

Orexin 1 Receptor Antagonist SB-334876 Impairs Sustained Attention but Only at High, Non-Clinically Relevant Doses

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The hypothalamic orexin (hypocretin) system affects psychological functions such as arousal, wakefulness, motivation, and sleep. Due to its influence in motivation, orexin-1 receptor antagonist SB-334876 shows promise as a therapeutic for substance use disorder due to its effect in suppressing drug seeking behavior. Knowing the role of OxR1 signaling in cue-driven motivation, we wanted to determine SB-334876's effect on sustained attention using the rodent psychomotor vigilance task. The 30 min operant chamber task, "rPVT" measures changes in sustained attention and fatigue with parameters such as performance accuracy, motor speed, premature responding, and lapses in attention. We validated the ability of rPVT task by modulating norepinephrine signaling with amphetamine, guanfacine, and atipamezole to be able to produce bidirectional attention modulation effects. Once it was determined rPVT can assess sustained attention we investigated the effects of orexin-1 receptor antagonist SB-334876 on this paradigm. Results showed a dose dependent effect with atipamezole, guanfacine, and amphetamine where the larger dose showed a decrease in performance while the moderate dose showed a slight increase and lowest stayed at baseline. This effect was apparent when looking at accuracy and reaction time. Looking at SB, we see a prominent decrease in performance and sustained attention in the highest dose, 30 mg/kg, whereas the low and moderate doses stayed at baseline. With these results, it can be concluded that SB-334876 orexin 1 receptor antagonist can be a promising therapeutic to suppress drug seeking behavior because it does not have a significant impact on sustained attention in clinically relevant dosage (3 and 10 mg/kg). Supported by NIH Grants R00DA045765 and R25ES020721.

