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DAT atypical inhibitors as novel antipsychotic drugs

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Despite its classification as a psychiatric disease, schizophrenia is both a behavioral and a biological disorder resulting in neurocognitive dysfunction. Social and economic costs of schizophrenia are extremely high compared to its incidence and prevalence, however, due to a heterogeneous pattern of brain pathology and symptoms and to an unknown etiology, developing an effective treatment has been really challenging. Among the many neurochemical hypothesis, the dysregulation of dopaminergic neurotransmission has been considered as a central dogma of schizophrenia over the last few decades. In fact, patients with this pathology exhibit increased dopamine (DA) synthesis and release in the striatum which seems to correlate with positive symptoms and moreover, most of the effective antipsychotic drugs (APDs) are D2-receptor antagonists. Unfortunately, chronic treatment with APDs is associated with the induction of extrapyramidal side effects (EPS). In order to identify new possible APDs with a novel mechanism of action and potentially less EPS we tested 3 different compounds generated from the structural modification of vanoxerine (or GBR12909), a known atypical inhibitor of the presynaptic DA transporter (DAT) with cocaine-like activity but cardiotoxic properties that have precluded its clinical use. Preliminary *in vitro* studies showed that DAhLIs (DAT atypical inhibitors) are able to bind to DAT and inhibit DA reuptake. Additionally, our *in vivo* results showed that DAhLI i) have putative central effects, ii), unlike vanoxerine, reduce novelty-induced locomotor activity, and iii) counteract cocaine stimulating effects, suggesting that DAhLI may potentiate DA reuptake via DAT. These compounds may provide a way to reduce DA extracellular levels and DA neurotransmission with a selective action on active DA synapses, thus with reduced EPS typical of D2 antagonists, representing a new promising class of presynaptic APDs.