Selective Blockade of the Orexin-1 Receptor: Attenuating the Reward System in the Brain Associated With Cocaine Addiction

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Cocaine addiction remains a large problem in the United States, with 1.5 million users ages 12 and older reported in 2014. Despite this fact, there are currently no drugs approved by the FDA for the treatment of cocaine addiction. The reward system associated with cocaine, i.e. the release and prevented reuptake of dopamine within the brain, has been widely targeted as a possible treatment for addiction. The development of selective receptor antagonists of Orexin-1 (OX₁), a G-protein coupled receptor, has become a major focus of research directed at attenuation of this reward system, as the blockade of the OX₁ receptor has been shown to reduce cocaine-seeking behavior under cue- and stress-induced reinstatement.

Originally, dual antagonists for both the OX₁ receptor and the closely related OX₂ receptor were developed for treatment of insomnia, as seen with the approved drug suvorexant (trade name Belsomra). OX₁-selective antagonists have since been developed as therapeutics in order to further elucidate the physiological role of the OX₁ receptor relative to drug addiction. SB-334867 was the first OX₁-selective antagonist reported, with a ~50-fold higher selectivity over OX₂. Other selective antagonists include GSK-1059865 and ACT-335827, although these compounds still retain significant OX₂ activity. Most recently, SAR studies focusing on tetrahydroisoquinoline-containing compounds has led to the discovery of several analogues with high OX₁ selectivity that hold promise as cocaine addiction treatments (see figure below).

Overall, cocaine, its use, and the class of OX₁-selective antagonists provide an interesting perspective, one that highlights both cocaine’s initial praise as a wonder-drug and its more widely recognized misuse as an illegal substance.

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5 Yang, L. P. Drugs. 2014, 74, 1817−1822.