Receptor Binding Profiles of Atypical Antipsychotics: Mechanisms of Therapeutic Actions and Adverse Side Effects

Mechanisms of Therapeutic Actions and Adverse Side Effects

All antipsychotics (both conventional and atypical) bind to some degree at dopamine D2 receptors. It is believed that D2 antagonism mediates antipsychotics' ability to reduce positive symptoms of schizophrenia, including hallucinations and delusions. What sets the atypical antipsychotics apart from conventional is the propensity of atypicals to bind additional receptors in antagonistic or agonistic manners. Binding to additional dopaminergic, serotonergic, adrenergic, and cholinergic receptors has additional consequences, such as lessening some of the symptoms of schizophrenia or mitigating side effects caused by D2 antagonism. For example, in addition to D2 antagonism, most atypical antipsychotics also act in an antagonistic fashion at serotonergic 5HT2A receptors. This 5HT2A antagonism is theorized to reduce the extrapyramidal symptoms (EPS) and hyperprolactinemia caused by chronic D2 antagonism.

The vast molecular polypharmacy of atypical antipsychotics is associated not only with additional therapeutic benefits; binding to some receptor types increases a drug's propensity to cause adverse side effects. Chronic D2 antagonism is linked with EPS, tardive dyskinesia, and hyperprolactinemia, which are common side effects associated with conventional antipsychotics. Although additional binding properties of atypical antipsychotics lower the risk of some D2 antagonism-associated side effects, the more complex binding profiles of atypical antipsychotics can lead to other serious side effects. Most notably, the binding of atypical antipsychotics to 5HT1A, 5HT2A, and/or H1 receptors has been linked with cardiometabolic effects that can greatly compromise a patient's physical well-being.

Each atypical antipsychotic agent has a binding profile that differs from other antipsychotics. An antipsychotic's binding profile is a summation of the receptors to which it binds, the strength of the binding to individual receptor types (binding affinity or Ki), and the action of the drug on that receptor type (antagonism, partial agonism, etc.). The unique binding profile lends each antipsychotic its own set of therapeutic effects and adverse side effects. This contrast in binding profiles can lead to differences in the therapeutic actions and adverse side effects. For example, atypical antipsychotics are generally associated with fewer EPS and tardive dyskinesia compared to conventional antipsychotics. However, atypical antipsychotics can still cause adverse effects, such as hyperprolactinemia and metabolic disturbances.

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