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Meeting abstract

Search for novel antipsychotic drugs: dopamine forever?

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During the history of antipsychotic medications, the dopamine D_2 receptor has been the crucial main target of drug action. Typical antipsychotics, which dominated the first 25 years of antipsychotic treatment as well as atypical antipsychotics, medications of the last three decades, all retained dopamine D_2 receptor antagonism as the basic mode of action. Whether the superior side-effect profile (fewer extrapyramidal symptoms) of atypical antipsychotic agents is due to their serotonin 5-HT_{2A} receptor antagonist activity or to their looser binding to the dopamine D_2 receptor is still a matter of debate. Brain imaging studies demonstrating a strong relationship between dopamine D_2 receptor occupancy and clinical effects and side effects of antipsychotics gave fundamental support for a central role of dopamine D_2 receptors in the pathology and therapy of schizophrenia. The clinical failure of alternative approaches lacking the D_2 component, such as selective serotonin 5-HT_{2A} and dopamine D_4 receptor antagonists further pointed at the indispensable role of D_2 antagonism. The recently developed atypical antipsychotic agent, aripiprazole, while preserving the predominant D_2 action, introduced a new pharmacological approach: dopamine D_2 receptor partial agonism. An appropriate degree of partial agonism presumably results in effective blockade of overstimulated dopamine D_2 receptors and improvement in psychotic symptoms, while it prevents the induction of extrapyramidal side effects or secondary negative symptoms by avoiding complete silencing of dopaminergic transmission. In recent years, the glutamatergic hypothesis for the pathology of the disease has gradually gained acceptance. Beside theoretical considerations, this concept was initially fuelled by some successful trials with the glutamate NMDA receptor co-agonists glycine, D-cycloserine and D-serine on the negative symptoms of the disease. However, their efficacy was modest and these compounds were still applied as adjunct therapy to the standard D_2 dopaminergic antipsychotics. The most recent and, perhaps, most promising "challenge" to the D_2 centred therapy of schizophrenia has been the successful proof of concept trial with the selective metabotropic glutamatergic receptor $mGlu_2$/$mGlu_3$ agonist prodrug compound, LY2140023. However, confirmation of the clinical efficacy of the compound is still awaited, and it has been raised that the compound may eventually affect - though indirectly - dopaminergic mechanisms. It seems, despite several burial attempts and attractive alternative hypotheses and tremendous drug development efforts, the therapy of schizophrenia cannot - so far - detach itself from the dopaminergic system.