

Assessing the therapeutic and side-effect profiles of novel antipsychotic drugs through pre-pulse inhibition of startle and operant conditioning rate assay experiments

Abstract

Pre-pulse inhibition (PPI) of the startle response is an unconditioned neurological reaction that reflects the adaptability of the nervous system to external cues and warnings. When an organism is exposed to a low-intensity pre-stimulus 30-500 milliseconds prior to a high-intensity startling stimulus, the startle response to the strong stimulus is reduced, reflecting normal sensorimotor gating. PPI is an important phenomenon and research tool for the following reasons: First, patient populations with certain psychiatric disorders, including schizophrenia, exhibit deficits in PPI. Second, although experimentally induced PPI deficient rodents are not animal models of diseases such as schizophrenia per se, all widely prescribed antipsychotic medications improve PPI, and the paradigm is widely used to assess the efficacy of potential drug treatments for schizophrenia. This thesis aimed to assess the therapeutic and side-effect profiles of antipsychotic drugs. First, the ability of antipsychotic drugs to recover PPI in experimentally induced PPI deficient rodents was evaluated to determine the therapeutic effects. Next, the side-effects profile of these drugs was determined by recording the effects of the same drugs on the motor response rate of normal rats trained in a food maintained operant behavior task.

To create a PPI-deficient rodent, apomorphine, a dopamine receptor agonist, was used. Next, we assessed the ability of a novel dopamine D2 receptor antagonist, CTDP 30,852, to recover PPI. We found that this compound did not recover the apomorphine-induced deficit of PPI. On the other hand, the dopamine D2 antagonist haloperidol did appear to dose-dependently recover the PPI deficit, though the results did not reach statistical significance. The test for motor side-effects revealed that CTDP 30,852 had no effect on the rate of response of rats 5 trained on a food maintained operant behavior task, even at the highest dose, while haloperidol dose-dependently decreased the rate of response.

Interestingly, because CTDP 30,852 does not bind to sigma receptors whereas haloperidol does, an additional drug was evaluated to test the hypothesis that sigma receptor binding may be partly responsible for motor side effects. When administered alone, the sigma receptor agonist, DTG, resulted in a modest dose-dependent recovery of PPI. This novel finding warrants further investigation in order to evaluate sigma receptors as a potential target for novel antipsychotic drugs with fewer side effects.