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COMMENTARY

Dr. Seeman and his colleagues have provided a compilation of impressive and comprehensive discussions on the relationship between atypical and typical neuroleptics. First, they have made major contributions by applying a "radioligand-independent association constant" to these neuroleptics in a fashion that may allow their affinities to be compared more rationally in vitro. Second, they have tried to incorporate some aspects of endogenous dopamine that may modulate the apparent affinities of these neuroleptics in vivo. Thus, their in vitro and in vivo findings are correlated in a manner that is consistent with the results from recent studies available from positron and single photon emission tomography (PET and SPECT). Most important, they have attempted to use this approach to estimate the relative importance of serotonin and the D_4 dopamine subtype to the characteristics of atypical neuroleptics.

Seeman et al. have pointed out some apparent differences between the occupancy levels of clozapine after employing the commonly used PET radioligands [^{11}C]-raclopride and [^{11}C]-NMSP. Their results, quoted here, are comparable with those from our center. The mean D_2 occupancy $\pm$ SD is approximately 22% $\pm$ 11% after a treatment of 450 mg/day clozapine and 84% $\pm$ 11% after a treatment of 30 mg/day haloperidol (Conley et al. 1993; Kim et al. 1994) as compared to 48% with [^{11}C]-raclopride (Farde et al. 1992). The hypothesis that endogenous dopamine differences may affect occupancy levels is quite plausible. There now is a wealth of information from in vivo imaging studies regarding the effects of neurotransmitter modulations, the imaging of radioligands binding to their own receptors, and related receptor systems such as dopamine–dopamine and dopamine–serotonin interactions (Dewey et al. 1995; Laruelle et al. 1995). More recent studies have concentrated on the effects of endogenous dopamine on absolute receptor density measurements using raclopride (Wong et al. 1995). Hence, it is conceivable that the differences observed in the occupancy levels of clozapine may actually be differences in the characteristics of the radioligands. There is a noteworthy distinction between the D_4 affinity of raclopride and that of NMSP, in addition to their difference in susceptibilities to endogenous dopamine (Young et al. 1991). They interact in a fashion yet to be understood. Nevertheless, Seeman et al. provide an important step toward explaining the apparent discrepancies between these radioligands. Their review also provides investigators with a better understanding of the published studies to date. For example, using [^{11}C]-raclopride in vivo occupancy in studies remains the standard because of the pioneering work of Farde and his colleagues at the Karolinska Institute. Comparisons of dopamine occupancies using raclopride are meaningful as so much work has already been done—and will be done—with this radioligand. In comparison [^{11}C]-NMSP, related spiperone derivatives, and other radioligands may be less susceptible to endogenous dopamine, and they also may retain the advantage of having high D_4 affinities. First of all, they have the practical advantage of allowing both dopamine and serotonin measurements to be obtained in the same individual with a single PET scan. This is due to the tendency of NMSP to primarily estimate D_2-like occupancies in striatal areas and serotonin occupancies in cortical areas. NMSP has been successfully implemented in a number of studies (Conley et al. 1993; Kim et al. 1994; Goyer et al. in press). However, the problems associated with the lack of selectivity from ligands such as NMSP cannot be overlooked. Its advantages are balanced against its probable lower association with endogenous dopamine changes (Young et al. 1991). The work of Seeman et al. will help guide imaging researchers in designing their future experiments. This is vital to the development of this field as in vivo occupancy measures are best obtained in human tomographic imaging studies. For example, a past study using molindone by Wong et al. (1985) illustrated similar in vivo affinities between 5:1 equivalent doses of molindone versus that of haloperidol even though their in vitro affinities differed by a factor of 1 in 30. One possible explanation for this may be the presence of molindone metabolites with high D_2 affinity, whose effects can be seen by in vivo imaging, but not by in vitro studies (Wong et al. 1985; Wong and Yung 1993).

The radioligand-independent dissociation constants have important implications for in vivo imaging studies. One satisfying outcome is the relationship between K_{i_3} and K_I, which suggests a mutual consistency in the proposed modified dissociation constants. Indeed, suggesting the local effects of lipophilicity and so on bring to mind a recent problem posed by Delforge and colleagues (1996). These matters of possible heterogeneity in biological concentrations of plasma, receptor-free,

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and bound "compartments" are difficult to resolve with current in vivo technology. This raises new challenges for both imaging and in vitro studies (Wong and Gjedde, 1996a).

The haloperidol measurements of Seeman et al. with NMSP also are relevant and agree with our occupancy values of around 70% to 80% following 7.5 mg of oral haloperidol given 4 hours before the PET scan. This value has been seen to be relatively consistent over a large number of subjects since 1986 (Wong et al. 1986a, 1986b). This gives further confidence to the consistency of measures across the PET imaging field. Seeman et al. have referenced the seminal work of Smith et al. (1994) and Dewey et al. (1995) who demonstrated the relationship between dopamine and serotonin interactions and their roles in occupancy calculations. It has been suggested that the increased release of endogenous dopamine displaces some of the neuroleptic from D_2 dopamine receptors, thus alleviating some Parkinsonian symptoms. Many of the studies by Dewey et al. have been acute injections, however, and the effects of a chronic serotonin or dopamine blockade on dopamine and serotonin interactions, and others may need further clarification. For example, Tiihonen et al. (1996) showed a slight effect of chronic citalopram but not acute on raclopride binding; and their chronic findings were reversed from Dewey's acute study. Nevertheless, theirs is an interesting and plausible hypothesis.

Seeman et al. also suggest that the balanced 5-HT_2:D_2 relationship explaining low Parkinsonian symptoms in atypical neuroleptics may be inconclusive. Nevertheless, it should be noted that the effective 5-HT_2 occupancy may be modulated by endogenous serotonin just as dopamine D_2 measures may be modulated by dopamine. Although this has not been well documented in in vivo imaging studies, it still needs to be incorporated into the theoretical structure. Furthermore, this stresses the need for more 5-HT_2/–dopamine D_2 occupancy studies using in vivo PET imaging with ligands that bind to these and multiple sites. Then, the degree of endogenous dopamine may be directly measured and compared to in vitro studies.

The comments regarding D_4 dopamine receptors are provocative and very timely. Seeman et al. suggest that the blockade of the dopamine D_4 receptor may not be antipsychotic. Current clinical trials such as those of Kramer et al. (1996) suggest the same. However, an opposing view may be that the doses used in those studies may be insufficient and that higher doses are required to obtain meaningful results. Thus, for several reasons, it may be premature to exclude D_4 dopamine receptors from antipsychotic action. Nevertheless, the suggestion that D_4 may play a greater role in reducing extrapyramidal signs is an intriguing one and should stimulate further work in this area, if not with selected D_4 ligands, then with ligands having both D_2 and D_4 affinity.

Seeman et al. comment on the differences between certain radioligands, such as nemanopride, NMSP, and raclopride. It has been suggested that the former two bind more specifically to monomers than to dimers than does raclopride. Wong et al. (1992) demonstrated that there is an approximately proportional relationship between NMSP and raclopride, namely, that raclopride's B_{max} is on average 1.8 times greater than NMSP's B_{max}. It also was suggested that [^{11}C]-NMSP may demonstrate elevations that are slightly greater than those observed with [^{11}C]-raclopride in patients with schizophrenia (Wong in preparation). This is consistent with review of other work that has demonstrated receptor elevations with NMSP but not raclopride using both in vivo PET and in vitro postmortem studies (Gjedde et al. 1995). It is possible that these persistent findings of elevations using spiperone or NMSP derivatives may relate to some differentiating feature these ligands possess, such as the high susceptibility of raclopride to its own endogenous dopamine measurements that then suppresses apparent B_{max} elevations (Wong et al. 1995). Alternatively, as Seeman suggests, the monomeric component may be higher in a schizophrenic patient than the dimeric component, thus allowing derivatives such as NMSP or nemonapride to show changes in a striatal D_2-like receptor. This is a rather speculative, but interesting, possibility.

Seeman et al. have provided some precedents for this in relation to the alpha-adrenergic system. In any event, a mechanism for the effects of endogenous dopamine, for monomer–dimer relations, or for some as-yet undetermined mechanism is needed to explain the evidence that NMSP and spiperone derivatives show higher levels in striatal regions than does raclopride (Gjedde et al. in press). Going one step further, whatever the explanation for these NMSP findings may be, they appear to be part of a more generalized set of information relating to the role of dopamine in schizophrenia. In addition to D_2-like changes resulting from whatever cause (e.g., neuroleptic-induced vs. true biological effects), two articles have now appeared that demonstrate elevated dopadecarboxylase activity (Reith et al. 1994; Hietala et al. 1995). These articles establish the probability that dopadecarboxylase is elevated in schizophrenia. Finally, some of the work of Laruelle et al. (1995) and Breier (1996) have demonstrated elevations in dopamine release upon stimulation with IV amphetamine. This elevation may be more pronounced with low-specific-activity raclopride, but still needs to be confirmed (Wong and Gjedde 1996b).

Thus, findings, such as elevated D_2-like postsynaptic receptors, presynaptically elevated dopadecarboxylase, and elevated dopamine release directly relating to increased phasic release are consistent with a number of theories including, most notably, that of Grace (1993), who hypothesized that a low tonic dopamine would result from an increase in phasic dopamine. Further, unregulated

presynaptic synthesis enzymes and post synaptic receptors have been proposed by Reith et al. (1994) and Gjedde et al. (1993). Studies of schizophrenia using in vivo imaging will lead to a better understanding of the interactions between the dopamine, serotonin, and glutamate systems and the role of antipsychotic drug action, all of which are obviously interrelated. The studies of Seeman et al. justify a considerable impetus for further research in this area.

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