

EFFECT OF TYPICAL AND ATYPICAL ANTIPSYCHOTICS ON IN VIVO DOPAMINE TRANSMISSION IN DIFFERENT BRAIN AREAS

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Antipsychotic drugs (APDs) share the common pharmacological property of blocking dopamine D2 receptors, a feature that is also responsible for the occurrence of main adverse neurological effects of neuroleptics, namely extrapyramidal side effects after long term treatment. The new generation of antipsychotics, however, shows a lower incidence of side effects as compared to classical ones. Various hypothesis have been proposed to explain the properties of atypical APDs: blockade of 5-HT_{2A} receptors, high dissociation rate of drug - D2 receptor complex, mesolimbic selectivity, etc. We hypothesized that the atypical properties of different classes of APDs are the result of different mechanisms not only pharmacodynamic but also pharmacokinetic in nature. In order to test this hypothesis we studied different doses of various APDs, including haloperidol, clozapine, raclopride, chlorpromazine, risperidone, olanzapine, and amisulpride on their effects on extracellular dopamine (DA) in different terminal DA areas of rat: the medial prefrontal cortex (mPFCX), the nucleus accumbens (NAc) shell and the NAc core. All the typical and atypical APDs tested significantly and dose dependently, increased extracellular DA output in dialysates from the NAc shell, but after atypical APD the increase was preferential or depending on the drug selective in the NAc shell as compared to the NAc core. All atypical APD, with the exception of raclopride and amisulpride, increase DA output in dialysates from the PFCX. The two benzamides, raclopride and amisulpride, showed major differences in the time-course of the effects: while raclopride produced a sharp but short lasting increase of DA, amisulpride elicited a slow and long lasting increase. These observations suggest that different mechanisms might underlie the atypical properties of ADPs. Among drugs with rapid penetration into the brain compartments, such as haloperidol, chlorpromazine, clozapine and raclopride, atypical properties, as in the case of clozapine, critically depend from rapid D2 receptor dissociation. Conversely, among drugs with slow D2 receptor dissociation, as haloperidol, chlorpromazine, risperidone, olanzapine, raclopride and amisulpride, atypical properties depend from slow penetration of the blood brain barrier. Within this frame, blockade of 5-HT_{2A} receptors may be important for atypical aspect unrelated to extrapyramidal side effects and to clinical positive symptoms.