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Commentary

Sex Hormones: A New Treatment for Cocaine Abuse?

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Mello *et al* (2011; this issue) report that two neuroactive steroid hormones, progesterone and testosterone, dampen the reinforcing effects of cocaine in female rhesus monkeys. Their study with non-human primates provides a critical translational link between preclinical studies with rodents and clinical findings with humans. Studies with non-human primates are especially important in research involving sex hormones and sex differences because the menstrual cycle of these animals closely resembles that of humans. Mello *et al* have conducted a rigorous and comprehensive series of studies on the effects of progesterone and testosterone on the reinforcing and stimulus effects of cocaine in female rhesus monkeys. Interestingly, both hormones decreased the reinforcing effects of cocaine without altering either the animals' responding for food reward or their ability to discriminate cocaine from vehicle.

The finding that progesterone dampened cocaine reward is consistent with previous findings using both humans and non-humans, and extends our understanding of this drug–hormone interaction (for review see Evans and Foltin, 2010). This study confirms, in a non-human primate species, that higher circulating levels of progesterone reduce the reinforcing effects of cocaine, probably due to its neuroactive metabolites. Interestingly, the authors also show that progesterone does not affect food reward, so it is not nonspecifically decreasing motivated behaviors. Surprisingly, progesterone does not decrease the animals' ability to detect cocaine, using a behavioral procedure designed to assess 'subjective' effects of cocaine. This is surprising because it rules out a possible behavioral mechanism for the decreased reinforcing effects, and because progesterone does decrease the subjective effects of cocaine in women. It remains to be determined how progesterone (or any other substance) can decrease drug-taking behavior in animals in such a specific way without altering the perceived effects of the drug.

The finding that testosterone decreased responding for cocaine is novel, and in some respects counterintuitive. It is counterintuitive because human males are much more likely than females to abuse cocaine and other stimulants (Kandel *et al*, 1997), and so a hormone that makes female monkeys more male-like might be expected to increase the reinforcing effects of cocaine. On the other hand, several studies with laboratory animals suggest that female rodents and monkeys expend more effort to obtain cocaine rewards than males, suggesting that they may be more sensitive than males to the reinforcing effects of cocaine (Becker and Hu, 2008). It is not clear whether acute response to exogenous administration of testosterone in females sheds light on possible sex differences. Sex differences are likely to be influenced by organizational effects of hormones at critical developmental periods, at least as much as by momentary variations in the levels of circulating hormones. Nevertheless, the specific effects of exogenous testosterone on cocaine self-administration in female monkeys are intriguing and may open the door to further research on development of medications, including hormones, to decrease cocaine use.

This research illustrates the value of non-human primate models for substance abuse research. The study provides a comprehensive behavioral profile of the interactions between drugs and hormones, which includes motivational features (ie, self-administration), specificity (ie, cocaine *vs* food reinforcement), as well as important information about the drugs' discriminative stimulus effects. The measures and methods have a clear parallel in humans, and the results not only advance our understanding of drug–hormone interactions, but also provide an exemplary protocol for testing potential drug abuse medications. The finding that both hormones decreased the reinforcing effects of cocaine without affecting food reinforced behavior, raises the possibility that these or other hormones may be developed as safe and effective medications for cocaine abuse.

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DISCLOSURE

The author declares no conflict of interest.

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