN SCHIZOPHRENIA

The psychotic symptoms of patients with schizophrenia increase or become worse when challenged with psychostimulants at doses that cause little change in control patients. For example, the reviews by Lieberman et al. (1987) and by Curran et al. (2004) show that 74–78% of patients with schizophrenia became worse with additional or intensified psychotic signs after being given amphetamine or methylphenidate, compared to 0–26% induction of symptoms in control subjects (Table I). Moreover, the worsening of symptoms caused by the

TABLE II. Dopamine D2 receptors in rat or in knockout mouse striatum

	D2 increase (Ref.)	$D2^{High}$ increase (Ref.)
Dopamine supersensitivity caused by gene knockouts		
α2A adrenoceptor (Lähdesmäki et al., 2004; Juhila et al., 2005)	–	–
α-Synuclein (but not mice with spontaneous deletion) (Schlüter et al., 2003)	–	–
Cannabinoid receptor (CB,–/–) (Martin et al., 2000; Steiner et al., 1999)	1.4-fold (Houchi et al., 2005)	–
Catechol-*O*-methyl-transferase (Comt–/–) (Huotari et al., 2002, 2004)	0.99-fold (Huotari et al., 2004)	1.9-fold (Seeman et al., 2005a)
Dopamine D4 receptor (Drd4–/–) (Rubinstein et al., 1997; Kruzich et al., 2004)	0.91-fold (Seeman et al., 2005a)	1.9–9.9-fold (Seeman et al., 2005a)
Dopamine β-hydroxylase (Dbh–/–) (Weinshenker et al., 2002)	1.03-fold (Seeman et al., 2005a)	1.9–3.2-fold (Seeman et al., 2005a)
ERK1 (extracellular signal-regulated kinase) (Chen et al., 2004)	–	–
Glutamate receptor-A (GluR-A) (Vekovischeva et al., 2001)	–	–
G protein-coupled receptor kinase 6 (Gprk6–/–) (Gainetdinov et al., 2003)	0.88-fold (Seeman et al., 2005a)	1.6–4.4-fold (Seeman et al., 2005a)
Histamine H1 + H2 receptors double knockout (Iwabuchi et al., 2004)	–	–
Melanin-concentrating hormone-1 receptor (Smith et al., 2005)	1.09-fold (Smith et al., 2005)	–
mGluR2 (metabotropic glutamate receptor-2) (Morishima et al., 2005)	–	–
Norepinephrine transporter (Xu et al., 2000)	~1 (Xu et al., 2000)	–
PSD95 (postsynaptic density 95) (Yao et al., 2004)	–	–
RIIβ protein kinase A (–/–)/(+/–) (Brandon et al., 1998)	0.87-fold (Brandon et al., 1998)	1.48-fold (G.S. McKnight, P. Seeman, unpublished data)
RGS9 (regulator of G protein signaling-9) (Rahman et al., 2003)	1.07-fold (Rahman et al., 2003)	2.35-fold (J. Schwarz, P. Seeman, unpublished data)
RIM1 α (G protein Rab3A-interacting molecule) (Powell et al., 2004)	–	–
Serotonin-1B receptor (Bronsert et al., 2001)	–	–
Trace amine-1 receptor (Wolinsky et al., 2004)	–	2.6-fold (T. Wolinsky, T. Branchek, P. Seeman, et al., manuscript in preparation)
Tyrosine hydroxylase/Dbh ($Th^{-/-}$, $Dbh^{Th/+}$) (Kim et al., 2000; Zhou and Palmiter, 1995)	0.99-fold (Kim et al., 2000)	2.2-fold (Seeman et al., 2005a)
VMAT2(+/–) (vesicle monamine transport-2) (Wang et al., 1997; Takahashi et al., 1997)	0.98-fold (Takahashi et al., 1997)	–
Dopamine supersensitivity caused by lesions or drug treatment		
Amphetamine-sensitized rat (see also Robinson and Berridge, 2000)	0.98-fold (Seeman et al., 2002)	3.5-fold (Seeman et al., 2002)
Caesarian birth of rats (Boksa et al., 2002)	0.82-fold (Seeman et al., 2005a)	2–5.6-fold (Seeman et al., 2005a)
Caesarian birth and anoxia (Boksa et al., 2002)	1.02-fold (Seeman et al., 2005a)	2.3–5-fold (Seeman et al., 2005a)
Cholinergic lesion of cortex by saporin (Mattsson et al., 2004)	–	2.3-fold (A. Mattsson, L. Olson, S.O. Ögren, P. Seeman, unpublished data)
Clozapine (35 mg/kg for 9 days) (see also Seeger et al., 1982)	0.7-fold (Seeman et al., 2005a)	1.9-fold (Seeman et al., 2005a)
Ethanol withdrawal (Seeman et al., 2004; Suzuki et al., 1997)	0.96-fold (Seeman et al., 2005a)	3–3.7-fold (Seeman et al., 2005a)
Glucocorticoid (corticosterone 10 mg/kg, 5 days) (Przegalinski et al., 2000)	–	3.1-fold (P. Seeman, unpublished data)
Haloperidol (0.045 mg/kg for 9 days) (Kapur et al., 2003)	0.8-fold (Seeman et al., 2005a)	2.3-fold (Seeman et al., 2005a)
Lesion of neonatal hippocampus (Bhardwaj et al., 2003)	0.61-fold (Seeman et al., 2005a)	3.7-fold (Seeman et al., 2005a)
Lesion of neonatal hippocampus (Lillrank et al., 1999)	1.06-fold (Lillrank et al., 1999)	2.6-fold (B. Lipska, D. Weinberger, P. Seeman, unpublished data; see Fig. 5)
Lesion of entorhinal cortex (Sumiyoshi et al., 2004, 2005)	–	2-fold (Sumiyoshi et al., 2005)
Lesion of nigral neurones (Schwarting and Huston, 1996)	~1.3-fold (reviewed by Schwarting and Huston, 1996)	–
Olanzapine (0.75 mg/kg for 9 days)	0.6-fold (Seeman et al., 2005a)	2.1–2.4-fold (Seeman et al., 2005a)
Phencyclidine-sensitized rat (Robinson and Berridge, 2000; Seeman et al., 2005b)	–	2.8-fold (Seeman et al., 2005a)
Quinpirole-sensitized rat	–	1.5-fold (Seeman et al., 2005a)
Quetiapine (25 mg/kg for 9 days)	0.65-fold (Seeman et al., 2005a)	1.4–2.1-fold (Seeman et al., 2005a)
Reserpine (5 mg/kg for 3 days, 2 days no drug)	–	2-fold (P. Seeman, unpublished data)
Risperidone (0.75 mg/kg for 9 days)	0.67-fold (Seeman et al., 2005a)	1.6–3.2-fold (Seeman et al., 2005a)
Average ± SE	*0.94 ± 0.04*	*2.57 ± 0.2*

(*Continued*)

TABLE II. (Continued)

	D2 increase (Ref.)	$D2^{High}$ increase (Ref.)
Dopamine subsensitivity or no change in sensitivity		
Adenosine A_{2A} receptor (Chen et al., 2003) (subsensitive)	–	0.25-fold (J.F. Chen, M.A. Schwarzschild, P. Seeman, unpublished data)
GR kinase 3 (Gainetdinov et al., 2004) (subsensitive)	–	–
β-Arrestin-1 (Gainetdinov et al., 2004) (subsensitive)	–	–
β-Arrestin-2 (Beaulieu et al., 2005) (subsensitive)	–	–
Cannabinoid receptor (CB,–/–) (Houchi et al., 2005) (no sensitivity change?)	1.4-fold (Houchi et al., 2005)	–
Dopamine D1 receptor (Drd1a–/–) (no change in sensitivity) (El-Ghundi et al., 2001)	–	0.93-fold (Seeman et al., 2005a)
Dopamine D3 receptor (–/–) (no change in sensitivity)	–	0.97-fold (Seeman et al., 2005a)
Dopamine transporter knockdown (Zhuang et al., 2001)	0.99-fold (Zhuang et al., 2001)	–
GSK3β (glycogen synthase kinase 3) (GSK3ß+/–) (subsensitive) (P. Seeman, J. Woodgett, unpublished data; see Beaulieu et al., 2004)	–	1.19 (P. Seeman, J. Woodgett, unpublished data; see Beaulieu et al., 2004)
Histidine decarboxyase (HDC)(Kubota et al., 2002; Iwabuchi et al., 2004)	–	–
Histamine H1 receptor (Iwabuchi et al., 2004) (no sensitivity change)	–	~1-fold (K. Yanai, P. Seeman, unpublished data)
Histamine H2 receptors (Iwabuchi et al., 2004) (no sensitivity change)	–	~1-fold (K. Yanai, P. Seeman, unpublished data)
Histamine H3 receptors (Iwabuchi et al., 2004) (no sensitivity change)	–	~1-fold (K. Yanai, P. Seeman, unpublished data)
mGluR5 knockout (no change in sensitivity)	–	1.14-fold (P. Seeman, J. Roder, unpublished data)

(–), Not reported.

psychostimulants occurred in about two-thirds of patients despite being on antipsychotic medication, as indicated in Table I. Overall, the psychostimulants induced or enhanced psychotic-like symptoms in 40% of the schizophrenia patients compared to ~2% of the control subjects (Lieberman et al., 1987). Although it is not known whether the psychostimulants elicited new psychotic symptoms or intensified those that were present, Janowsky et al. (1977) found that methylphenidate induced "pathologic thinking" predominantly in individuals with schizophrenia.

ELEVATED $D2^{High}$ RECEPTORS AS A BIOMARKER FOR DOPAMINE SUPERSENSITIVITY AND PSYCHOSIS

Ever since the discovery of the antipsychotic receptor (Seeman et al., 1974, 1975, 1976), now known as the D2 dopamine receptor (see also Seeman 1984, 1985, 1989), many experiments have examined whether the density of these receptors change after a variety of treatments and in various psychomotor diseases, and whether such changes may be related to the dopamine supersensitivity that occurs after such treatments. The two most common types of experiments have been the denervation of the neostriatum and the long-term administration of antipsychotics, both procedures of which elevate the density of D2 receptors by only ~10–40% (Schwarting and Huston, 1996; Seeman, 1980). In fact, these small elevations of 10–40% do not appear to be sufficient to quantitatively explain the markedly enhanced behavioral dopamine supersensitivity (Mandel et al., 1993). Moreover, there are many instances of dopamine supersensitivity without any significant change in the density of D2 receptors (Table II; also see Alburges et al., 1993; LaHoste and Marshall, 1992; Mileson et al., 1991).

The D2 receptor, however, can exist in either a state of low affinity for dopamine, $D2_{Low}$, or in a state of high affinity for dopamine, $D2^{High}$, with $D2^{High}$ being the functional physiological state (George et al., 1985; McDonald et al., 1984; see Wreggett and Wells, 1995, for a general description of high- and low-affinity states). Nevertheless, very few publications have examined whether there are any changes in the proportions of D2 receptors in the two different states following various treatments (Gainetdinov et al., 2003; Hall and Sällemark, 1987; Seeman et al., 2002, 2004, 2005a). While the majority of these experiments, using homogenized striata, report that the proportion of $D2^{High}$ states is normally about 50%, the proportion of $D2^{High}$ receptors in rat striatal slices is 77% ± 3% (Richfield et al., 1989).

However, while the increase in behavioral dopamine sensitivity has been at least ~100–300% after denervation or after long-term antipsychotics (Randall, 1985), the D2 dopamine receptors have increased by only ~10–40% (Schwarting and Huston, 1996; Seeman, 1980). Moreover, even though most patients with schizophrenia are supersensitive to dopamine (Curran et al., 2004; Lieberman et al., 1987), the density of the total population of D2 receptors is elevated by only 20–50% in postmortem striatal tissues (Seeman, 1987;

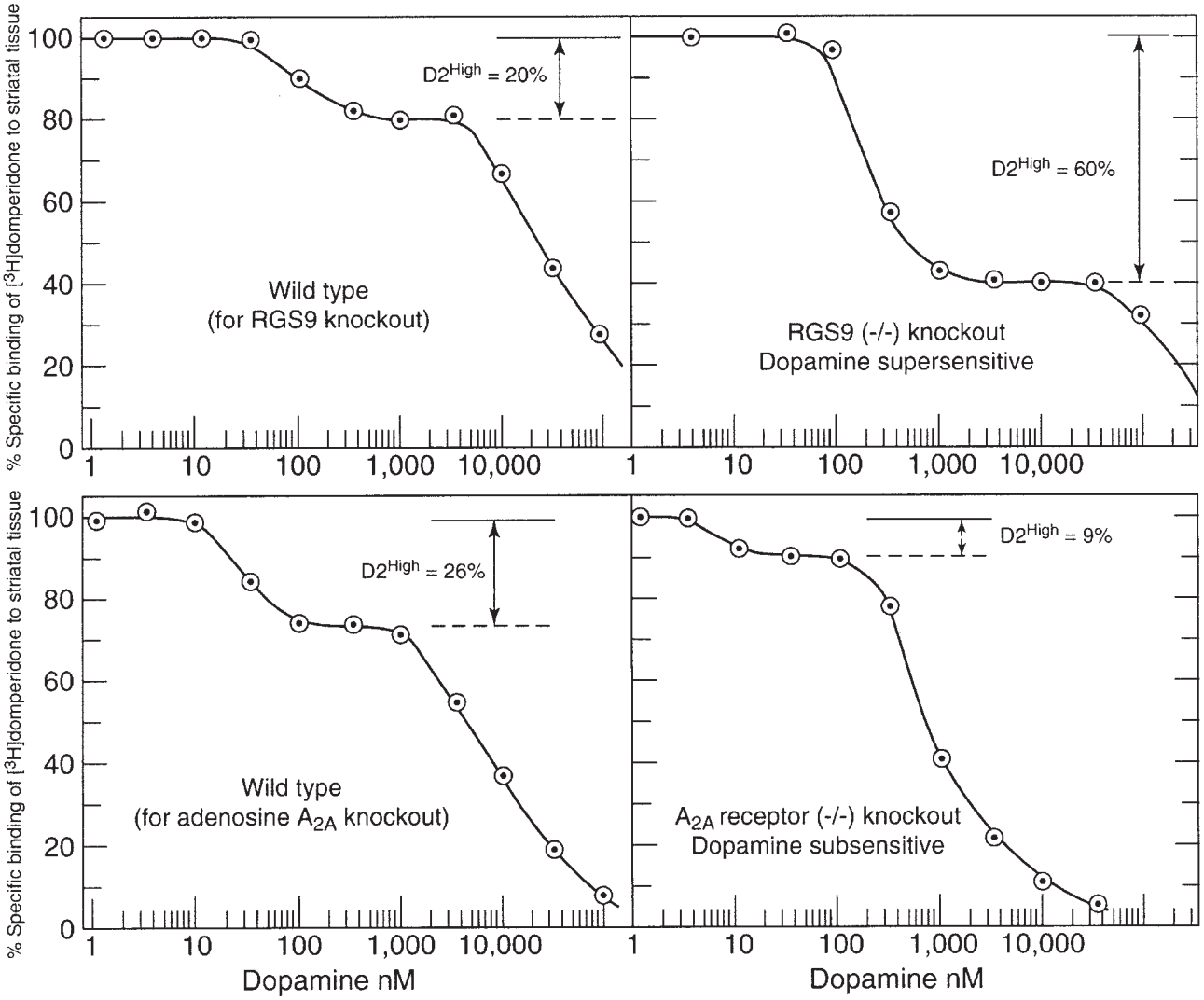

Fig. 2. Top: Knockouts of the genes for RGS9 receptors (in collaboration with J. Schwarz) induced an elevation of $D2^{High}$ receptors in the mouse striata, in keeping with an induction of behavioral dopamine supersensitivity (Rahman et al., 2003). Representative experiment, using 1.9 nM [^{3}H]domperidone (42 Ci/mmol) in 120 mM NaCl. Bottom: Knockouts of the gene for adenosine A_{2A} receptors (in collaboration with J.-F. Chen and M.A. Schwarzchild) markedly reduced the proportion of $D2^{High}$ receptors in the mouse striata, in parallel with the reduced behavioral dopamine supersensitivity (Chen et al., 2003). Representative experiment, using 4 nM [^{3}H]domperidone (68 Ci/mmol) in 120 mM NaCl.

Seeman et al., 1987), and marginally by 10–20% as monitored by positron emission tomography (PET) (Nordström et al., 1995; Tune et al., 1993; Wong et al., 1997).

A more relevant question to be considered here, therefore, has been whether the functional state of D2, or $D2^{High}$, is elevated in dopamine supersensitive conditions and in schizophrenia, because this topic has received little or no study.

GENE KNOCKOUTS

Experimentally, dopamine behavioral supersensitivity occurs after many types of brain lesions, drug treatment, and gene alterations. Table II lists examples of at least 20 gene knockouts that resulted in behavioral dopamine supersensitivity. Figure 2 shows examples of these results.

Interestingly, while some of these gene knockouts, such as genes for histamine receptors, metabotropic glutamate receptors, and RIIβ protein kinase A, are not directly involved with dopamine neurotransmission; the deletion of such genes resulted in the brain becoming supersensitive to dopamine, as indicated by behavioral tests with either amphetamine, apomorphine, cocaine, or methylphenidate.

Other knocked out genes, not listed in Table II and also not directly involved in dopamine transmission, such as $GABA_A$ receptors, appear to result in dopa-

mine hyperfunction (Yee et al., 2005), but do not lead to an increase in behavioral dopamine supersensitivity, as monitored by amphetamine-induced locomotion (Resnick et al., 1999; Yee et al., 2005).

In fact, of course, not all gene knockouts result in dopamine supersensitivity, because knockouts of many genes, such as those for adenosine A_{2A} receptors (Bastia et al., 2005; Chen et al., 2000, 2003), lead to dopamine subsensitivity. Indeed, in keeping with this reduction in dopamine sensitivity, the $D2^{High}$ receptors were reduced by 75% in the striata of adenosine A_{2A} knockout mice (Table II; Fig. 2).

Similarly, knockouts of the metabotropic glutamate receptor 5 (mGluR5) are not supersensitive (Chiamulera et al., 2001), and the proportion of $D2^{High}$ receptors did not increase (Table II).

In addition, knockouts of dopamine D1 receptors (Crawford et al., 1997; El-Ghundi et al., 2001; Xu et al., 1994; but see Karper et al., 2002), dopamine D3 receptors (Karasinska et al., 2005; but also see Accili et al., 1996; Aiba, 1999; Carta et al., 2000; and Xu et al., 1997), dopamine D5 receptors (Holmes et al., 2001), kinases, and arrestins (Table II) lead to dopamine subsensitivity, or do not cause any change in dopamine sensitivity (reviewed by Glickstein and Schmauss, 2001; Holmes et al., 2004; Sibley, 1999).

In some cases it is not obvious as to whether there is dopamine supersensitivity or subsensitivity. For example, in mice with the dopamine transporter (DAT) knocked down (Zhuang et al., 2001), apomorphine no longer has any locomotor-stimulating action. However, an analysis of the data of Zhuang et al. (2001) also shows that the apomorphine ED_{50}% dose required to inhibit locomotion went from a control value of 0.4 mg/kg down to 0.28 mg/kg, an apparent increase in dopamine sensitivity, but presumably presynaptic in nature (Seeman and Madras, 1998).

The same uncertainty exists for conditional calcineurin knockouts (Miyakawa et al., 2003). Although amphetamine stimulated locomotion to the same absolute level of ~1000 cm in calcineurin knockout mice and control mice, the basal activity of the knockout mice was about twofold higher than control, thus reducing the relative increment caused by amphetamine.

ELEVATION OF $D2^{High}$ IN DOPAMINE SUPERSENSITIVE ANIMALS, AND METHODS FOR MEASURING $D2^{High}$ RECEPTORS

In general, while the dopamine supersensitive knockout mice do not reveal a significant elevation in the density of dopamine D2 receptors, a major elevation of the order of 2.5-fold occurs in the proportion of D2 receptors in the high-affinity state, $D2^{High}$, in all these knockouts (Table II).

Although there are several methods to detect the proportion of $D2^{High}$ sites (Seeman et al., 2003, 2005a), the best method is to use the competition between dopamine and [^{3}H]domperidone to demarcate the high-affinity sites, as illustrated in Figure 3. In fact, all of the unpublished data in Table II were obtained using this method. Although [^{3}H]domperidone readily reveals the $D2^{High}$ component (Fig. 3), [^{3}H]spiperone does not (Fig. 3) (e.g., MacKenzie and Zigmond, 1984). The only publication using [^{3}H]spiperone and reporting an antipsychotic-induced increase in $D2^{High}$ proportions is that of Hall and Sällemark (1987); here too, however, the demarcation between the high- and low-affinity components was not obvious, requiring computer-assisted analysis and the controversial assumption that the two states of the receptor do not interconvert.

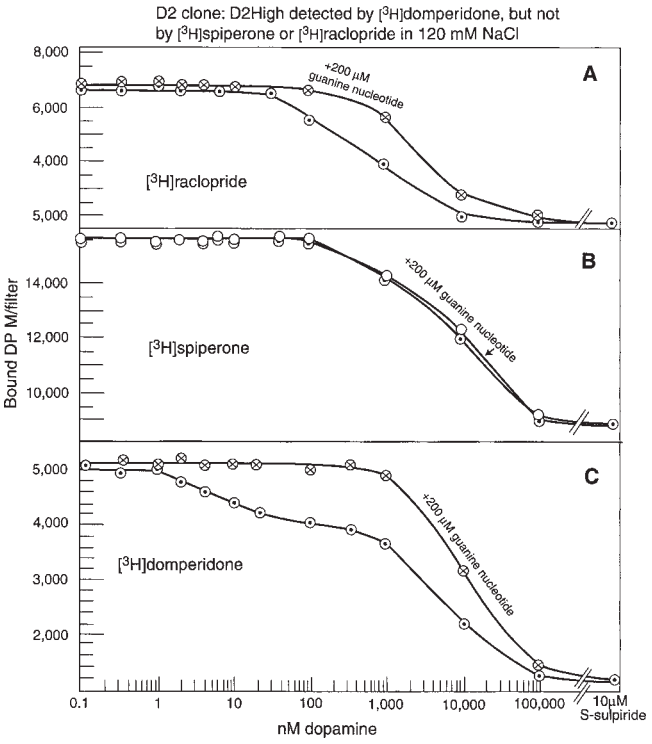

Fig. 3. Human cloned dopamine D2Long receptors in CHO cells: Although competition between dopamine and [^{3}H]spiperone (250 pM; 60 pM Kd), or competition between dopamine and [^{3}H]raclopride (2 nM; 1.9 nM Kd), revealed no obvious high-affinity component for dopamine at D2 receptors in isotonic NaCl, competition between dopamine and [^{3}H]domperidone (1.2 nM; 0.41 nM Kd) in isotonic NaCl revealed a clear high-affinity component for dopamine with a Ki of 1.9 nM. Representative experiments. The high-affinity states were entirely removed in the presence of 200 μM guanilylimidodiphosphate. Nonspecific binding defined by 10 μM *S*-sulpiride. (From Seeman et al., Synapse, 2003, 49, 209–215, reproduced by permission).

The method of competing dopamine with [^{3}H]domperidone is more convenient, more reproducible, and more readily understandable than the [^{3}H]raclopride saturation method (Fig. 4). The latter method defines the $D2^{High}$ receptors as those receptors made manifest by the addition of guanine nucleotide which converts the receptors from their state of high affinity to their

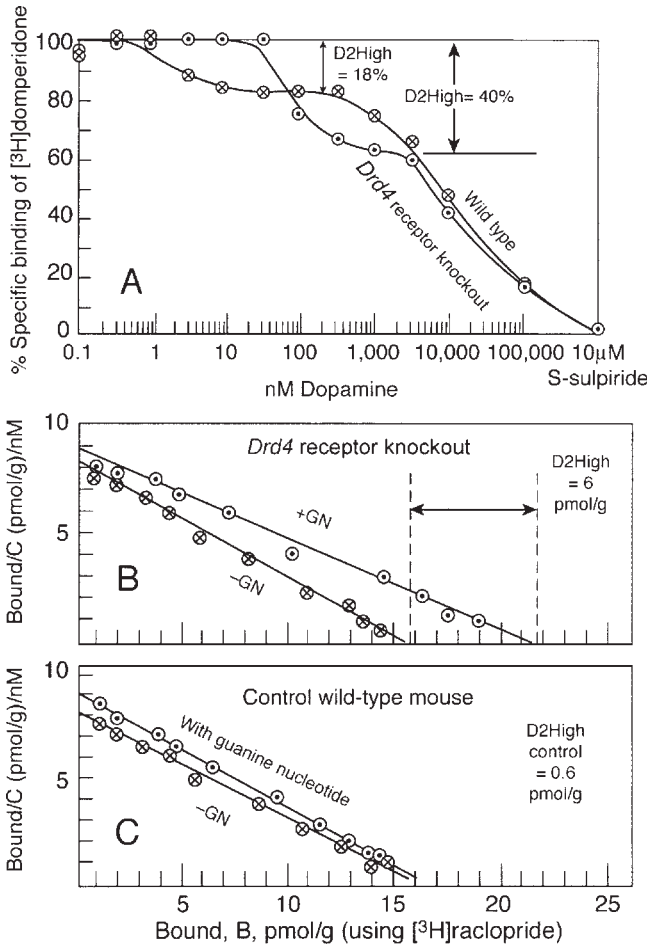

Fig. 4. (**A**) Using the method of dopamine/[^{3}H]domperidone competition, knockouts of the dopamine D4 receptor gene showed an increase of 222% in the proportion of D2^{High} receptors (from a control value of 18% to a value of 40%) (Reproduced with permission from Seeman et al., Proc Nat Acad Sci USA, 2005a, 120:3513–3518). (**B**) Using the method of saturating the D2 receptors with [^{3}H]raclopride, the difference in D2 density (B_{max}) with and without guanine nucleotide (200 μM guanilylimidodiphosphate) was 6 pmol/g. This represents a 10-fold increase in the density of D2^{High} receptors, when compared to the control value of 0.6 pmol/g in Figure 2C (Reproduced with permission from Seeman et al., Proc Nat Acad Sci USA, 2005a, 120:3513–3518).

state of low affinity for endogenous dopamine, thus increasing the binding of [^{3}H]raclopride.

Compared to [^{3}H]spiperone or [^{3}H]raclopride, which easily permeate cell membranes, it is likely that [^{3}H]domperidone more readily reveals the high-affinity state for the D2 receptor (Fig. 3) because [^{3}H]domperidone does not permeate cell membranes (see Refs. in Seeman et al., 2003), and therefore, preferentially labels the D2 receptors that are facing the synaptic space. This view is supported by the fact that the apparent density of D2 receptors, as labeled by [^{3}H]domperidone, is about half that labeled by [^{3}H]raclopride. For example, the density (or B_{max}) of D2 receptors in the rat striatum for [^{3}H]domperidone is 13 ± 1 pmol/g (mean ± SE; n = 3), while that for [^{3}H]raclopride is 18 ± 0.5 pmol/g (mean ± SE; n = 53), regardless of how the striatal tissue is homogenized (P. Seeman, unpublished data). Furthermore, the density of the [^{3}H]domperidone sites is markedly increased by 44% (P. Seeman, unpublished data) when saponin (3–10 μg/ml of holothurin A) is added to permeabilize the homogenized striatum (Seeman, 1974; Seeman et al., 1973) and to permit [^{3}H]domperidone to label internalized D2 receptors. Thus, by apparently labeling D2 receptors primarily on the exterior aspect of the cell membrane, [^{3}H]domperidone more readily detects D2^{High} receptors. This is because the low-affinity receptors have already been internalized premortem (Ko et al., 2002), and the low-affinity receptors are essentially not accessible to [^{3}H]domperidone unless the tissue is permeabilized.

In contrast to the elevation of D2^{High} in the supersensitive animals, the striata from the knockout mice did not show any increase in the density of D1 receptors or in the proportion of D1^{High} or D3^{High} receptors (Table III).

LESIONS

Many types of brain lesions have been proposed as models for schizophrenia, including lesions of the neonatal hippocampus (Bhardwaj et al., 2003; Lillrank et al., 1999; Lipska et al., 1991, 1993, 2003; Lipska and Weinberger, 1993; Schroeder et al., 1999; Wan et al., 1996; Wan and Corbett, 1997; Wood et al., 1997), the cerebral cortex (Mattsson et al., 2004), the entorhinalcortex (Sumiyoshi et al., 2004, 2005; Uehara et al., 2000), and the medial prefrontal cortex (Flores et al., 1996a,b; Jaskiw et al., 1990). The striata from adult rats that have been lesioned neonatally generally do not show any elevations in D2 receptors (Flores et al., 1996a,b; Lillrank et al., 1999; Schroeder et al., 1999) but do reveal two–four-fold elevations in the proportion of D2^{High} receptors (Fig. 5; Table II).

Although dopaminergic denervation of the striatum in MPTP-treated monkeys is not accompanied by an increase in D2 receptors labeled by [^{11}C]raclopride (Doudet et al., 2000), there is likely to be a significant elevation in D2^{High} receptors, which in principle, could be measured by [^{11}C]PHNO (Willeit et al., 2006; Wilson et al., 2005).

The neonatally lesioned hippocampus is a particularly interesting model for schizophrenia, because many studies have found a small (4%; Nelson et al., 1998) but significant reduction in the volume of the hippocampus bilaterally in schizophrenia (Geuze et al., 2005). The reduction in the hippocampus volume, however, does not appear to progress over several years (DeLisi et al., 1997; Lieberman et al., 2001). While such reductions in the hippocampus volume are not specific to schizophrenia (Geuze et al., 2005), the decreases are also found in unaf-

TABLE III. Dopamine D1 and D3 receptors in rat striatum or in knockout mouse striatum

	D1 Increase (Ref.)	$D1^{High}$ Increase[a]	$D3^{High}$ Increase[b]
Dopamine supersensitivity caused by gene knockouts (Ref.)			
Cannabinoid receptor (CB,−/−) (Martin et al., 2000; Steiner et al., 1999)	1.15-fold (Houchi et al., 2005)	–	–
Dopamine β-hydroxylase (Dbh−/−) (Weinshenker et al., 2002)	1.17-fold (Schank et al., 2005)	1.8-fold (D. Weinshenker, P. Seeman, unpublished data)	–
G protein-coupled receptor kinase 6 (Gprk6−/−) (Gainetdinov et al., 2003)	1.06 (Gainetdinov et al., 2003)	1-fold (Gainetdinov et al., 2003)	–
RIIβ protein kinase A (−/−)/(+/−) (Brandon et al., 1998)	0.83-fold (Brandon et al., 1998)	0.96-fold (G.S. McKnight, P. Seeman, unpublished data)	1.02-fold (G.S. McKnight, P. Seeman, unpublished data)
Tyrosine hydroxylase/Dbh ($Th^{-/-}$,$Dbh^{Th/+}$) (Kim et al., 2000; Robinson et al., 2004; Zhou and Palmiter, 1995;)	–	1.2-fold (R. Palmiter, S. Robinson, P. Seeman, unpublished data)	4.8%/3% (1.6-fold) (R. Palmiter, S. Robinson, P. Seeman, unpublished data)
VMAT2(+/−) (vesicle monamine transporter-2) (Wang et al., 1997; Takahashi et al., 1997)	1.08-fold (Takahashi et al., 1997)	1.7-fold (Seeman et al., 2002)	–
Dopamine supersensitivity caused by lesions or drug treatment (Ref.)			
Amphetamine-sensitized rat (see also Robinson and Berridge, 2000)	0.95-fold (Seeman et al., 2002)	0.93-fold (Schank et al., 2005)	–
Caesarian birth of rats (Boksa et al., 2002; Juarez et al., 2005)	1.1-fold (Juarez et al., 2005)	–	–
Caesarian birth and anoxia (Boksa et al., 2002; Juarez et al., 2005)	1.08-fold (Juarez et al., 2005)	–	–
Lesion of entorhinal cortex (Sumiyoshi et al., 2004, 2005)	–	1.19-fold (Sumiyoshi et al., 2005)	2.9%/5.2% (0.56-fold) (T. Sumiyoshi, P. Seeman, unpublished data)
Quinpirole-sensitized rat	–	1.03-fold (H. Szechtman, M. Perreault, P. Seeman, unpublished data)	7.9%/5% (1.6-fold) (H. Szechtman, M. Perreault, P. Seeman, unpublished data)
Reserpine (5 mg/kg for 3 days, 2 days no drug)	–	∼1.1-fold (Schank et al., 2005)	–

(–), Not reported.
[a]Proportion of $D1^{High}$ defined by dopamine/[^{3}H]SCH23390 competition, where 1–100 nM dopamine inhibited 10–15% of [^{3}H]SCH23390 sites for the control value of $D1^{High}$.
[b]Proportion of $D3^{High}$ receptors measured by dopamine/[^{3}H]domperidone competition in presence of 15 nM pramipexole. Pramipexole occludes $D3^{High}$ in cloned D3 receptors at 3.5 nM, but blocks cloned D2 receptors above 75 nM (Seeman and Ko, 2005). % Refers to the proportion of [^{3}H] domperidone sites that labeled D3 receptors, normally 3–8%.

fected members of the same family (Tepest et al., 2003).

PSYCHOSTIMULANTS AND CAESARIAN BIRTH

Important animal models for human psychosis include psychostimulant models (Lieberman et al., 1990; Tenn et al., 2003, 2005; Ujike, 2002; Yui et al., 1999) and the model of birth hypoxia during Caesarian section delivery (Boksa and El-Khodor, 2003; El-Khodor and Boksa, 1998). With regard to the Caesarian section/hypoxia model, it is important to note that adult rats born by Caesarian section (with or without added anoxia) have been shown to exhibit dopamine supersensitivity such as enhanced amphetamine-induced locomotion (reviewed by Boksa and El-Khodor, 2003).

Rats that have been sensitized by amphetamine (Tenn et al., 2003; Ujike, 2002), phencyclidine (Morris et al., 2005; see Allen and Young, 1978, for patients), or quinpirole (Lomanowska et al., 2004; Szechtman et al., 2001) become supersensitive to dopamine agonists (Robinson and Becker, 1986; Robinson and Berridge, 2000). The sensitization by dopamine agonists appears to stem primarily from the D2 receptor (Ujike et al., 1990), although D1 presumably cooperates (Vezina, 1996). The striata from such supersensitive rats do not reveal any increase in dopamine D1 or D2 receptors, but do show a two–four-fold elevation in the proportion of $D2^{High}$ receptors (Seeman et al., 2002, 2005a; Tables II and III).

While dopamine D2 receptors may be lower in cocaine, ethanol, and methamphetamine abusers (Volkow et al., 2001), the proportion of their $D2^{High}$ receptors is likely to be elevated, in accord with the clinical observation that such individuals are dopamine supersensitive (see earlier section).

While the phencyclidine and ketamine psychostimulants are usually recognized as NMDA antagonists (Krystal et al., 2005; Lahti et al., 2001), it is important to note that such drugs have a dopamine agonist component of action (Greenberg and Segal, 1985; Ögren and Goldstein, 1994), particularly at the $D2^{High}$ receptor (Kapur and Seeman, 2002; Seeman, 2004; Seeman et al., 2005b; Seeman and Lasaga, 2005) and possibly at the D1 receptor (Tsutsumi et al., 1995). Ketamine-related compounds such as MK801, therefore, may have a double action at both NMDA and dopamine D2 receptors; for example, even in dopamine-depleted mice, haloperidol, despite its negligible affinity for NMDA receptors, reduced MK-801 ambulation by ∼40% (Chartoff et al., 2005).

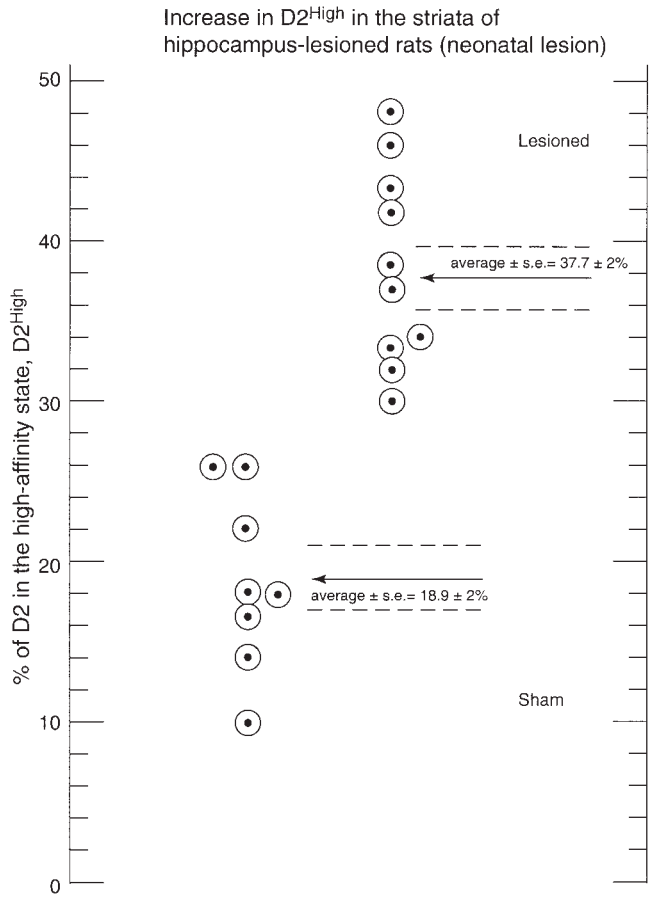

Fig. 5. Elevated proportions of D2^{High} dopamine receptors in the striata of adult rats that had received ibotenic acid bilateral lesions of the ventral hippocampus at 7 days of age (Lipska et al., 1993). The total density of D2 was 12.7 ± 0.6 pmol/g in sham control samples and 9.9 ± 0.2 pmol/g in lesion samples, as measured separately using [^{3}H] raclopride. This reduction of 22% matched the 15% reduction found by Schroeder et al. (1999), using [^{3}H]spiperone. Instead of washing, a final concentration of 200 μM Gpp[NH]p (guanilylimidodiphosphate) was added to convert the D2 receptors to their low-affinity state, thus minimizing the masking of D2 receptors by endogenous dopamine (Unpublished data of B. Lipska, D. Weinberger, and P. Seeman).

Striata from rats born by Caesarian section (Boksa et al., 2002; Juárez et al., 2005) also revealed a two–six-fold elevation in the proportion of D2^{High} receptors, but no increase in the total population of D1 or D2 receptors (Tables II and III).

STEROIDS

Steroid-induced psychosis is a common complication of glucocorticoid treatment in humans. In fact, in parallel to the human condition, rats given high doses of corticosterone for 5 days become dopamine supersensitive and respond to amphetamine with increased locomotor activity (Przegalinski et al., 2000). The striata from such corticosterone-treated rats show a threefold elevation in D2^{High} receptors (Table II). In fact, the secretion of glucocorticoids is a factor in determining the extent of dopamine supersensitivity in stressed subjects (Deroche et al., 1995).

ANTIPSYCHOTIC DRUGS

In addition to the long-term therapeutic use of glucocorticoids, the therapeutic long-term use of antipsychotics is known to elicit dopamine supersensitivity (Dewey and Fibiger, 1983; Jenner et al., 1982; Seeger et al., 1982; Seeman, 1980; Smith and Davis, 1975; VonVoigtlander et al., 1975). The antipsychotic-induced elevation of D2^{High} receptors is consistent with this induced supersensitivity. In the case of long-term treatment by antipsychotics, the density of D2 receptors in the rat striatum generally increases by 10–40% (reviewed by Seeman, 1980). The proportion of D2^{High} receptors, however, increases considerably by a factor of two–four-fold (Table II). From a clinical point of view in treating psychosis, however, the antipsychotic-induced supersensitivity is counterproductive, requiring an increase in the antipsychotic dose to prevent a possible clinical relapse of the patient (Chouinard, 1991; Chouinard et al., 1978; Kirkpatrick et al., 1992).

Not all antipsychotics, however, elicit the same degree of dopamine supersensitivity or elevation of D2^{High} receptors, because there are fundamental differences between different groups of antipsychotics. For example, the traditional antipsychotics such as haloperidol and chlorpromazine bind tightly to the dopamine D2 receptor, with dissociation constants lower than 2 nM, and slowly dissociate from the D2 receptor in vitro or in vivo (Seeman and Tallerico, 1999; reviewed by Seeman, 2001, 2002). The newer or so-called atypical antipsychotic drugs such as quetiapine, clozapine, paliperidone, amisulpride, and aripiprazole rapidly dissociate from the D2 receptor in vitro and in vivo, with rapid dissociation times (50% reduction in binding in 60 s or less) from the cloned D2 receptor (Seeman, 2002, 2005), and clinical dissociation times of hours, thus minimizing clinical side effects. In accord with this fast-off-D2 principle for the atypical antipsychotics, it is not surprising that clozapine and quetiapine induce the lowest elevation of D2^{High} receptors, in contrast to the elevations elicited by haloperidol and olanzapine, as shown in Figure 6.

ARE ELEVATED D2^{High} RECEPTORS LOCATED PRE- OR POSTSYNAPTICALLY?

Dopamine D2 receptors in the rat striatum are located postsynaptically on cell bodies (medium spiny neurons) as well as presynaptically on nerve terminals of neurones from the substantia nigra and the cerebral cortex (Fig. 7; Sesack et al., 2003). Therefore, the elevation of D2^{High} receptors may occur in either the presynaptic or the postsynaptic receptors. One possible method for determining which set of these D2^{High}

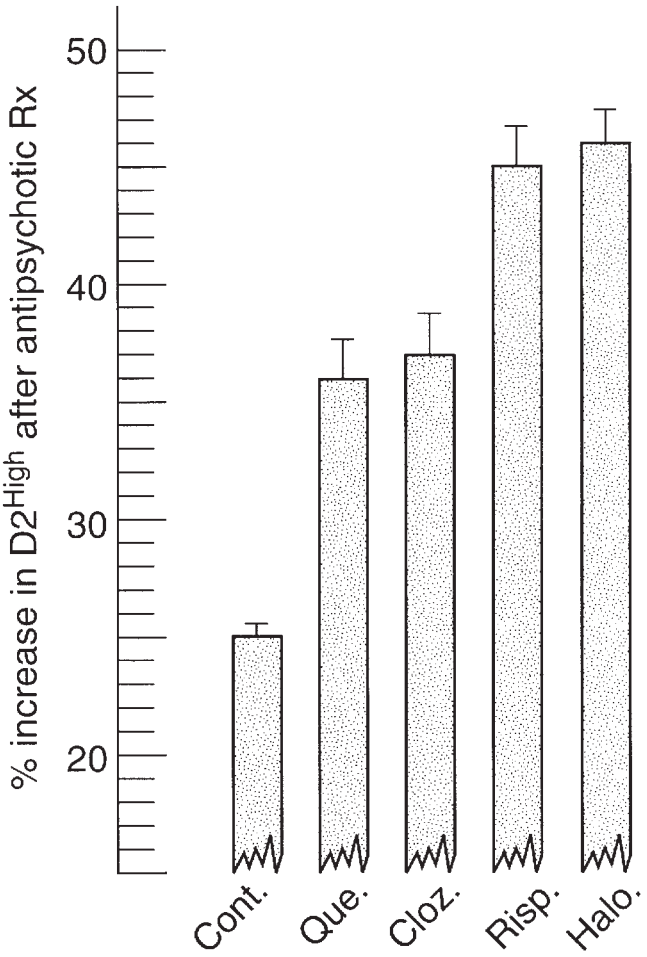

Fig. 6. The atypical antipsychotics clozapine and quetiapine induced significantly less elevation of $D2^{High}$ receptors compared to the older antipsychotics haloperidol, olanzapine, and risperidone. The antipsychotics were given at doses that were clinically equivalent, using doses that all led to the same therapeutic D2 occupancy of 60–80% in the rat striatum in vivo (Kapur et al., 2003). Haloperidol (0.045 mg/kg), olanzapine (0.75 mg/kg), risperidone (0.75 mg/kg), quetiapine (25 mg/kg), and clozapine (35 mg/kg) were given i.p. daily for 9 days.

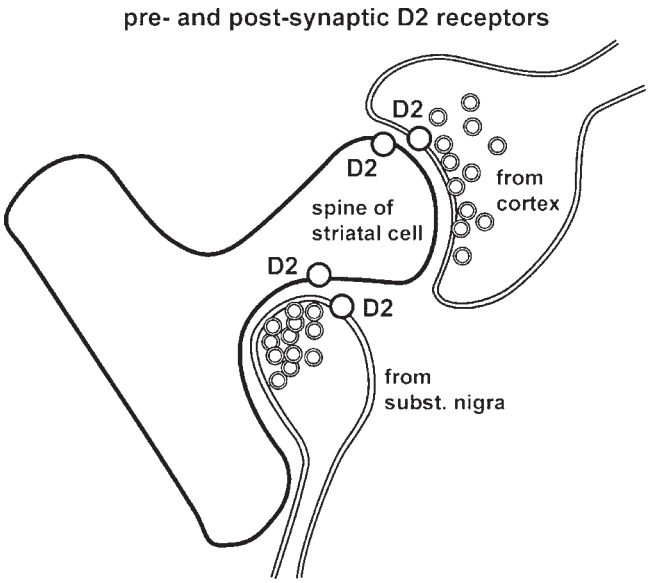

Fig. 7. Dopamine D2 receptors are located postsynaptically on medium spiny neurons in the striatum, and presynaptically on neurons from the cerebral cortex and the substantia nigra. Elevated $D2^{High}$ receptors may occur at any of these three sites. The work of Usiello et al. (2000) indicates that D2Short and D2Long are predominantly located presynaptically and postsynaptically, respectively (Figure reproduced with permission from Sesack et al., Ann N Y Acad Sci, 2003, 1003, 36–52).

receptors is altered is to measure the D2Short and D2Long proteins in the striatal tissue. This suggestion is based on the work of Usiello et al. (2000) who have shown that D2Short and D2Long are predominantly located presynaptically and postsynaptically, respectively. In fact, although it is generally assumed that dopamine supersensitivity is related to postsynaptic alterations, it is known that altered dopamine sensitivity of the presynaptic system does occur (King et al., 1994). Such presynaptic alterations may underlie the enhancement of quinpirole sensitization by the κ opiate agonist (Perreault et al., 2005).

REVERSAL OF BOTH DOPAMINE SUPERSENSITIVITY AND THE ELEVATED $D2^{High}$ RECEPTORS

Because the dopamine supersensitivity model is useful for determining the biochemistry underlying clinical psychosis, the prevention of such sensitization by dopamine D1 blockade (Akiyama et al., 1994; Kuribara 1995; Pierre and Vezina, 1998) may provide clues to the psychotic mechanisms involved, as well as promise in arresting the progress of human psychosis.

In the same way as D1 blockade prevents the development of psychostimulant-induced behavioral dopamine supersensitivity (Pierre and Vezina, 1998), the coadministration of a D1 blocker (SCH 23,390) with amphetamine, using the identical protocol of Pierre and Vezina (1998), blocks the elevation of $D2^{High}$ receptors in the striatum (P. Seeman, unpublished data) (Fig. 8).

This prevention of $D2^{High}$ elevation by a D1 antagonist may be based on the link between D1 and D2 receptors, either by coactivation in the same neuron or different neurons (Hersch et al., 1995; Le Moine and Bloch, 1995; Lee et al., 2004; Surmeier et al., 1996) or as a D1/D2 dimer (see also Winterer and Weinberger, 2004, for an analysis of D1 and D2 synaptic signaling). In fact, because clozapine effectively blocks D1 receptors with a dissociation constant of 90 nM (almost identical to its dissociation constant of 75 nM at D2; Seeman, 2001), clozapine also prevents amphetamine-induced sensitization (Meng et al., 1998; Phillips et al., 2001). Curiously, sensitization to cocaine is apparently not blocked by D1 antagonism (Mattingly et al., 1996).

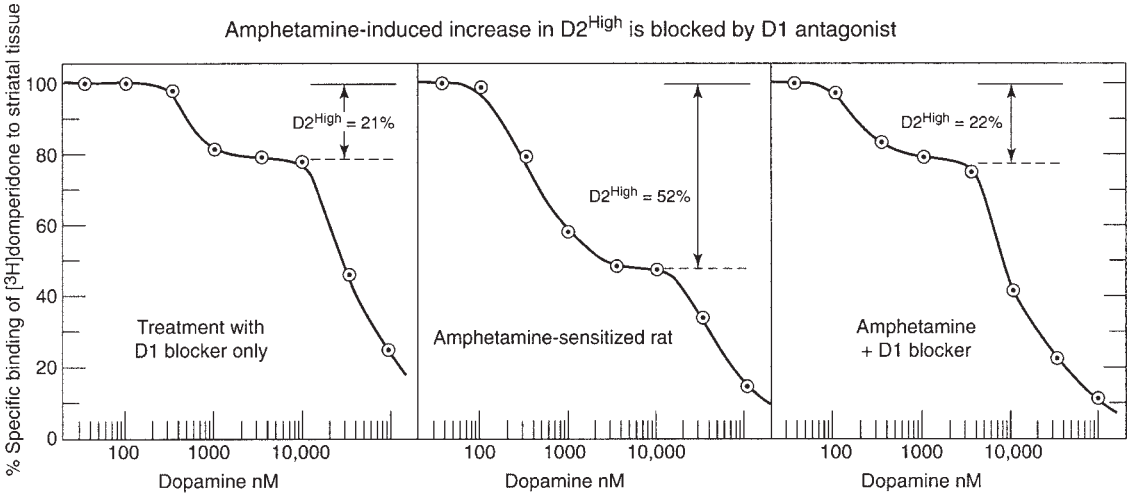

Fig. 8. The administration of amphetamine (method of Pierre and Vezina, 1998) induced a marked increase in the proportion of $D2^{High}$ receptors in rat striatal tissue, in parallel with the behavioral dopamine supersensitivity induced by amphetamine. Cotreatment of the rats with 0.2 mg/kg SCH23390 to block D1 receptors prevented the amphetamine-induced elevation of the $D2^{High}$ receptors (P. Seeman, unpublished data), in parallel to the D1 blockade of behavioral dopamine supersensitivity elicited by amphetamine (Pierre and Vezina, 1998). Representative experiments, using 2 nM [^{3}H]domperidone (68 Ci/mmol) in 120 mM NaCl.

It is important to emphasize that, despite these D1/D2 interactions, the clinical use of D1 antagonists does not alleviate schizophrenia or the other psychoses. Such D1/D2 interactions are not sufficiently strong or adequate to activate the antipsychotic pathway, whatever these steps may be.

The long-term blockade of D2 receptors can also prevent the sensitization and dopamine supersensitivity elicited after neonatal hippocampal lesions. For example, Richtand et al. (2006) found that a low dose of risperidone (0.045 mg/kg) given between 35 and 56 days postnatally suppressed or prevented development of dopamine supersensitivity in rats with neonatal lesions of the hippocampus, as tested on day 57. Although a higher dose of risperidone (0.085 mg/kg) did not suppress or prevent the development of dopamine supersensitivity, the proportion of risperidone and its active metabolite, 9-hydroxyrisperidone, varies considerably (the metabolite is 30–60% of the total risperidone in plasma), and this variation may depend on the dosage.

Nevertheless, the suppression or inhibition of the development of dopamine supersensitivity in the lesioned rats by risperidone would be expected to be mirrored by a corresponding block in the elevation of $D2^{High}$ states in lesioned animals (Fig. 5). The risperidone inhibition of dopamine supersensitivity is consistent with the clinical finding by McGorry et al. (2002) that risperidone delayed or protected by 6 months prepsychotic patients from developing characteristic schizophrenia. Therefore, it is possible that the biomarker of elevated $D2^{High}$ states may become a useful index to test whether various medications inhibit the progress of sensitization and the development of dopamine supersensitivity.

It should be noted that the prevention of psychostimulant sensitization by D1 blockade is not unique, because the blockade of β-adrenoceptors by timolol (Colussi-Mas et al., 2005) and the block of dopamine D3 receptors by nafadotride (Richtand et al., 2000) also prevent amphetamine-induced sensitization.

THE PHYSICAL EXISTENCE OF THE $D2^{High}$ STATE

Dopamine D2 receptors belong to a group of more than one thousand receptors known to be associated with G proteins. The binding of an agonist to such a G-linked receptor occurs in two concentration ranges. Low nanomole concentrations of the agonist binds to the high-affinity state of the receptor, while high micromole concentrations bind to the low-affinity state of the receptor. Generally, it is the high-affinity state of the receptor that is the functionally active state of the receptor, because the agonist affinities for the high state are usually identical to the concentrations that elicit the physiological action of the agonists. This holds for many neurotransmitter receptors, including dopamine D2 receptors (George et al., 1985; McDonald et al., 1984), cholinergic muscarinic receptors (Birdsall et al., 1977), α_2-adrenoceptors (Thomsen et al., 1988), and β_2-adrenoceptors (Stadel et al., 1981). (It should be noted that each tissue has spare receptors, and when these are irreversibly blocked, the agonist concentrations that are functional under these conditions can

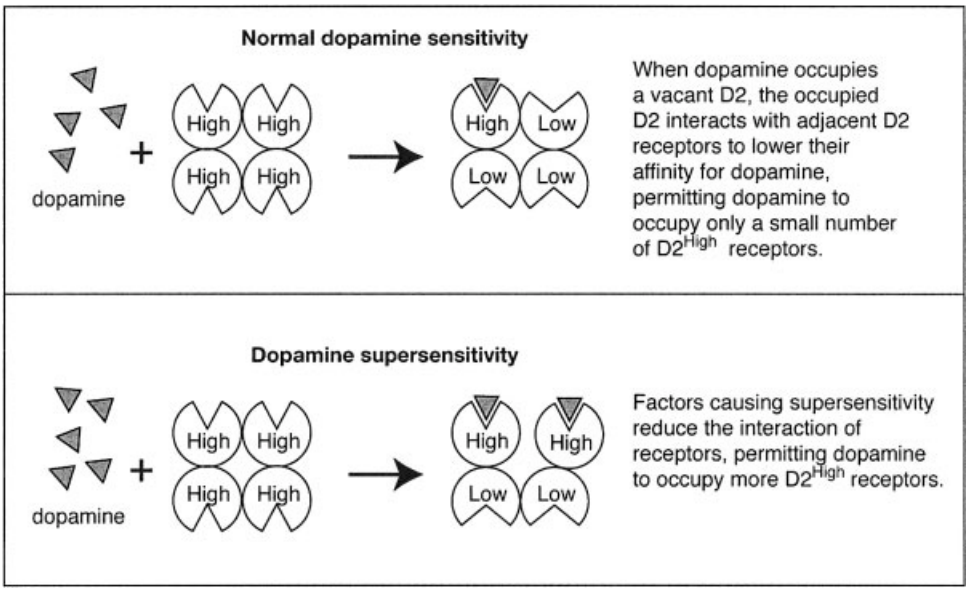

Fig. 9. Illustration of negative cooperativity or receptor–receptor negative interaction (Chidiac et al., 1997; Sum et al., 2001) between dopamine D2 receptors, and how dopamine supersensitivity can arise from a reduction of such a negative interaction. Four D2 receptors are drawn as a tetramer, all four of which are in the high-affinity state when vacant and not occupied by dopamine. The binding of a single molecule of dopamine to any of the four unoccupied D2 receptors exerts a negative effect on the other three receptors, lowering their affinity for dopamine. (The situation is analogous to that for hemoglobin where the hemoglobin chains interact to alter the affinities for oxygen; Gourianov and Kluger, 2005.) However, in striatal tissues from animals that are supersensitive to dopamine, the factors contributing to dopamine supersensitivity would reduce the negative interaction between the D2 receptors. This reduction in negative cooperativity would leave more D2 receptors in the high-affinity state and allow them to be occupied by dopamine.

correlate with the agonist concentrations acting at the low-affinity state of the receptor).

There are at least two views of the physical existence of the high-affinity state. The traditional view is that the high-affinity state of the receptor exists when the receptor, R, is associated with the G protein, and the agonist, D, binds to this high-affinity state to form the "ternary complex," namely DRG (De Lean et al., 1980). This view of the receptor proposes that the low-affinity state occurs when the G protein is not associated with the receptor.

However, there are many significant short-comings with this view of the high-affinity state of the receptor in the ternary complex model, as pointed out by Green et al. (1997). For example, the ternary complex suggests that RG should have a transient existence. This is the not the case, however, because it has been found that the purified muscarinic RG is stable (Wreggett and Wells, 1995). Moreover, the purified muscarinic receptor, free of G and GDP, clearly shows high-affinity and low-affinity states (Wreggett and Wells, 1995).

An alternate view of the high-affinity state of the receptor is the "cooperativity" model, as worked out by Wells and coworkers (Chidiac et al., 1997; Sum et al., 2001). The cooperative model proposes that the receptor cooperates with other receptors to form a dimer, a tetramer, or a larger oligomer. The receptor is in the high-affinity state when it is vacant and unoccupied by the agonist. However, when the agonist binds to the vacant receptor, the occupied receptor interacts or "cooperates" with the other receptors (within the tetramer) such that the affinity of the other receptors for the agonist is markedly reduced (Chidiac et al., 1997; Sum et al., 2001). This reduced affinity for the agonist is a result of "negative cooperativity" between the receptors, and corresponds to the low-affinity state of the receptor.

In other words, if there is very strong negative cooperativity, then the second, third, and fourth receptors (within the tetramer) would hardly bind the agonist, and only the high-affinity sites would be observed in the competition between, say, dopamine and [^{3}H]domperidone, all taking place at the first receptor. These events are depicted in a diagram in Figure 9.

According to this negative cooperativity model, therefore, the increased number of D2 receptors in the high-affinity state, $D2^{High}$, found in the striata of supersensitive animals may be attributed to a reduction in the overall negative cooperativity between the receptors, as illustrated in Figure 9. Therefore, to determine the molecular mechanism of dopamine supersensitivity, it will be essential to determine the factors that reduce negative cooperativity among the D2 receptors or that alter the association of the receptor with its G protein. The role of guanine nucleotides in regulating the overall sensitivity of the dopamine D2 receptors would be to alter the extent of the receptor–receptor negative cooperativity.

BIOCHEMICAL FACTORS PROMOTING THE $D2^{High}$ STATE

The rate of interconversion between the high- and low-affinity states of a G protein-linked receptor is generally of the order of minutes or seconds (Posner et al., 1994). There are many factors that increase the prevalence of the high-affinity state, and therefore, increase the sensitivity of the tissue to the agonist. The following proteins are a few of the numerous proteins and factors that alter the dopamine sensitivity of a tissue.

G proteins

Generally, the level of G proteins do not change in dopamine supersensitive conditions. For example, long-term antipsychotic treatment or reserpine-induced supersensitivity is not accompanied by any change in the protein levels of Gαi1, Gαi2, or Gαo, as seen by immunoblotting or by toxin-catalyzed ADP ribosylation (Butkerait et al., 1994; Meller and Bohmaker, 1996). This also holds for behavioral sensitization by cocaine, where no expression changes were found in Gαs or Gαo, but Gαi1 expression was transiently increased while Gαolf was reduced (Perrine et al., 2005); more importantly, the protein levels of these latter four α-subunits were not significantly altered by cocaine. However, short-term cocaine treatment increased the protein levels of Gαq and Gα11 (Carrasco et al., 2004). In addition, few changes occur in the expression of Gq, G11, and Gz after dopamine denervation of the rat striatum (Friberg et al., 1998).

RGS proteins, or regulators of G protein signaling, activate the breakdown of GTP which transiently attaches to the G protein (Neubig, 2002; Neubig and Siderovski, 2002; Xu et al., 1999). Thus, the RGS proteins essentially act as GTPase activators to shorten or terminate the action of an agonist.

RGS9 (Regulator of G protein-signaling 9) is localized in the retina (as RGS9-1) and in the striatum and the hippocampus (as RGS9-2) (Gold et al., 1997). This protein colocalizes with D2 receptors in the striatum and accelerates the termination of D2-triggered events (Kovoor et al., 2005) by increasing the rate of hydrolysis of GTP bound to the α subunit of the G protein (Neubig and Siderovski, 2002; Siderovski et al., 1999). As summarized by Traynor and Neubig (2005), RGS proteins limit the strength of the steady-state signal, because there is a balance between the rate of receptor-stimulated binding of GTP and the rate of hydrolysis of GTP (Cabrera-Vera et al., 2004). A reduction in RGS9, as occurs in RGS9 knockout mice, leads to behavioral dopamine supersensitivity (Rahman et al., 2003) and a marked increase in the proportions of $D2^{High}$ receptors in the striatum (Table II; Fig. 2), even though the total density of D2 receptors does not change (Rahman et al., 2003).

Consistent with the dopamine supersensitivity of RGS9 knockout mice, overexpression of RGS9 on one side of the brain (nucleus accumbens) reduced the dopamine sensitivity of the injected side (Rahman et al., 2003). Moreover, although estrogen can both diminish and enhance the action of dopamine, the psychostimulant-enhancing action of estrogen is accompanied by a reduction in the expression of RGS9 (Sharifi et al., 2004). It should be noted, however, that a reduction in RGS9 expression is not specifically associated with enhanced dopamine neurotransmission, but is also associated with a marked enhancement of behavioral responses to acute and chronic morphine (Zachariou et al., 2003).

Some, but not all, postmortem schizophrenia prefrontal cortex tissues reveal a 40% reduction in RGS9 expression (Mirnics et al., 2001). Moreover, the expression of RGS9 was reduced after amphetamine (Burchett et al., 1998, 1999) and after the dopamine agonist quinpirole (Taymans et al., 2003). Altogether, therefore, the data for RGS9 suggest that this gene may be a significant susceptibility gene for schizophrenia. In fact, the gene for RGS9 is located in chromosome region 17q21-25 (Zhang et al., 1999), a region which contains at least one marker linked to schizophrenia (Cardno et al., 2001).

Because RGS9-1 in the retina is anchored to the membrane by protein R9AP (Hu and Wensel, 2002), a defect in this anchoring protein markedly reduces the action of RGS9-1, thus prolonging the action of the agonist on the receptor. This principle has been illustrated clinically in the case of people with genetic defects in R9AP in their prolonged response to light (Blumer, 2004; Nishiguchi et al., 2004). In the striatum, RGS9-2 is anchored to the membrane by R7BP, a protein that is related to R9AP, but no clinical defects have yet been reported in R7BP.

RGS4 has received considerable attention as a possible susceptibility gene for schizophrenia, because there is a weak association with schizophrenia (Chowdari et al., 2002; Williams et al., 2004), and because it is reduced in schizophrenia prefrontal cortex (Mirnics et al., 2001). Knockouts of this gene, however, did not reveal any obvious spontaneous locomotor hyperactivity (Grillet et al., 2005), as occurs in animals sensitized by psychostimulants. Psychostimulants, such as amphetamine or cocaine, did not alter the expression of RGS4 (Burchett et al., 1998; Ingi et al., 1998; Taymans et al., 2003); quinpirole elevated the expression of RGS4 (Taymans et al., 2003, 2004). Moreover, overexpression of RGS4 on one side of the brain did not cause any change in apomorphine-induced circling (Rahman et al., 2003), consistent with the knockout data that RGS4 does not have a role in altering dopamine supersensitivity and is unlikely to have a role in eliciting psychosis.

RGS2 is slightly reduced in postmortem schizophrenia brain (Mirnics et al., 2001), but amphetamine, methamphetamine, and cocaine all elevate its expression (Burchett et al., 1998, 1999; Ingi et al., 1998; Taymans et al., 2003), suggesting that RGS2 is an unlikely candidate for contributing to dopamine supersensitivity or psychosis.

Protein kinase A (PKA), protein kinase C (PKC), and G protein receptor kinases (GRKs) phosphorylate serine and threonine within the intracellular loops and the tail regions of the receptor (Ferguson, 2001). The kinases are activated by intracellular increases in cyclic AMP, Ca^{2+}, and diacylglycerol. The phosphorylation of the receptor leads to the binding of arrestins to uncouple the receptor from the G protein (Pippig et al., 1993). A reduction in one of these kinases, therefore, as in knockouts of G protein receptor kinase 6, would result in dopamine supersensitivity (Gainetdinov et al., 2003) and a considerable increase in the proportions of $D2^{High}$ receptors in the striatum (Table II).

Although GRK6 knockout mice are supersensitive to dopamine with elevated $D2^{High}$ states, GRK2 heterozygotes were not found to be generally supersensitive to various doses of amphetamine, cocaine, or apomorphine, with the exception of a single dose of 20 mg/kg cocaine where supersensitivity occurred. Surprisingly, GRK3 knockout mice are dopamine subsensitive to cocaine and apomorphine, while GRK4 and GRK5 knockout mice show no change in behavioral dopamine sensitivity (Gainetdinov et al., 2004).

GTP exchanges with the GDP bound to the α subunit of the G protein, resulting in a rapid subsecond dissociation of the entire agonist–receptor–G protein–GDP aggregate (Herrmann et al., 2004; Posner et al., 1994; Roberts et al., 2004), followed by the dissociated subunits (α and βγ) of the G protein eliciting the tissue responses.

Arrestins prevent the receptor from exchanging GTP for GDP on the G protein α subunit, thereby inactivating the G protein and the receptor (Gainetdinov et al., 2004). In principle, therefore, arrestin-knockout mice should be dopamine supersensitive. In fact, however, mice with knocked out β arrestin-1 or β arrestin-2 (which prefers D2 receptors; Macey et al., 2004) were slightly less sensitive to cocaine, and considerably less sensitive to apomorphine (Gainetdinov et al., 2004).

IS THERE A COMMON BASIS FOR DELUSIONS AND HALLUCINATIONS IN THE PSYCHOSES?

It appears reasonable to consider $D2^{High}$ to be the common target for the convergence of the various psychosis pathways, because $D2^{High}$ receptors are consistently elevated in all the animal models of the various human psychoses (Table II, and Fig. 10), and because virtually all psychoses respond to D2 blockade, with the possible exception of prolonged, never-treated psychosis.

ARE DOPAMINE SUPERSENSITIVE MODELS RELATED TO THE RISK FOR PSYCHOSIS?

The various animal models for human psychosis are associated with dopamine supersensitivity and reveal elevated $D2^{High}$ receptors (Table II, and Fig. 10). It is reasonable to suppose, therefore, that factors or altered genes that lead to dopamine supersensitivity can also increase the risk for psychosis or schizophrenia. More specifically, as Table II indicates, dopamine supersensitivity and elevated $D2^{High}$ occurs in rats as a consequence of factors known to elicit psychosis in humans, including amphetamine (Curran et al., 2004; Lieberman et al., 1990; Stéphane et al., 2005; Strakowski et al., 1996, 1997; Yui et al., 1999), phencyclidine (Allen and Young, 1978), cocaine (Brady et al., 1991), corticosterone, brain damage, ethanol, birth trauma, and genetic alterations. Moreover, the dopamine supersensitivity and elevation of $D2^{High}$ receptors elicited by antipsychotics readily explains antipsychotic-induced supersensitivity psychosis (Lu et al., 2002; Prien et al., 1969; Whitaker, 2004; see also Schooler et al., 1967).

In fact, the common target of $D2^{High}$ elevation in drug abuse and in the models of psychosis may partly explain the well known fact that schizophrenia patients commonly overuse substances, with ~4% addicted to alcohol, ~6% addicted to amphetamine, and ~17% being abusers of cocaine.

Consistent with the hypothesis of $D2^{High}$ being the convergent target for various psychoses is the fact that all psychoses respond to treatment with D2 antagonists, including phencyclidine psychosis (Giannini et al., 1984, 1984–85). In fact, the effective treatment of phencyclidine psychosis by haloperidol (Giannini et al., 1984–85) is particularly significant, because haloperidol does not block NMDA receptors, indicating that the D2 target is critically and primarily active in phencyclidine psychosis. Moreover, the D2 receptor is the common target for all antipsychotics, including both the traditional and the newer ones (Miyamoto et al., 2005; Seeman, 2001).

Because the $D2^{High}$ receptor is the functional state of the dopamine receptor (George et al., 1985; McDonald et al., 1984), it is reasonable to consider the elevated $D2^{High}$ receptors to be related to some of the clinical signs and symptoms of psychosis. It is even likely that the fluctuations in the clinical intensity of psychotic signs and symptoms are related to the fluctuating proportions of $D2^{High}$ and $D2_{Low}$ (Fig. 11). This relation will need to be tested when the selective imaging of $D2^{High}$ in patients becomes possible by radioactive $D2^{High}$-selective agonists (Seeman et al., 1993; Willeit et al., in press; Wilson et al., 2005).

While the psychotic signs might be related to $D2^{High}$, the gene for D2 may or may not be associated with schizophrenia. In fact, present data show that there is a significant association of the D2 gene with schizophrenia (Dubertret et al., 2004; Glatt et al., 2003; Hirvonen et al., 2005; Jonsson et al., 1999, 2003; Lawford et al., 2005; Virgos et al., 2001). Moreover, unmedicated patients have "an increased occupancy of D2 receptors by dopamine at baseline in schizophrenia in comparison with healthy controls" (Abi-Dargham,

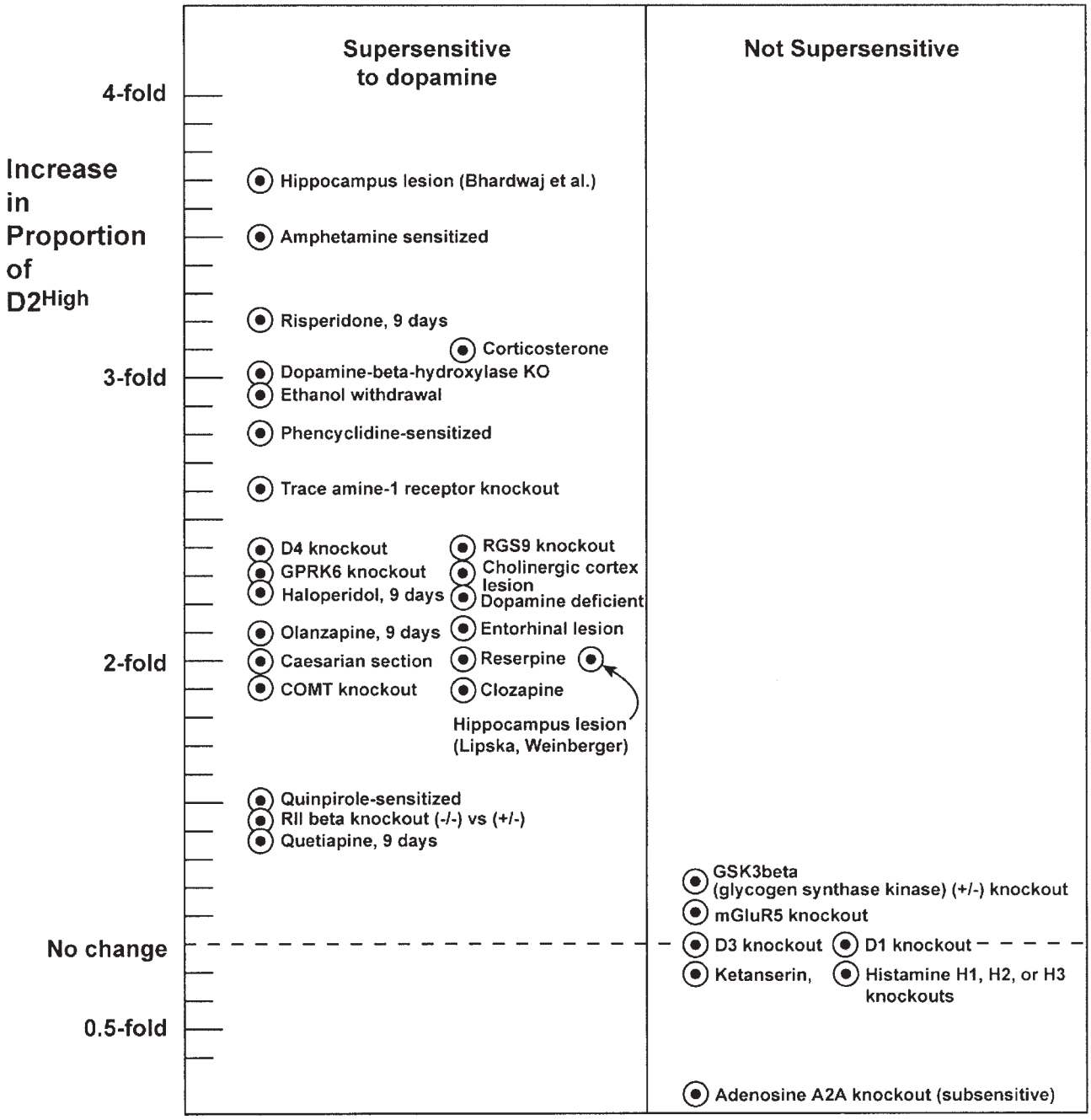

Fig. 10. Summary of elevated D2^{High} receptors in striata from animals made dopamine supersensitive by lesions, drugs, and gene knockouts. D2^{High} receptors were only elevated in striata from animals that had become dopamine supersensitive. The two points indicating "hippocampus lesion" (3.7-fold) and "amphetamine" were done by the method of [^{3}H]raclopride saturation (i.e., Scatchard analysis) with and without guanine nucleotide (Seeman et al., 2005a), and this method tended to reveal very high increases in the proportion of D2^{High} sites. The method used for most of the other types of experiments was the method of competition between dopamine and 2 nM [^{3}H]domperidone. Using this latter method, the bilateral hippocampus lesion data in Figure 4 revealed an increase of 2.5-fold. (From Table II and Seeman et al., 2005a).

2004), indirectly indicating an increase in the proportion of D2^{High} receptors with endogenous dopamine tightly occupying the high-affinity state of D2 (Abi-Dargham et al., 2000; Seeman and Kapur, 2000; Seeman et al., 2002, 2004).

A more difficult question is whether a risk factor or a risk gene can be ruled out as a risk if that factor or altered gene does not lead to dopamine supersensitivity and elevated D2^{High}. For example, deletion of the gene for glycogen synthase kinase 3 (or GSK3β+/−) caused

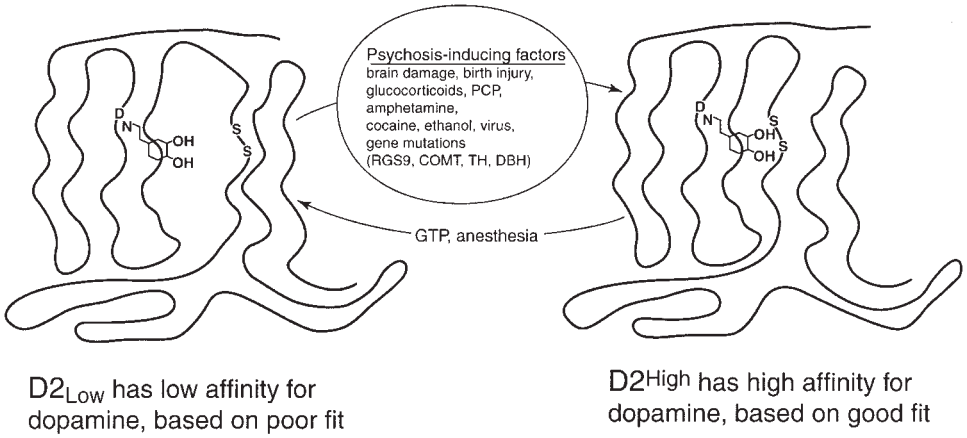

Fig. 11. Summary diagram depicting the good fit between dopamine and the three amino acids of D (aspartic acid) and S (serine), comprising the high-affinity state of D2, or $D2^{High}$. The low-affinity state, $D2_{Low}$, is considered to have a poor fit between dopamine and the three amino acid residues (Seeman et al., 1985). Although the two states constantly interconvert in a matter of seconds or minutes (Posner et al., 1994), there is a shift toward an increase in the number of $D2^{High}$ states in response to psychosis-inducing factors, as listed. Guanyl nucleotides (such as GTP or guanilylimidodiphosphate) or anesthesia promote a shift to the low-affinity state (Seeman and Kapur, 2003). Examples of gene mutations or deletions are RGS9 (regulator of G protein signaling), COMT (catechol-*O*-methyl-transferase), TH (tyrosine hydroxylase), and DβH (dopamine-β-hydroxylase).

dopamine subsensitivity (Beaulieu et al., 2004) and did not elevate $D2^{High}$ more than 1.19-fold (Table II). Therefore, using the criteria of dopamine supersensitivity and elevated $D2^{High}$, it appears unlikely that GSK3β is a psychosis risk gene, in agreement with the lack of an association to schizophrenia (Ikeda et al., 2005; Nadri et al., 2004; but see Emamian et al., 2004).

MULTIPLE PATHWAYS, MULTIPLE GENES, MULTIPLE CAUSES

If indeed there are multiple neural pathways that mediate psychosis and converge to the same set of brain $D2^{High}$ targets, it suggests that there are multiple causes and presumably multiple genes associated with psychosis in general and schizophrenia in particular. It is even likely that different pedigrees have different sets of risk genes for schizophrenia. Some schizophrenia pedigrees, for example, have a unique translocation of a chromosome segment (1q42 relocated to 11q14) (Blackwood et al., 2001; St. Clair et al., 1990). Other schizophrenia pedigrees have chromosome segments that translocate and disrupt brain-expressed genes DISC1 and DISC2 on chromosome 1 (Ekelund et al., 2001; Millar et al., 2000).

Different schizophrenia pedigrees may have different sets of susceptibility genes, and different family members within a pedigree may have a different inheritance of the several genes involved in the set of risk genes. As noted by Millar et al. (2003), this situation is analogous to Hirschsprung disease (aganglionic megacolon), where there is one gene of major effect, with two other genes of less major effect (Gabriel et al., 2002), and analogous to neurofibromatosis where the same genetic error can result in different clinical phenotypes (Carey and Viskochil, 1999).

This speculation, if true, may partly explain the difficulty in identifying and replicating susceptibility genes for schizophrenia; for example, although strong linkage of schizophrenia to chromosome region 1q21-22 was found in a group of Celtic families (with a 6.5 LOD or log-of-the-odds score; Brzustowicz et al., 2000), a larger heterogenous set of families did not detect this linkage (Levinson et al., 2002). As pointed out by Millar et al. (2003), many studies have found strong linkage with high LOD scores between 3.6 and 7.7, including those at chromosome regions 2q35, 6q25, and 18q12 (see also Fig. 1), but these findings can be diluted and minimized when massive numbers of families are pooled and meta-analyzed.

Therefore, the possibility of multiple psychosis pathways and the possibility of different risk genes in different pedigrees may limit the biological value in using meta-analysis of whole-genome linkage scans (Maziade et al., 2001; Mowry et al., 2004) to detect risk genes (Badner and Gershon, 2002).

Given the rich neural interconnections in the brain, it is reasonable to expect that the striatum develops biochemical alterations after neonatal lesions or during sensitization by psychotomimetics. For example, there are extensive projection fibers of afferents and efferents between the cerebral cortex and the subcortical structures of the putamen and the caudate nucleus, as well as afferents and efferents between the hippocampus, the amygdala, and the nucleus accumbens, as depicted in Figure 12. Additional intergyral fibers and longitudinal fasciculi interconnect the occipital, frontal, and temporal lobes. Neonatal lesions of the cortex or hippocampus, therefore, would be expected

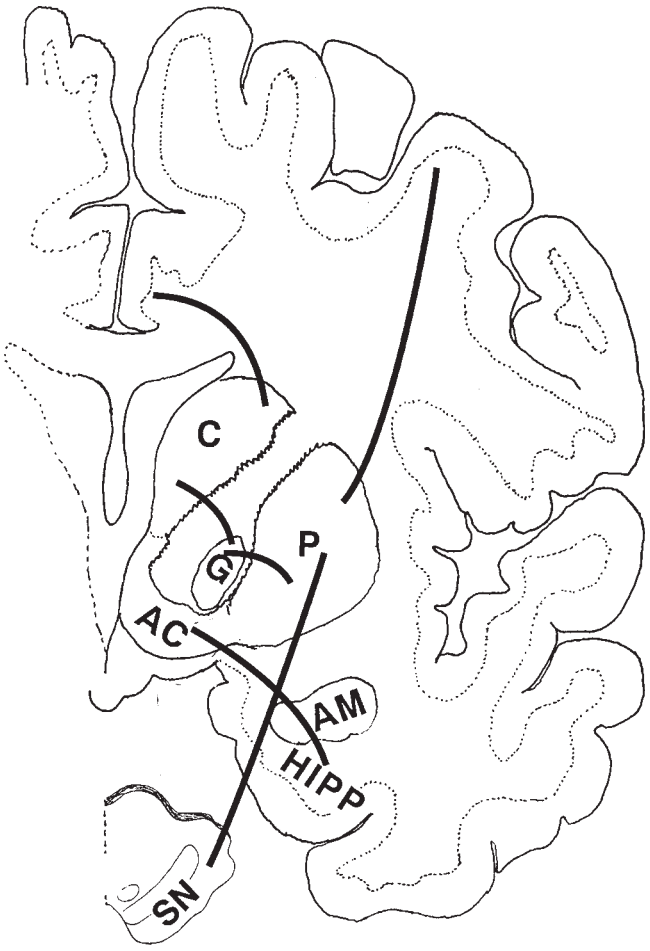

Fig. 12. Examples of extensive neural interconnections in the brain, and extensive projection fibers of afferents and efferents between the cerebral cortex and the subcortical structures of the putamen (P) and the caudate nucleus (C), as well as extensive afferents and efferents between the hippocampus (HIPP), the amygdala (AM), and the nucleus accumbens (AC). Neonatal lesions of the cortex or hippocampus, therefore, would be expected to have compensatory alterations within the caudate nucleus and the putamen. SN, substantia nigra; G, globus pallidus.

to have compensatory alterations within the caudate nucleus and the putamen. Sensitization by psychotomimetics would also be expected to lead to changes in biochemical sensitivity in the dopamine-rich striatum during the course of several weeks.

FUTURE RESEARCH ON $D2^{High}$

There is a wide variety of additional knockout mice that have not yet been tested for dopamine supersensitivity. On the basis of the present hypothesis that dopamine supersensitivity and elevated $D2^{High}$ receptors are biomarkers of psychosis risk factors and risk genes, such testing should reveal additional susceptibility genes for psychosis and schizophrenia. In particular, there are many proteins which regulate the high-affinity state of D2 receptors (see above section), and many proteins which directly interact with D2, including calcium sensor-1 (NCS-1; Bai et al., 2004; Bergson et al., 2003; Kabbani et al., 2002; Koh et al., 2003) and calnexin (Hazelwood et al., 2005). Either knockouts of genes for these proteins, or specific drug antagonism of these proteins, may lead to the discovery of critical proteins associated with risk for psychosis or schizophrenia.

Finally, aside from genes and psychostimulants, there are other factors that are associated with psychosis or schizophrenia, such as prenatal influenza (Beraki et al., 2005; Brown et al., 2004), prenatal drug treatment (e.g., reserpine), and obstetrical complications (see Refs. in McNeil et al., 2000), most of which are known to induce dopamine supersensitivity (Beraki et al., 2005; Boksa et al., 2002) and elevated $D2^{High}$ receptors (Table I).

This review focuses on a possible final common pathway—dopamine supersensitivity and elevated $D2^{High}$ receptors—through which the positive signs of psychosis (hallucinations and delusions) are mediated. The hypothesis is that this mechanism is also operative in the psychosis of schizophrenia.

Furthermore, and most important, the main point in this review is that elevation of $D2^{High}$ receptors may be a necessary minimum for psychosis, although it is not likely to be sufficient for full expression of the psychotic features. This is similar to the findings of Hirvonen et al. (2005), showing 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 (Corripio et al., 2006; Glenthoj et al., 2005). Future work may show that direct measurement of $D2^{High}$ receptors by means of radioactive (+)PHNO (Wilson et al., 2005) may become an even more reliable biomarker for prognosis and outcome. Although extensive meta-analyses on 3707 schizophrenia patients and 5363 control subjects reveals a consistent association of schizophrenia with the Serine311Cysteine polymorphism of D2 (Glatt and Jönsson, 2006), this biomarker by itself is not diagnostic for single individuals.

Although this review summarizes molecular dopamine supersensitivity as a possible basis of the positive signs of psychosis, less is known about the basic biology underlying the negative aspects of psychosis, especially cognition, which is diminished by ~5% to ~10% in schizophrenia individuals. Recent work, however, has found that overexpression of D2 in the striatum (Kellendonk et al., 2006) or overexpression of the human COMT-valine gene (Chen et al., 2005) leads to cognitive deficits in animals.

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 reduced 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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