

# SEX DIFFERENCES IN MOTIVATION FOR COCAINE AS A FUNCTION OF STAGE OF ADDICTION

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Although patterns of addiction have been studied extensively in men, the mechanisms of the addiction process in women are still unclear. By analyzing differences in cocaine reinforcement in animals as a function of sex and addiction stage, the biological basis of addiction in men and women, as well as effective treatments, could be better understood. Because extended drug access coupled with an extended abstinence period appears to be critical for observing addiction-like behaviors, 5 female and 7 male rats were studied following either short access (ShA; ~2-hour sessions at 1.5 mg/kg dose) or extended access (ExA; 24-hour sessions at 1.5 mg/kg dose) to cocaine self-administration. Following a 14-day abstinence period, both males and females were reintroduced to cocaine, but this time under a progressive ratio (PR) schedule and at a lower dose (0.5 mg/kg). Under the PR schedule, the rat's response requirement to obtain a cocaine delivery increased progressively throughout the session. The breakpoint, or final ratio completed, is an indicator of the rat's motivation to obtain the drug. Results show that female rats responded at substantially greater levels than did males under the PR schedule. These observations indicate that females are more motivated to obtain cocaine, and they are consistent with clinical finding showing that women progress more rapidly to addiction than men. Because recent studies have suggested that interactions between dopamine and estrogen may result in an increased sensitivity to cocaine's reinforcing effects, future studies will examine the effects of site-specific dopamine receptor antagonism on cocaine self-administration in females with and without estrogen.

## INTRODUCTION

Although men are more likely to use and abuse illicit drugs,<sup>1</sup> women may in fact be more vulnerable than men in some aspects of addiction.<sup>2,3</sup> For example, women have been shown to acquire cocaine dependence at a faster rate than men, meaning they take less time to display addiction-like behaviors.<sup>4,5</sup> Women also self-administer cocaine for longer periods following abstinence.<sup>6</sup> In addition, women involved in clinical laboratory studies report higher craving levels, indicating an increased sensitivity to the drug's effects.<sup>7</sup>

These observations are supported by data collected from animal studies. In rats, acquisition of drug self-administration during the initiation stage is faster in drug-naïve females than males.<sup>8</sup> Under a schedule with short access (ShA) to the drug, females work harder to obtain drugs<sup>9</sup> suggesting that, like humans, female rats are more sensitive to drug's reinforcing effects. However, most preclinical studies have focused on the initiation stage; little is known about sex differences in later stages.

Studies have also demonstrated that increased contact with the drug, under an extended access (ExA) schedule, correlates to higher self-administration levels following abstinence.<sup>10,11</sup> Therefore, sex differences and overall intake should be considerably greater following ExA. The abstinence period has been shown to be critical for the development of addiction-like behaviors in rats as well. This experiment aims to determine if sex differences in vulnerability to addiction may be due to biological factors (ie, pharmacokinetic, hormonal, physiological, etc.), as opposed to sociocultural factors (ie, maternal re-

sponsibility, social stigma, drug availability, etc.) by analyzing cocaine motivation as a function of sex and addiction stage.

## METHODS/MATERIALS

After acclimating to the laboratory environment, rats underwent jugular surgery to implant a catheter into the circulatory system. At least 24 hours after the surgery, cocaine self-administration began using a fixed-ratio 1 schedule (FR20). Under this program, rats were allowed to obtain a maximum of 20 infusions a day at a 1.5 mg/kg dose. Each session was initiated with two priming doses of the drug. During sessions, the left levers within each operant chamber extended, allowing the rat to receive one infusion of cocaine for each response.

For the ShA rats, this program ran until the animal achieved 5 stable consecutive sessions (defined as obtaining all 20 infusions available). Daily sessions were around 2 hours in duration. For the ExA experiment, rats were required to achieve only 2 stable consecutive sessions on FR20 before gaining 24-hour access to cocaine through a discrete trial (DT-4) schedule (4 infusions/hour available every 15 minutes). After 10 days of 24-hour access, rats were reintroduced to FR20 for 2 days in order to equate males and females on intake. Beginning on day 1 of the FR20 program, female rats were vaginally swabbed to determine estrous cycle phase.

Following the 5<sup>th</sup> stable consecutive session for ShA and the 2<sup>nd</sup> FR20 session following DT-4 for ExA, rats began a 2-week abstinence period,

where they did not have access to cocaine. Beginning on day 12, females were vaginally swabbed for the last 3 days of the 2-week period.

Following completion of the abstinence period, both ShA and ExA rats were introduced to a progressive-ratio schedule (PR) of cocaine self-administration at a 0.5 mg/kg dose. Under PR, the rat's response requirement to obtain a cocaine delivery increased progressively throughout the session (ie, 1, 2, 4, 6, 9, 12, 15, 2, 25, 32, 40, 50, etc.). This lower dose of cocaine was selected because it is more sensitive to between subject differences than the higher cocaine dose. The first 3 stable sessions under PR were then recorded.

## RESULTS

We found that females in both ShA and ExA groups were consistently more motivated to obtain the drug and displayed higher breakpoints than males. Sex differences were more prevalent following ExA than following ShA. For example, males tested following ExA self-administration demonstrated 28.7% higher breakpoints than males tested following ShA self-administration. In contrast, females tested following ExA self-administration demonstrated 45.7% higher breakpoints than females tested following ShA self-administration.

## DISCUSSION

The data collected are consistent with the stated hypothesis and previous studies.<sup>6,8</sup> Observations indicate females' heightened sensitivity to cocaine's reinforcing effects, particularly following ExA self-administration. These results are also consistent with clinical data showing more rapid transition to addiction following initial use in women.<sup>4,5,12</sup> The importance of the access condition in developing addiction-like behaviors was also supported by these findings.<sup>10,11</sup>

These results could lead to a better understanding about the addiction process in women. By knowing more about the time it takes to meet the criteria for addiction as well as trends in motivation for the drug, sex-specific treatments could be developed. In females, interactions of dopamine and estrogen may be responsible for the increase sensitivity to drug's reinforcing effects observed in this experiment. Future studies will examine the effects of site-specific dopamine receptor antagonism on cocaine self-administration in females with and without estrogen.

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