Schizophrenia Diagnosis and Treatment

Philip Seeman

University of Toronto, Toronto, Ontario, Canada

Keywords

Correspondence

Philip Seeman, University of Toronto, 260 Heath Street West, Unit 605, Toronto, Ontario, Canada M5P 3L6.
Tel.: 1-416-486-3456;
E-mail: Philip.Seeman@utoronto.ca

doi: 10.1111/j.1755-5949.2011.00250.x

It used to be said that “Schizophrenia is as schizophrenia does,” meaning that the illness defies definition. This has not changed. Diagnoses are fluid [1] and, in many instances, the psychosocial imprint overshadows the biology. It is not surprising, therefore, that the focus of research attention shifts, from street drugs [2,3] to social isolation, to genetic mutations [4].

Despite this wide range of research strategies, a common component or a final common path for the varied signs and symptoms of schizophrenia continues primarily to be disturbed dopamine pathways in the brain, with modifying influences from serotonin [5] and glutamate neurotransmission. The research path to uncovering the biological source of schizophrenia veers from one strategy to another, but, as a general rule, it's important to build on strength. The dopamine basis is an important strength [6,7], although there are many biochemical pathways that are critical in influencing dopamine neurotransmission [8].

Given that there are many avenues to schizophrenia, it continues to be surprising that primarily dopamine-interfering drugs are currently successful in the clinic, but drugs affecting serotonin or glutamate transmission are still under investigation. A window to new therapeutics may be the recent discovery of receptor dimers and multimers [9].

The abiding art of psychiatry is becoming more scientific. The alleviation of signs and symptoms in schizophrenia generally occurs when 60–70% of brain dopamine D2 receptors are occupied by antipsychotic medications [10,11]. Dopamine D3 receptors are much less occupied by antipsychotics.

In addition, there continues to be an active search for reliable bio-markers of schizophrenia or the prodrome to schizophrenia. Although considerable data indicate elevations of dopamine D2High receptors in animal models of schizophrenia [2,7], the levels of D2High *in vivo* in animals and in schizophrenia patients are technically difficult to measure. In principle, radioactive

dopamine agonists would be expected to prefer attaching to D2High receptors, while radioactive dopamine antagonists should label both D2High and D2Low receptors.

However, some studies report that radioactive dopamine agonists and antagonists have equal preference for D2High and D2Low receptors [12], while other studies find that agonist binding is consistently more sensitive to competition by endogenous dopamine [13–17], suggesting a difference between the properties of D2High and D2Low receptors. Moreover, the density of D2High receptors labeled by the radioactive agonist [³H]NPA differs by 25% to 50% from the density of D2 receptors labeled by the radioactive antagonist [³H]raclopride [18]. In addition, the *in vivo* binding of [¹¹C]raclopride and [¹¹C]MNPA go in opposite direction in animals under stress [19].

However, a bio-marker search for elevated D2High receptors in dopamine-supersensitive mice (genetically depleted of dopamine beta-hydroxylase) found a rise of 9% in the apparent BP_{ND} (Binding Potential) for D2High receptors¹, using only a single dose of intravenous [¹¹C]MNPA [20]. Unfortunately, the procedure used for [¹¹C]MNPA binding [20] did not determine baseline binding by co-administering a non-radioactive congener [21,17]. They also found an increase of 12% (from 44% to 56%) in the proportion of

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¹The rise occurred in the Binding Potential or BP_{ND}, where ND refers to the nondisplaceable density (B_{ND}) of receptors. The BP_{ND} is the density, B_{ND}, divided by the dissociation constant of the radioactive ligand (K; i.e., BP_{ND} = B_{ND}/K). Although not measured *in vivo*, the correct receptor density, B, is the displaceable component of ligand binding, as measured *in vivo* using a coinjected drug to determine the baseline amount of ligand binding.

D2High receptors labeled by [^3H]methylspiperone and competed by dopamine [20]. It would have been preferable if the latter study had been done with [^3H]domperidone, which more readily reveals elevated D2High receptors [7].

In fact, while the BP_{ND} of D2High receptors, using the [^{11}C]PHNO agonist, was found normal in 13 untreated schizophrenia individuals [22], a preliminary result on schizophrenia-like prodromal subjects indicates an elevation in D2High receptors, as labeled by [^{11}C]PHNO [23].

A second possible bio-marker of schizophrenia is the increased releasability of dopamine triggered by an intravenous injection of amphetamine [6], based on the principle that endogenous dopamine competes with the injected radio-ligand [24]. It is also

possible that the increased release of dopamine from the presynaptic terminal leads to an increase in the number of D2 receptors in the D2High state [25].

With many probable causes for the conditions we call schizophrenia [7], it may be difficult to find a single bio-marker or treatment that addresses all the varieties of these illnesses. However, the search continues, and this Special issue on Schizophrenia, by outlining current research approaches, moves us closer to finding improved diagnosis and treatment.

Conflict of Interest

The author has no conflict of interest.

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