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**MEETING ABSTRACT**

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The fast-off hypothesis revisited: a functional kinetic study of antipsychotic antagonism of the dopamine D₂ receptor

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Newer, “atypical” antipsychotics carry a lower risk of motor side effects than older, “typical” compounds. It has been proposed that a ~100-fold faster dissociation from the dopamine D₂ receptor (D₂R) distinguishes atypical from typical antipsychotics. Furthermore, differing antipsychotic D₂R affinities have been suggested to reflect differences in dissociation rate constants (k_off), while association rate constants (k_on) were assumed to be similar. However, it was recently demonstrated that lipophilic accumulation of ligand in the cell interior and/or membrane can cause underestimation of k_off, and as high-affinity D₂R antagonists are frequently lipophilic, this may have been a confounding factor in previous studies. In the present work, a functional electrophysiology assay was used to measure the recovery of dopamine-mediated D₂R responsivity from antipsychotic antagonism, using elevated concentrations of dopamine to prevent the potential bias of re-binding of lipophilic ligands. The variability of antipsychotic k_on was also reexamined, capitalizing on the temporal resolution of the assay. k_on was estimated from the experimental recordings using a simple mathematical model assumed to describe the binding process. The time course of recovery from haloperidol (typical antipsychotic) was only 6.4–2.5-fold slower than that of the atypical antipsychotics amisulpride, clozapine, and quetiapine, while antipsychotic k_offs were found to vary more widely than previously suggested. Finally, affinities calculated using our k_on and k_off estimates correlated well with functional potency and with affinities reported from radioligand binding studies. In light of these findings, it appears unlikely that typical and atypical antipsychotics are primarily distinguished by their D₂R binding kinetics.

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