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COMMENTARY

In their manuscript, Seeman and colleagues propose that atypical antipsychotic drugs may be distinguished from typical antipsychotic drugs by either their low affinity for D_2 dopamine receptors or their selectivity for D_4 dopamine receptors. The idea that atypical antipsychotic drugs have a relatively low affinity for D_2 dopamine receptors is a now widely accepted view since others (Meltzer et al. 1989; Roth et al. 1995) have previously reported that atypical antipsychotic drugs as a group tend to have significantly lower affinities for D_2 dopamine receptors than typical antipsychotic drugs.

Some of the other conclusions that Seeman and colleagues arrive at are not uniformly held, however. This commentary focuses on the second conclusion of Seeman and colleagues; namely, that some atypical antipsychotic drugs are selective for D_4 dopamine receptors. In arriving at this conclusion, Seeman and colleagues cite an earlier work (Roth et al. 1995) and state that "perlapine, olanzapine, and clozapine are (found to be) selective for the dopamine D_4 receptor, compared to the dopamine D_2 receptor." Of the three compounds, only perlapine was actually selective with a D_2: D_4 ratio of 63, but olanzapine (D_2:D_4 = 4.6) and clozapine (D_2:D_4 = 5.3) can only be said to *prefer* D_4 over D_2 receptors. Using the numbers supplied in Table 1 by Seeman and colleagues, generally lower selectivity ratios are found with perlapine (2) olanzapine (1.85), and clozapine (28). One could argue that clozapine *is* moderately selective for D_4 receptors, but this is clearly not the case for the other ligands studied.

It also should be noted that clozapine and related atypical antipsychotic drugs have high affinities for a number of other neurotransmitter receptors. For instance, using [^{3}H]-clozapine, Glatt, et al. (1995) demonstrated that clozapine's primary receptor sites in the brain resembled muscarinic and the 5-HT_6–like serotonin receptors. In addition, we and others have demonstrated (Meltzer et al. 1989; Roth et al. 1992, 1994) that clozapine and other atypicals had high affinities for at least four serotonin receptors, including the 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7. In fact, most of the tested atypical antipsychotic drugs had *higher* affinities for one or more of these four serotonin receptors than for the D_2 dopamine receptor. In many instances, the affinities for one or more serotonin receptors were also *higher than their D_4 dopamine receptor affinities* (Roth et al. 1994, 1995). In this regard, it should be noted that many of the new and therapeutically effective atypical antipsychotic drugs (e.g., sertindole, olanzapine, seroquel, risperidone, and ziprasidone) were developed with a specific preference for 5-HT_{2A} over D_2 dopamine receptors.

Why then all the fuss about the D_4 dopamine receptor? Seeman and colleagues give several reasons why the D_4 dopamine receptor may be a more attractive target for atypical antipsychotic drug development than other neurotransmitter receptors. This commentary focuses on three. First, Seeman and colleagues cite prior studies in which they and others found elevated amounts of "D_4-like receptors" in schizophrenic striata (Seeman et al. 1993; Murray et al. 1995; Sumiyoshi et al. 1995). More recent studies (Lahti et al. 1996) using a D_4-selective radioligand found that D_4 receptors are virtually absent in both control and schizophrenic striata. These findings would appear to negate this particular justification for using the D_4 receptor as a target of drug development.

Second, Seeman and colleagues speculate that D_4 dopamine receptors might "mitigate against the extrapyramidal side effects of dopamine D_2 antagonists by activating locomotion." Because there are few, if any, D_4 receptors in the striatum, it is difficult to imagine how this could occur. The authors state, in this regard, that "nafadotride, for example, a D_3 receptor antagonist, activates locomotion in rats (Sautel et al. 1995)." There is no reason to believe, however, that because a D_3 antagonist activates locomotion a D_4 antagonist will do the same.

Third, Seeman and colleagues find that the 5-HT_{2A}:D_2 ratio proposed by others (Meltzer et al. 1989; Leysen et al. 1994) is not uniformly able to distinguish typical and atypical antipsychotic drugs. Part of their main argument derives from the use of "radioligand-independent dissociation constants" that, superficially at least, appear to represent a more precise manner of measuring drug affinities for receptors. Without discussing the rationale behind the analysis, several inconsistencies were noted for the 5-HT_{2A} data. In particular, the plots for several of the compounds (fluphenazine, haloperidol, seroquel, and thioridazine) had positive slope factors. How could the dissociation constant possibly increase while the partition coefficient decreases? Because only two data points were used by Seeman and colleagues to calculate the "radioligand-independent dissociation constants," these values are not particularly reliable.

In conclusion, Seeman and colleagues have persuasively argued that atypical antipsychotic drugs have a rel-

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atively low affinity for D_2 dopamine receptors. About this conclusion there is little disagreement. Clinical trials with D_4-selective compounds are under way, and based on early animal testing one can predict that these compounds might be of little utility as discrete therapeutic agents for treating active psychosis. With respect to the D_4 dopamine receptors and the treatment of schizophrenia, there has been much sound and fury, but little bona fide significance.

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