# SYNAPTIC EVENTS AND LONG TERM NEUROADAPTIVE CHANGES INVOLVED IN ANTIPSYCHOTIC ACTION: A COMPARISON BETWEEN FIRST AND SECOND GENERATION DRUGS

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Antipsychotic drugs (APDs) represent the first-line treatment for the cure of schizophrenia. There is a clear distinction between the so-called first generation (FG) APDs, such as haloperidol, and second-generation (SG) agents. While all drugs share the ability to interfere with dopaminergic transmission, primarily through a blockade of D2 receptors, several relevant differences do exist in terms of short-term synaptic events as well as of long-term adaptive changes set in motion by prolonged treatment with these agents.
Indeed while FG-APDs are characterized by a potent blockade of dopamine D2 receptors, most SG-APDs share a high affinity a number of serotonin receptors, primarily 5HT2a. The distinct receptor binding profiles between APDs is undoubtedly relevant for the rapid effects of these drugs aimed at normalizing dysfunctions that contribute to psychosis. Moreover these short-term mechanisms might also contribute to the onset of side effects that not only discriminate FG vs. SG-APDs (EPS), but allow a differentiation among SG agents.
The difference between APDs can not be limited to their binding profiles since the interaction with different classes of receptors initiates long-term neuroplastic changes, which have a strong impact on brain function and are crucial for stable therapeutic improvement. Indeed, despite the fact that schizophrenia is characterized by changes in the function of different neurotransmitter systems, there is now compelling evidence that the disease is associated with deficits in the expression and function of proteins important for cellular plasticity and resiliency. Preclinical studies from different laboratories, including our own, have demonstrated that SG-APD can normalize deficits in the expression of the neurotrophin BDNF, an important player in synaptic plasticity. Moreover prolonged drug treatment can alter the function and responsiveness of intracellular signalling proteins that represent a converging point for the activity of different receptors that are target of APDs. Altogether these data suggest a superior impact on neuronal plasticity and cellular function of SG-APDs with respect to classical drugs. We believe that these adaptive changes may improve brain plasticity and provide a relevant contribution to the functional recovery of schizophrenic patients.