



Orexin receptor antagonism and schizophrenia: addressing attentional impairment in an NMDA receptor hypofunction model of psychosis

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Abstract

Attention is the psychological process by which the external world is actively perceived, interpreted, and navigated, allowing for organisms to selectively focus on relevant stimuli at the exclusion of irrelevant noise and distraction. Schizophrenia is a neuropsychiatric condition that arises from excitatory imbalances throughout the brain and is associated with not only hallucinations and delusions, but treatment-resistant attentional impairments, providing a clinical impetus to explore alternate antipsychotic targets. Receptors of the hypothalamic orexin system represent promising targets, as they are expressed on numerous attention- and schizophrenia-relevant nuclei. The experiments included in this dissertation tested the capacity for orexin receptor antagonists to treat attentional and electrophysiological deficits associated with a commonly-employed rodent model of psychosis. It was found that the dual orexin receptor antagonist filorexant and the selective orexin-1 receptor inhibitor SB-334867 both improved performance in a sustained visual attention task for rats co-administered a low dose of the psychotogenic N-methyl-D-aspartate receptor antagonist dizocilpine. However, for mice given a higher concentration of dizocilpine, filorexant was unable to improve deficient synchronization of neuronal firing at frequencies in the gamma band that coincide with attentional processing. Taken together, these findings are the first to reveal a potential dissociation of the efficacy of anti-orexinergic compounds for the treatment of attentional impairments in animal models of schizophrenia; namely, the behavioral abnormalities which arise from low degrees of psychotomimesis may be more easily reversed than the anomalous neuronal oscillatory activity present in a more potently psychosis-like state.