Cocaine Conditioned Place Preference Results in Orexin Receptor Changes

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Cocaine Use Disorder (CUD) is a significant public health challenge due to the lack of effective treatments. Identifying brain regions involved in CUD can reveal potential therapeutic targets. The hypothalamic orexin (hypocretin) system, which regulates reward and arousal, is a promising target. Our lab found an increased orexin cell number and activity post-cocaine self-administration, lasting for five months, suggesting synaptic plasticity in orexin neurons and altered signaling in key reward and arousal centers. However, it's unclear if these changes affect orexin receptor expression. Using a preclinical CUD model called Conditioned Place Preference (CPP) in rodents and qPCR analysis, we investigated orexin receptor changes. Rats underwent CPP with either 10mg/kg cocaine or saline injections. Post-CPP, we quantified orexin 1 and orexin 2 receptor expression in the hippocampus, lateral hypothalamus (LH), ventral tegmental area (VTA), and dorsal raphe. Cocaine CPP rats showed increased orexin1 receptor expression in the VTA and elevated orexin precursor, prepro-orexin, in the LH compared to saline CPP rats, while other regions showed no change. These findings suggest that altered orexin signaling in the VTA modulates reward processing and arousal, influencing addictive behaviors. Targeting the orexin system, particularly orexin 1 receptors in the VTA, may offer new therapeutic strategies to reduce cocaine's reinforcing effects.