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Animal models of Schizophrenia indicate a requirement for the improvement of Antipsychotic Drugs: Understanding their mechanism of action is the first step

Uzuneser Taygun C, Weiss Eva-Maria, Wrosch Jana K and Müller Christian P
University Hospital of Erlangen, Germany

Schizophrenia is a neuropsychiatric disorder, causing psychosis, affective and cognitive disturbances in patients. Even though the etiology of schizophrenia has not yet been clearly understood, neurochemical and behavioral abnormalities involved in the disease state can be mimicked in animals. We sensitized rats by repeated amphetamine (AMPH) exposure, which caused schizophrenia-related disruptions, including exaggerated locomotor response to subsequent AMPH-challenge, anxiogenic behavior, sensorimotor gating deficits, short-term object memory deficits, and post mortem neurochemical abnormalities. In order to reverse these disruptions, we used haloperidol (HAL), a clinically used antipsychotic drug. We administered it continuously for 14 days using two doses; the higher dose (0.5 mg/kg/day) being therapeutically effective, and the lower dose (0.05 mg/kg/day) mainly blocking presynaptic auto-receptors. Higher dose HAL reversed the elevated locomotor response to AMPH and sensorimotor gating disruptions, yet lost its efficacy with time. Lower dose HAL was effective in reversing anxiogenic behavior, sensorimotor gating deficits, and memory deficits, yet it even exacerbated the locomotor response to AMPH. These results, as well as findings in the literature suggest that clinically used antipsychotic drugs require improvement. For this purpose, as a second experiment, we examined the mechanism of action of HAL. Previous findings suggest that the weak-base property of HAL enables it to be accumulated in acidic organelles, and released use-dependently. To understand the functional consequences of the accumulation process, we designed a HAL-analogue that lacks this accumulation property, and showed the absence of accumulation in vitro using the fluorescent dye LysoTracker Red. Later, by using the same AMPH exposure regimen, we tested the efficacy of the analogue compound in rats. We found that the HAL-analogue had no effect on the reversal of AMPH-induced behavioral deficits. These results suggest that the accumulation property of HAL is critical in mediating its antipsychotic effects. The requirement of accumulation may also explain the delayed antipsychotic efficacy in patients.

taygun.uzuneser@uk-erlangen.de