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Research Report

The extra-adrenal effects of metyrapone and oxazepam on ongoing cocaine self-administration

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ABSTRACT

Investigation of the role of stress in cocaine addiction has yielded an efficacious combination of metyrapone and oxazepam, hypothesized to decrease relapse to cocaine use by reducing stress-induced craving. However, recent data suggest an extra-adrenal role for metyrapone in mediating stress- and addiction-related behaviors. The interactions between the physiological stress response and cocaine self-administration were characterized in rodents utilizing surgical adrenalectomy and pharmacological treatment. Male Wistar rats were trained to self-administer cocaine (0.25 mg/kg/infusion) and food pellets under a concurrent alternating fixed-ratio schedule of reinforcement. Surgical removal of the adrenal glands resulted in a significant decrease in plasma corticosterone and a consequent increase in ACTH, as expected. However, adrenalectomy did not significantly affect ongoing cocaine self-administration. Pretreatment with metyrapone, oxazepam and their combinations in intact rats resulted in a significant decrease in cocaine-reinforced responses. These same pharmacological treatments were still effective in reducing cocaine- and food-reinforced responding in adrenalectomized rats. The results of these experiments demonstrate that adrenally-derived steroids are not necessary to maintain cocaine-reinforced responding in cocaine-experienced rats. These results also demonstrate that metyrapone may produce effects outside of the adrenal gland, presumably in the central nervous system, to affect cocaine-related behaviors.

1. Introduction

The relationship between stress, drug craving and relapse is not a novel concept; this phenomenon has been known to the lay public for many years (Goeders, 2010). Scientists and clinicians have also recognized the association between drug addiction, stress and the subsequent activation of the hypothalamic-pituitary-adrenal (HPA) axis (Adinoff, 2004; Brady and Sinha, 2005; Brady and Sonne, 1999; Koob, 2010; Koob and Zorrilla, 2010; Kreek et al., 2005). In general, addictive drugs tend to alter HPA axis activity (Lovallo, 2006). For example. cocaine and other psychomotor stimulants increase HPA axis activity (Goeders, 2002, 2004), as does cigarette smoking (Mendelson et al., 2005; Steptoe and

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Ussher, 2006) and alcohol intoxication and withdrawal (Adinoff et al., 1998, 2003).

For many years, our laboratory has investigated the interactions between cocaine reinforcement and stress, with special emphasis on the HPA axis. Our early hypothesis was that an intact HPA axis was crucial for cocaine reinforcement since higher levels of corticosterone were correlated with lower thresholds for the acquisition of cocaine self-administration (Goeders and Guerin, 1994, 1996b) and since adrenalectomy prevented the acquisition of cocaine self-administration in naïve rats (Goeders and Guerin, 1996a). This effect was partially reversed with the addition of corticosterone to the rats' drinking water. In other experiments, we investigated a variety of drugs that alter HPA axis activity via different mechanisms with the intent of identifying compounds that would decrease cocaine self-administration in rats. One class of drugs, the glucocorticoid synthesis inhibitors (e.g., metyrapone and ketoconazole) block the rate-limiting step of 11β-hydroxylation (Colby et al., 1973; Engelhardt et al., 1985; Engelhardt and Weber, 1994; Haleem et al., 1988; Sonino, 1987; Thienpont et al., 1979) to reduce plasma levels of the major HPA axis steroids (i.e., corticosterone in rodents, cortisol in humans). However, the ability of these drugs to attenuate intravenous cocaine self-administration in rats does not always correlate with reductions in plasma corticosterone (Goeders et al., 1998; Goeders and Guerin, 2008). Other drugs we have tested, including the corticotropin-releasing factor (CRF) receptor antagonist CP 154,526 (Goeders and Guerin, 2000) and the benzodiazepines oxazepam (Goeders and Guerin, 2008), alprazolam (Goeders et al., 1993), and chlordiazepoxide (Goeders et al., 1989) also decreased cocaine self-administration without producing a systematic effect on plasma corticosterone. Most recently we tested the efficacy of a combination of metyrapone and oxazepam at doses that had no effect on cocaine self-administration by themselves, but did so when administered together (Goeders and Guerin, 2008). Although these combinations were effective at reducing cocaine self-administration, there were no significant differences in plasma corticosterone, suggesting that the maintenance of cocaine self-administration may not be dependent on circulating glucocorticoids. Surprisingly, these results indicate that a combination of low doses of metyrapone and oxazepam (MET/OX) may result in a different mechanism of action than either drug on its own. This was confirmed in a double-blind placebo-controlled clinical trial, demonstrating that MET/OX can reduce cocaine use and craving in cocaine-dependent adults. Importantly, this trial also showed minimal treatment-related clinically significant side effects, suggesting that MET/OX does not induce adrenal insufficiency or benzodiazepine-related sedation and is clinically well-tolerated for human administration (Kablinger et al., 2012).

These unique properties of combining low doses of MET and OX suggest a common mechanism of action between the two drugs, independent of the HPA axis and plasma glucocorticoids. Research from other laboratories has demonstrated a role for metyrapone in enhancing GABA-related behaviors such as the anxiolytic and antidepressant effects of ethanol (Hirani et al., 2005, 2002). These GABAergic properties derive from the ability of metyrapone to enhance the production of neuroactive steroids (e.g., THDOC and allopregnanolone) which act as positive allosteric modulators of $GABA_A$ receptors (Belelli and Lambert, 2005; Rupprecht et al., 1998). Oxazepam also functions as a $GABA_A$ receptor positive allosteric modulator and is the final metabolite of several other benzodiazepine derivatives (Greenblatt, 1981; Greenblatt et al., 1975).

The experiments described in this manuscript were designed to answer two questions regarding the role for the HPA axis in cocaine reinforcement. The first was whether or not an intact HPA axis is actually necessary for ongoing cocaine self-administration to continue. This was accomplished by training rats to self-administer cocaine. Once self-administration stabilized, the rats were adrenalectomized and then retested for cocaine self-administration. The second question was whether or not the HPA axis (i.e., adrenally-derived corticosterone) is involved in the ability of metyrapone (MET) and oxazepam (OX), and the combination of metyrapone and oxazepam (MET/OX), to reduce cocaine self-administration by testing the effects of these drugs before and after adrenalectomy. Overall, the results of these experiments demonstrate that the mechanism(s) through which these drugs decrease cocaine taking is located outside of the adrenal gland.

2. Results

In the first experiment, adrenalectomy reduced plasma corticosterone from approximately 250 ng/ml to less than 10 ng/ml (Table 1), indicating that the surgery was successful. Surprisingly, rats continued to self-administer cocaine following adrenalectomy (Fig. 1). Initially, the levels of self-administration between adrenalectomized and sham-treated animals were indistinguishable (30±5 infusions/session, sham-treated; 27±3 infusions/session, adrenalectomized), but were slightly lower than pre-surgery baselines for both groups of animals (36±7 infusions/session, sham-treated (SHAM); 36±4 infusions/session, adrenalectomized (ADX)). Following an additional three weeks of self-administration, the SHAM animals had increased their levels of self-administration to a mean of 43±6 infusions/session, while cocaine intake remained relatively stable for the ADX rats (28±2 infusions/session). A similar effect was observed with food self-administration. There were no differences between the groups immediately following the one-week recovery from surgery (91±7 foods/session, SHAM; 89±4 foods/session, ADX). Following an additional three weeks of self-administration, the number of food presentations received

Table 1 – Surgical adrenalectomy (ADX) significantly reduced plasma corticosterone (Experiment 1).

Effects of ADX on plasma corticosterone (ng/ml)

	PRE-1 day	POST-1 week	POST-1 month
SHAM	238.50±99.17	270.80±45.87	285.80±32.99
ADX	249.80±34.83	5.40±2.99*	8.60±4.62*

* $p<0.05$ Compared to sham-operated (SHAM) rats.