

Gender Differences in Cocaine Self-Administration in Rats: Relevance to Human Drug-Taking Behavior

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INTRODUCTION

Recent data indicate that there is an interaction between psychostimulant drugs and gonadal hormones. Mello and colleagues (1994) have collected convincing evidence suggesting that psychomotor drugs can disrupt or alter ovarian and hypophysial hormonal function. The reverse of this also appears to be true; that is, these hormones can affect the physiological and behavioral response to cocaine (Glick et al. 1983; Van Haaren and Anderson 1994) as well as to other drugs of abuse such as amphetamine (Beatty and Holzer 1978; Brass and Glick 1981; Camp et al. 1986) and alcohol (Sutker et al. 1983). This chapter presents data suggesting that ovarian hormones also can influence the reinforcing effects of cocaine in laboratory animals as well as a discussion of whether these data have clinical relevance to drug addiction in women.

PHYSIOLOGICAL AND BEHAVIORAL INFLUENCE OF HORMONES

Although the precise mechanisms through which hormonal systems affect physiological responses remain unclear, there are several possibilities. One way that ovarian hormones could influence the response to psychomotor stimulants is through alterations in drug metabolism. Some degradative enzymes in the liver are steroid sensitive, and hormonal fluctuations across the estrous cycle may lead to alterations in the half-life of various drugs. Some evidence demonstrates that estrogen may even protect female rats against cocaine toxicity, possibly through alterations in drug metabolism (Morishima et al. 1993).

The peripheral effects of gonadal hormones are well recognized, and increasing evidence suggests that hormonal systems may influence the

behavioral response to psychomotor stimulants via central nervous system mechanisms as well (Camp et al. 1986; Morse et al. 1986; Wilson 1992; Diaz-Veliz et al. 1994). Cocaine and amphetamine act as indirect agonists at dopamine terminals by causing the release or inhibition of dopamine reuptake into the presynaptic terminal. The reinforcing action of psychostimulant drugs is a result of the augmentation of dopamine transmission in the nucleus accumbens and possibly other forebrain structures (Roberts 1992, pp. 73-90). These dopamine systems, which are essential to the reinforcing action of drugs, also are modulated by ovarian hormones. Receptors for both estrogen and progesterone are widespread throughout the central nervous system and appear to be particularly dense within the mesostriatal and mesolimbic dopamine pathways (see Maggi and Perez 1985 for a review). Estrogen reportedly potentiates amphetamine-induced dopamine release and reduces striatal dopamine concentrations; at the same time, it appears to initiate increases in dopamine turnover and receptor binding (see Maggi and Perez 1985 for a review). In summary, the biochemical response to amphetamine is altered by estrogen, and dopamine turnover varies across the estrous cycle. In addition, evidence indicates that the brain is one of the primary sites of hormonal interaction, and it is conceivable that ovarian hormones directly alter dopamine function, which, in turn, regulates hormonal cycles to influence observed behavioral responses.

Given that ovarian hormones exert a physiological influence on dopaminergic systems, it is not surprising that hormone levels can modulate the behavioral response to dopaminergic drugs (Beatty and Holzer 1978; Brass and Glick 1981; Glick et al. 1983; Camp et al. 1986; Van Haaren and Anderson 1994). Estrogen also has been reported to increase the stereotyped behaviors produced by the administration of dopamine agonists in rats. For example, Beatty and Holzer (1978) found that female rats demonstrated more intense and prolonged stereotypies in response to high doses (i.e., 5 mg/kg) and greater stimulant effects in response to low doses (1.5 mg/kg) of *d*-amphetamine than their male counterparts. Similarly, Camp and colleagues (1986) found that ovariectomies attenuated amphetamine-induced rotational behavior, although castration had no effect. From these and other observations, it was suggested that endogenous hormonal systems facilitate activity within the mesostriatal dopamine system.

Other evidence suggests that the differential sensitivities to both cocaine (Glick et al. 1983) and amphetamine (Brass and Glick 1981) may be related to gender-specific asymmetrical distributions in brain levels of dopamine and norepinephrine (Dark et al. 1984) and that such asymmetries may vary with the strain of animal employed (Brass and Glick 1981; Haney et al. 1994). Furthermore, apomorphine and amphetamine have significant effects on the performance of animals in learning situations, and these responses are modified by the estrous cycle and by estradiol (Diaz-Veliz et al. 1994).

EFFECTS OF GENDER AND STEROID LEVELS

Despite the considerable evidence for physiological and behavioral interactions of ovarian hormones with psychostimulant drugs, few studies have examined whether the reinforcing effects of psychostimulant drugs might be affected also by gender or by steroid levels. The authors and colleagues have addressed this question in several self-administration experiments (e.g., Bennett et al. 1988; Roberts et al. 1987, 1989). Animals were implanted with chronically indwelling intravenous cannulae. During initial training, the intravenous delivery of cocaine was made contingent on a single lever response (FR 1). After animals had demonstrated a stable pattern of cocaine self-administration, a progressive ratio (PR) schedule was imposed. Under this schedule, the first response of the daily session resulted in the delivery of a single drug infusion. Thereafter, the response requirements increased through an exponential function (i.e., 2, 4, 6, 9, 12, 15, 20, etc.) until self-administration behavior ceased. The final ratio achieved during the session was defined as the "breaking point," which provided an indication of the motivational state of the animal. This PR schedule has been used to examine how the motivation to self-administer cocaine is influenced by pharmacological treatments or neurotoxic lesions. The breaking point has been shown to be sensitive to alterations in unit injection dose of cocaine and to pretreatment with dopaminergic antagonists.

Female rats responded to much higher breaking points than male rats. More interesting, however, was that the motivation to self-administer cocaine fluctuated across the estrous cycle. Female rats responded to dramatically higher final ratios during the day of estrus compared with the days of metestrus, diestrus, and proestrus (Roberts

et al. 1989). Figure 1 shows examples of the cumulative records for a female rat during various stages of the estrous cycle. The results show that cocaine has a higher reinforcing efficacy during the day of estrus. These data have been replicated and extended by Grimm and See (1994), who reported that breaking points fluctuate across the estrous cycle and, furthermore, that injections of 17- β -estradiol increase the reinforcing efficacy of cocaine. Because the alterations in cocaine self-administration in the laboratory were not observed for the FR 1 schedule, the hormonal influence appears to be specific to the motivational state of the animal but has no influence on the response rate.

SUMMARY

The results of this study suggest that ovarian hormones influence the motivation of rats to self-administer cocaine. The obvious and important question is whether these data have any clinical implications for drug abuse in humans. The self-administration paradigm is an animal model for the study of drug reinforcement and has been used in several different applications—as a tool to investigate the specific brain regions and neurochemical mechanisms involved in the rewarding properties of drugs of abuse and as a model to evaluate the relative reinforcing value of novel compounds and offer predictions about the potential abuse liability in humans. However, like all models, the self-administration paradigm offers predictions rather than definitive answers. The value of any model must be evaluated ultimately by the accuracy of its predictions, for example, how well it predicts abuse liability or patterns of drug use.

Through use of the self-administration paradigm as a model of human drug-taking behavior, it was demonstrated that steroid function affected the reinforcing properties associated with cocaine use in rats. However, it also should be emphasized that the estrous cycle of the rat is very different from the menstrual cycle in women. Estrus is a behavioral term that denotes “sexual receptivity,” which is confined to a few hours during the 4-day rodent estrous cycle. Because there are vast differences between the species with respect to sexual motivation, one also might expect different hormonal interactions in the brain.

The main objective of the self-administration experiments was to identify possible estrogen-dopamine interactions in the rat brain as

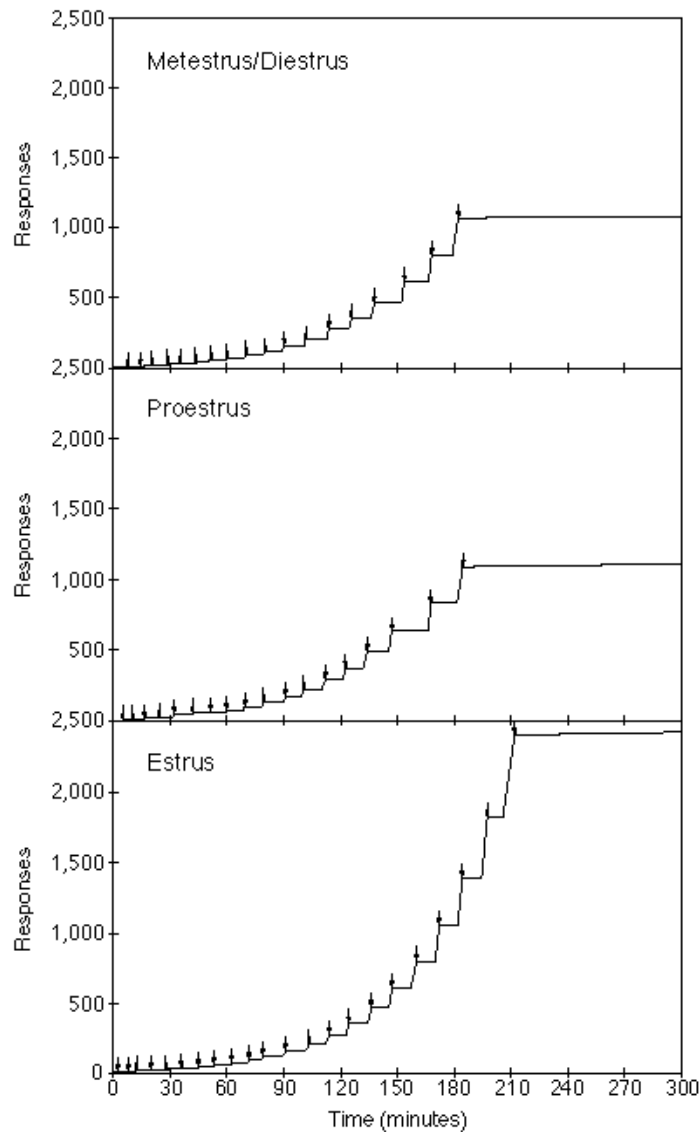


FIGURE 1. Cocaine self-administration during various stages of the estrous cycle in the rat. Each line represents a cumulative record of a female rat responding on a progressive ratio schedule. Vertical increments indicate lever responses. Arrows indicate the time of each cocaine injection. The first response during the daily 5-hour session was reinforced. The response requirements for each subsequent injection escalated exponentially (Roberts et al. 1989). Group data showed that female rats responded to significantly higher breaking points during estrus.

indicated by observed behavioral responses. Such effects might serve as a model for neuroscientists interested in brain-hormone interactions. In this respect, these experiments were highly relevant. They were not intended to “model” cocaine effects in women, although the experiments do offer an interesting prediction and suggest that gender and menstrual cycle changes could have an important influence on cocaine reinforcement. Preliminary clinical evidence indicates that male human subjects displayed significantly higher plasma cocaine levels than female volunteers who were given identical intranasal dosages of cocaine (Lukas et al. 1996). Furthermore, differences in plasma levels also were seen between women in the follicular phase and women in the luteal phase of the menstrual cycle. Physiological and psychological measures of the cocaine response paralleled these plasma differences (Lukas et al. 1996). Clearly, gender and hormonal influences must be explored as factors in human drug abuse.

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ACKNOWLEDGMENT

This chapter was prepared with support from National Institute on Drug Abuse contract no. N01DA-3-7302.

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