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SEX AND DRUGS: COMMENT ON “EVIDENCE FOR INVOLVEMENT OF ER β AND RGS9-2 IN 17- β ESTRADIOL ENHANCEMENT OF AMPHETAMINE-INDUCED PLACE PREFERENCE BEHAVIOR” BY SILVERMAN AND KOENIG

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When thinking of the “typical” drug user, most of us would picture a young adult male. Indeed, this population has the highest rates of illicit drug use in the United States. According to the 2004 National Survey on Drug Use and Health, 38% of men ages 18-25 used an illicit drug in the past year (SAMHSA, 2005). However, drug use among young women is not far behind. Some 30% of women age 18-25 used an illicit drug in 2004 (SAMHSA, 2005). Research over the past 10 years in both humans and laboratory animals has investigated the neurobiologic basis of sex differences in susceptibility to drug use and drug dependence. In view of the increased prevalence of drug use in men, it is perhaps surprising that women show greater responses to cocaine (Quinones-Jenab, 2006), including both increased craving and anxiety. Likewise, female rats exposed to stimulants acquire both sensitization and self-administration more rapidly than males. A similar bias towards females has been reported for self-administration of caffeine, opiates, alcohol and phencyclidine in rats and monkeys (Roth et al, 2004). Not surprisingly, these sex differences in response to stimulants are sensitive to gonadal steroid hormones, particularly in females. Estrogen enhances both amphetamine-stimulated behavior and dopamine release in the nucleus accumbens (Acb) of female rats (Becker, 1999). The foregoing observations suggest that females may be particularly susceptible to drug dependence. This argues for an urgent need to understand the mechanisms through which ovarian steroids enhance responses to drugs.

In this issue, Silverman and Koenig (2007) investigated the effects of estrogen on an intracellular mediator of dopamine D2 receptor activity. Regulator of G protein signaling (RGS) 9-2 is a member of a large family of proteins that stimulate GTPase activity of the G protein α subunits (Rahman et al, 2003). RGS9-2 is selectively localized to the dorsal and ventral striatum, where it has been implicated in neuroadaptations to chronic drug exposure in male rats and mice. Chronic exposure to cocaine increases levels of RGS9-2 in the nucleus accumbens and caudate-putamen (Rahman et al, 2003). Furthermore, overexpression of RGS9-2 reduces behavioral responses to dopamine agonists (Rahman et al, 2003), while deletion of RGS9-2 enhances responsiveness to stimulants and opioids (Zachariou et al, 2003). These responses are consistent with the role of RGS proteins to attenuate G protein-mediated signaling.

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Dr. Koenig's laboratory is the first to examine RGS9-2 in females and to investigate the regulation of RGS9-2 by sex steroid hormones. Previously, his group reported that estrogen selectively decreases levels of RGS9-2 in the shell of nucleus accumbens, but not the core (Sharifi et al, 2004). The shell of nucleus accumbens is strongly implicated in drug dependence (Di Chiara et al, 2004), whereas the core is more concerned with motor control (Zahm, 1999). In addition, the accumbens shell has substantial connections with steroid-responsive brain regions that control reproductive function (Zahm, 1999). The finding that estrogen reduces RGS9-2 in accumbens shell provides a possible mechanism to account for estrogen stimulation of drug responsiveness. If RGS9-2 inactivates G-protein coupled responses, estrogen-induced inhibition of RGS9-2 should enhance the response to stimulants. This was the hypothesis tested in Silverman and Koenig (2007).

The authors examined conditioned place preference to a low dose of amphetamine in ovariectomized female rats with and without chronic estrogen and progesterone exposure. At 1.0 mg/kg, amphetamine induced a conditioned place preference in ovariectomized rats with estrogen and progesterone replacement. However, untreated ovariectomized females failed to express a preference for the environment paired with low-dose amphetamine. Behavioral responses to amphetamine and estrogen were accompanied by reduced levels of RGS9-2 in the shell of nucleus accumbens. The stimulatory effect of hormone replacement was presumably mediated by estrogen, since there were no differences between females receiving estrogen alone vs those treated with estrogen plus progesterone. A second experiment showed that the effects of estrogen are transduced via the beta form of the estrogen receptor (ER β). Replacement of ovariectomized females with the ER β agonist diarylpropionitrile mimicked the effect of estradiol, whereas the ER α agonist propylpyrazoletriol was without effect.

One of the key features of this study is the threshold dose of amphetamine used to test conditioned place preference. Silverman and Koenig (2007) point out that drug doses and pairings must be carefully titrated to reveal the stimulatory effects of estrogen. Stimulants and steroids are each reinforcing. When exposed to 4 pairings of 5 mg/kg cocaine, conditioned place preference was induced in ovariectomized female rats with and without estrogen treatment (Russo et al, 2003). At high doses, estrogen can induce conditioned place preference in female rats (Frye and Rhodes, 2006), similar to testosterone-induced conditioned place preference in males (Alexander et al, 1994). Because female rats can respond to either amphetamine or estrogen, it becomes important to determine the cellular mechanisms for their interaction. Silverman and Koenig's data on the importance of ER β and RGS9-2 are important steps in this regard. It has previously been shown that RGS9-2 reduces the activity of dopamine D2 receptors (Rahman et al, 2003), and that estrogen acting through ER β increases D2 receptors (Le Saux et al, 2006). Silverman and Koenig's study unites these two lines of evidence by showing that estrogen reduces RGS9-2 via ER β . Future studies, possibly involving estrogen effects on RGS9-2 in β ERKO mice, will be important to establish a causal link between estrogen, ER β , and RGS9-2.

The current findings suggest additional intriguing questions. Do estrogens act directly on cells of the nucleus accumbens, or are hormonal stimuli transduced in steroid-sensitive afferents to Acb? Acb is reported to contain ER β -positive neurons (Shugrue and Merchenthaler, 2001). However, the number of labelled cells and the intensity of staining is weak. Creutz and Kritzer (2004) report that midbrain neurons expressing ER β do not project to Acb. However, Acb receives substantial input from other brain regions rich in steroid receptors, including the bed nucleus of the stria terminalis (Zahm, 1999). Thus, there are opportunities both for direct actions of estrogen on Acb via ER β as well as indirect effects of estrogen. If estrogen modifies drug responses through binding to ER β in Acb, there is the additional question of genomic vs non-genomic effects. Estrogen has rapid non-genomic effects as well as classic genomic actions, and ER β may contribute to both (Herrick et al, 2006).

The increasing prevalence of drug use among women, coupled with the enhanced responsiveness to drug effects, give cause for some concern. Ongoing research efforts to develop pharmacologic therapies combating drug reinforcement and drug craving should take into account the unique susceptibility of women. Ultimately, these data add to the diverse actions of estrogen mediated via ER β . In addition to modifying responses to drugs of abuse, estrogen has been shown to affect a broad range of neural systems, including learning and memory, motor function, and mood (Bodo and Rissman, 2006). The distribution of ER β in brain areas not classically involved in sexual behavior or reproductive function provides a mechanism for these effects. Data from studies such as those of Silverman and Koenig (2007) paint a richer portrait of estrogen as more than just a reproductive hormone, but as a global modulator of neural activity.

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