Reviewing past studies exploring the effects of steroids on cocaine-use behaviors

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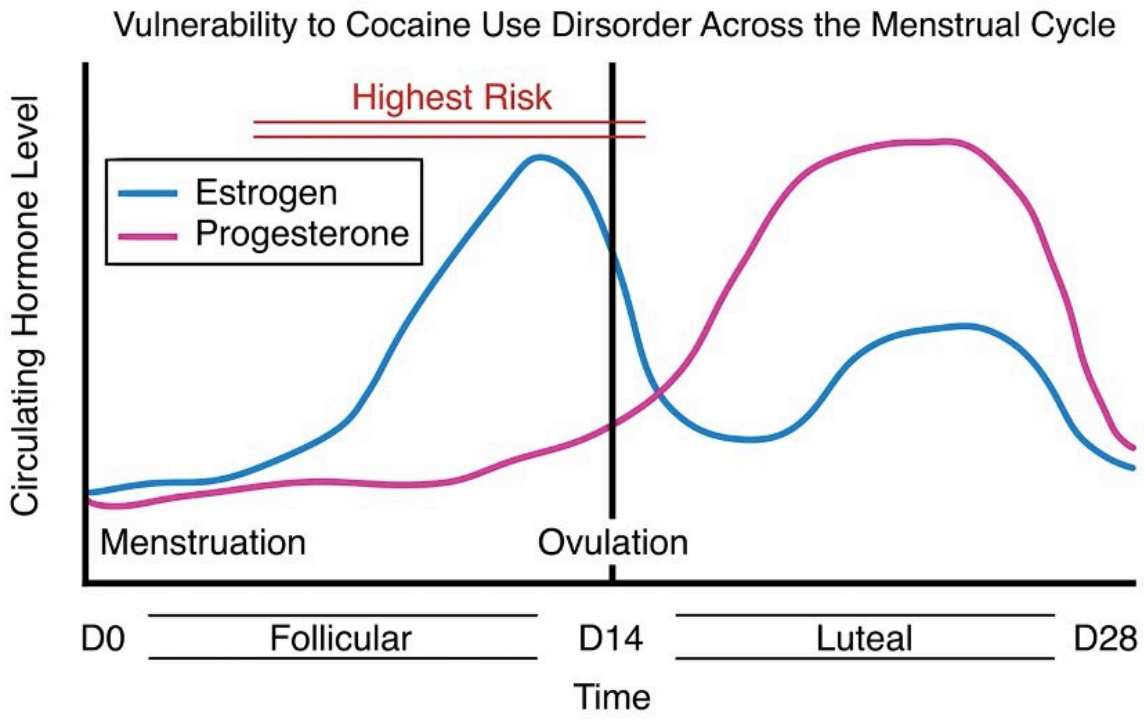

Vulnerability to cocaine use disorder across the menstrual cycle. The menstrual cycle is typically approximately 28 days long and consists of two phases – the follicular and luteal phases. During the follicular phase, circulating estrogen increases following menstruation. Ovulation occurs at the end of the follicular phase and is followed by the luteal phase, which is characterized by high levels of circulating progesterone. Cocaine craving and reward are lower in women in the luteal phase than in the follicular phase, and estrogen and progesterone respectively increase and decrease cocaine-related behaviours in female animal models of cocaine use disorder. Thus, risk of relapse is likely highest during the

follicular phase of the menstrual cycle, when circulating estrogen is high and progesterone is low. Credit: Peart et al.

Past research findings suggest that women who are addicted to cocaine are more sensitive to cocaine-related stimuli that make them crave the drug and relapse into addiction. However, other studies suggest that steroid hormones can modulate cocaine cravings, which could help to reduce the risk of relapse in people with cocaine-use disorders.

Researchers at University of Guelph and University of Florida have recently reviewed several past studies exploring the link between steroid hormones and cocaine-related behaviors. Their paper, published in *Neuroscience & Biobehavioral Reviews*, summarizes some of the most crucial findings gathered by neuroscientists so far, highlighting possible avenues for the development of new treatments for cocaine-use disorders.

The recent review paper was a joint effort between Davin Peart, a student at University of Guelph, and Carly Logan, then a student at University of Florida, supervised by Jennifer Murray and Lori Knackstedt, respectively. Peart and Logan had initially written two separate review papers, which were later integrated and revised by their supervisors and another student of Murray, Allyson Andrade, with the aim of identifying the endocrinological mechanisms underlying observed gender differences in vulnerabilities to cocaine-use disorder.

"We hoped that synthesizing this information would bring potential pharmacological targets for the treatment of this disorder to the attention of readers," Murray and Peart told *Medical Xpress*, via email. "We started by reviewing studies that worked with humans with cocaine use disorder."

The studies reviewed by Murray, Peart and their colleagues showed that women tend to progress more quickly from casual cocaine use to cocaine abuse. In addition, women appear to be more vulnerable to cocaine craving than men when presented with cues that are related to cocaine.

Interestingly, past research found that a woman's heightened sensitivity to cue-related cocaine craving appears to be lower during the luteal phase of the menstrual cycle (i.e., the time between ovulation and the start of a woman's next menstruation). On the other hand, these cravings appeared to increase during the follicular phase of the menstrual cycle (i.e., the time between the end of menstruation and the beginning of ovulation). The follicular phase is known to be characterized by low levels of progesterone in the body.

"These findings suggests that women may be more vulnerable than men to cocaine use disorder in a hormone-dependent way," Murray and Peart explained. "Therefore, we determined that estrogen and progesterone receptors could be targets with high therapeutic potential for the treatment of cocaine use disorder. To investigate this further, we reviewed animal literature to identify the brain regions mediating endocrinological influences on cocaine use."

When reviewing past experiments on animals, Murray, Peart and their colleagues found that they confirmed the findings of studies on humans. Specifically, female rats also appeared to be more sensitive to cocaine-induced behaviors than male rats, but that this sex difference can be eliminated by blocking the effects of estrogen (but not progesterone) in the brain. On the other hand, the injection of estrogen in areas of the brain associated with motivation-related behaviors appeared to increase cocaine-induced behaviors in female rats.

"For example, cocaine-induced dopamine release in the nucleus accumbens and dorsal striatum (both are brain regions linked with

reward processing and motivation) underly its rewarding and reinforcing properties and this induction of dopamine release is increased by estrogen," Murray and Peart said. "Additionally, the activation of glutamate output from the medial prefrontal cortex (a brain region associated with goal-directed behavior) is involved in the resumption of cocaine use following abstinence, and glutamate neurons in this brain region are activated by estrogen."

Based on the findings they reviewed, the researchers concluded that estrogen might facilitate the transmission of dopamine and glutamate. This means that the higher vulnerability to cocaine use disorder observed in women could ultimately be linked to differences in hormone, specifically estrogen, production.

Murray, Peart and their colleagues also wanted to examine the potential of progesterone as a therapeutic agent to reduce cocaine cravings. In fact, past studies with humans have found that administering progesterone can reduce cocaine cravings and reward-seeking behaviors.

"Administering progesterone has also been shown to decrease cocaine seeking elicited by stress, cocaine cues, or cocaine itself in male and female rats using a model of relapse," Peart and Murray explained. "Indeed, administering progesterone or its metabolite allopregnanolone decreases dopamine release in the medial prefrontal cortex and nucleus accumbens. Therefore, we propose that it may be an option for treatment of cocaine use disorder in humans trying to maintain abstinence from cocaine use to prevent relapse."

Overall, the recent review paper by this team of researchers suggests that researchers and physicians should pay greater attention to the relationship between cocaine use disorder and estrogenic medications, such as some birth control pills, breast cancer treatments, and bone

health medications, among others. Currently, selective estrogen receptor modulators (i.e., drugs that can activate or block estrogen receptors in various tissues and thus alter estrogen in different parts of the body) are widely prescribed for a variety of clinical purposes. Examples of these drugs are tamoxifen, typically used to treat breast cancer, and raloxifene, used to prevent or treat bone loss (osteoporosis) after menopause.

Some studies have already found that selective estrogen receptor modulators can act on brain circuits underlying cocaine-induced behaviors in female rats. Peart, Murray and their colleagues hope that their review paper will encourage other research teams to assess these effects further and explore the utility of steroids as possible treatments for cocaine-use disorder.

"Specifically, future research may continue to identify brain regions mediating the effects of estrogen on cocaine sensitivity and evaluate the effects of selective estrogen receptor modulators in these regions in animal models of cocaine use disorder," Peart and Murray said. "These types of studies may aid in identifying selective estrogen receptor modulators with maximum therapeutic efficacy against cocaine use disorder and minimum side effects."

More information: Davin R. Peart et al, Regulation of cocaine-related behaviours by estrogen and progesterone, *Neuroscience & Biobehavioral Reviews* (2022). DOI: 10.1016/j.neubiorev.2022.104584