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Neuroadaptations and Behavioral Profiles Associated with Cocaine Self-Administration in Rhesus Monkeys (Macaca Mulatta)

Nina M Shinday, *University of Massachusetts - Amherst*

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First Advisor
James K. Rowlett

Second Advisor
Jerrold S. Meyer

Third Advisor
Melinda A. Novak

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Abstract
Cocaine abuse and addiction are widespread problems with profound medical and socioeconomic consequences. At present, the neurobiological adaptations associated with short- and long-term cocaine abuse are not well understood, which contributes to the lack of availability of broadly

effective treatments for this type of addiction. Recently, some studies have implicated GABAA receptor subtypes in the neuroadaptations underlying addiction. To explore the contributions of GABAA receptors to the neurobiological basis of cocaine abuse, we utilized a non-human primate model of cocaine self-administration and examined changes in species typical behaviors, and corresponding alterations in three GABAA receptor subtypes within five reward-related areas of the brain. Sixteen rhesus monkeys either self-administered cocaine intravenously (1-hr/day, 0.03 mg/kg/injection of cocaine) or received passive infusions of saline yoked to the cocaine injections (yoked control). Monkeys either self-administered cocaine for ~10 days (short-term group) or ~100 days (long-term group). Twenty-four hours after the last session, animals were sacrificed and brains were removed. We examined alterations in α1, α2, and α3 subunit-containing GABAA receptors (α1, α2, and α3GABAA receptors) using immunohistochemistry (IHC), in situ hybridization (ISH), and real-time PCR experiments (RTPCR) within reward-related areas of the brain including the nucleus accumbens, ventral tegmental area, caudate, putamen, and anterior cingulate cortex. Long-term cocaine taking animals self-administered cocaine in a cyclical pattern, and increased number of cocaine injections taken within the initial portion of daily self-administration sessions. We observed behavioral alterations in behaviors including locomotor, stereotypic, scratching and affiliative behaviors. IHC results demonstrated alterations in α1GABAA receptors within all regions of interest after long-term self-administration. After short-term cocaine self-administration decreases in α3GABAA receptors were observed in all regions examined. When examining transcript levels using ISH and RTPCR, we found relatively few changes in comparison to protein alterations. The notable change was a decrease of all three receptor mRNAs within the anterior cingulate cortex after short-term cocaine exposure. The present model of drug may expand our understanding of addiction-related behaviors and the role of GABA in addiction. Furthermore, our findings suggest GABAA receptors may serve as viable targets for pharmacotherapeutic approaches to treat addiction.