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Opioid and cocaine combined effect on cocaine-induced changes in HPA and HPG axes hormones in men

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ABSTRACT

Nalbuphine, a mixed mu-/kappa-opioid analgesic, may have potential as a new medication for the treatment of cocaine abuse. Kappa-opioid agonists functionally antagonize some abuse-related and locomotor effects of cocaine, and both kappa-selective and mixed mu-/kappa-opioids reduce cocaine self-administration by rhesus monkeys. Because cocaine's interactions with the hypothalamic-pituitary-adrenal and (HPA) hypothalamic-pituitary-gonadal (HPG) axes may contribute to its reinforcing properties, we examined the effects of cocaine alone and in combination with nalbuphine. Neuroendocrine effects of a single dose of cocaine alone (0.2 mg/kg, IV), with nalbuphine (5 mg/70 kg, IV)+cocaine (0.2 mg/kg, IV) in combination were compared in seven adult men (ages 18–35) who met DSM-IV criteria for current cocaine abuse. Cocaine alone, and in combination with nalbuphine was administered on separate test days under placebo-controlled, double blind conditions. Cocaine stimulated ACTH, cortisol, and LH, whereas cocaine+nalbuphine in combination produced a smaller increase in ACTH, and decreased cortisol and LH. Thus it appears that nalbuphine attenuated cocaine's effects on ACTH, cortisol, and LH. These data are consistent with our earlier report that nalbuphine modestly attenuated cocaine's positive subjective effects, and that the subjective and cardiovascular effects of cocaine+nalbuphine in combination were not additive.

1. Background

Cocaine abuse continues to be a major public health problem, and the adverse medical consequences of cocaine abuse and dependence on cardiovascular, cerebrovascular, pulmonary, and immune function contribute to the social and economic costs (Mendelson and Mello, 2008; SAMHSA, 2006). As yet, no effective pharmacotherapies have been developed, but advances in understanding the neurobiological bases of cocaine abuse have led to identification of some novel pharmacological approaches to treatment. There is emerging evidence from preclinical studies that the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes may be important for cocaine's abuse-related effects (Goeders, 1997, 2002a,b). The intriguing possibility that rapid changes in anterior pituitary,adrenal and gonadal hormonal levels may be related to cocaine's reinforcing effects is suggested by clinical and preclinical studies (see (Goeders, 1997, 2002a,b; Mello and Mendelson, 2002) for review). For example, the IV cocaine-induced increase in adrenocorticotropin hormone (ACTH) parallels increases in plasma cocaine levels and reports of positive subjective effects (Mendelson et al., 2002; Sholar et al., 1998).

ACTH stimulation after cocaine administration has been consistently observed in both humans and animals (see (Mello and Mendelson, 2002) for review). Several lines of evidence suggest that cocaine's effects on ACTH may reflect stimulation of endogenous hypothalamic corticotropin-releasing factor (CRF). The amplitude of ACTH pulsatile release is controlled by CRF, and the frequency of ACTH pulses appears to reflect an intrinsic secretory rhythm of the anterior pituitary corticotrophs (Carnes et al., 1990; Gambacciani et al., 1987; Mershon et al., 1992). In preclinical studies, adrenalectomized rats did not learn to self-administer cocaine, and pharmacological blockade of corticosterone synthesis by metyrapone significantly decreased cocaine self-administration (Goeders and Guerin, 1996). Moreover, corticosterone administration facilitated cocaine self-administration (Mantsch et al., 1998), and corticosterone levels after cocaine self-administration sessions were cocaine dose-dependent (Goeders and Guerin, 1996; Mantsch et al., 2000). Importantly, administration of a CRF-1 antagonist decreased IV cocaine self-administration by rats with minimal effects on food-maintained responding (Goeders and Guerin, 2000).

Similarly, cocaine consistently stimulates LH release in male and female subjects in numerous preclinical and clinical studies. For example, significant IV cocaine-induced dose-dependent increases in LH levels were observed in male rhesus monkeys (Mello et al., 2004, 1993b), early follicular phase female rhesus monkeys (Mello et al., 1989, 1990a,b, 1993b), and cocaine abusers (Mendelson et al., 2003, 2001). Transient elevations in LH levels were observed in luteal phase

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rhesus monkeys and maximal effects occurred after repetitive cocaine administration (Evans and Foltin, 2006). Incremental changes in LH levels were documented under exogenous progesterone administration in ovariectomized rhesus monkeys (Mello et al., 2004). When women were studied in both follicular and luteal phases of the menstrual cycle, only a high cocaine dose significantly augmented LH levels compared to baseline (Mendelson et al., 2001).

No changes in testosterone levels have been detected in clinical studies after acute IV (Mendelson et al., 1989, 2003), intranasal (Heesch et al., 1996), or chronic cocaine administration (Mendelson et al., 1988). However, persistent cocaine use was shown to negatively affect sexual functioning in cocaine abusers and cocaine-dependent individuals (Saso, 2002). In preclinical studies, the effects of cocaine on testosterone have been inconsistent. For example, in rhesus monkeys, a 50% increase in testosterone levels from the average baseline was observed after high dose IV cocaine administration (Mello et al., 1993b). In another study, however, the same dose of IV cocaine did not produce any significant changes in testosterone (Mello et al., 2004). Similarly, no alterations in serum testosterone levels were observed after a higher dose of i.p. cocaine administered acutely to male rats (Walker et al., 2001). Acute high doses of i.p. cocaine were shown to significantly increase serum testosterone levels with subsequent significant serum testosterone decrement persisting for 2 h (Berul and Harclerode, 1989). However, in another study, the same dose of cocaine was shown to decrease testosterone levels in a single administration (Festa et al., 2003). "Binge-like" patterns of cocaine administration decreased testosterone levels in male rats (Festa et al., 2003). Repetitive low dose, but not high dose, cocaine injections have also been reported to elevate serum testosterone levels in male rats (Rodriguez et al., 1992). However, testosterone levels declined after chronic administration of high dose cocaine, and lighter weight seminal vesicles and epididymis were documented in this group (Berul and Harclerode, 1989). In another study, higher cocaine doses administered IP in a "binge-like" pattern over a period of several weeks also reduced plasma testosterone levels in rats (Sarnyai et al., 1998). Significant damage to male gonads, including marked reduction in testicular weight and seminiferous tubule size/diameter, were observed beginning after two weeks of daily high dose IP cocaine administration (Barroso-Moguel et al., 1994; Yang et al., 2006). In cocaine-dependent population, a " greater number of abnormal sperm, lower sperm counts and instances of lower motility" were reported (Bracken et al., 1990; George et al., 1996).

As discussed above, cocaine-induced hypogonadism in cocaine abusers and dependent individuals may produce a significant impairment in their daily lives. Therefore, restoring normal gonadal functioning should be considered as one of the critical therapeutic objectives while treating cocaine abuse/dependence. It is especially important since gonadal steroids are known not only to regulate reproductive function but also to exert a crucial influence on plasticity and overall activity of CNS (Quiñones-Jenab, 2006). The existing evidence in the literature suggests that cocaine interacts with sex hormones on three major levels: via affecting steroids' secretion, metabolism and clearance rates (Quiñones-Jenab, 2006), via alteration of "rapid non-genomic mechanisms", including "modulation of extracellular monoamines and opioids" (Quiñones-Jenab, 2006; Chen et al., 2003) and via slower genomic mechanisms, such as synthesis of new proteins (early genes for e.g. c-*fos*, dynorphin and/or late genes for e.g. opioid and monoamine receptors (Quiñones-Jenab, 2006). As a result, cocaine may significantly alter "biological and long-term adaptive changes in neuronal function" and overall brain plasticity as it was demonstrated in a number of preclinical studies (Quiñones-Jenab, 2006; Chen et al., 2003; Chin et al., 2002; Quiñones-Jenab et al., 2000a,b,c).

Major neurotransmitter systems are involved in pathogenesis of cocaine abuse, such as dopaminergic, noradrenergic and serotonergic (Johanson and Fischman, 1989; Dackis and Gold, 1988; Gawin, 1988; Kleber and Gawin, 1984; Woolverton and Johnson, 1992; Spealman et al., 1992; Bergman et al., 1990; Millman, 1988). Interestingly, HPA and HPG axes hormones are documented to share the same modulatory monoaminergic mechanisms as most stimulants, including cocaine (Weiner et al., 1988; Barraclough et al., 1984; Taleisnik and Sawyer, 1986). These systems also play a vital role in modulating HPA and HPG axes under stressful conditions. For example, activation of the hypothalamic alpha-1 and beta-receptors was reported to be stimulatory to CRF release, while stimulation of alpha-2 receptors was shown to inhibit CRF levels (Plotsky et al., 1989). Moreover, tyrosine-hydroxylase-positive terminals were demonstrated to innervate both GnRH perikarya and dendrites in the medial preoptic area of the hypothalamus. (Chen et al., 1989). Additionally, stimulation or inhibition of LH release was observed within catecholamine-GnRH axis (Rivier and Rivest, 1991). Specifically, stimulation of alpha-1 receptors was reported to be responsible for a preovulatory LH surge (Condon et al., 1989), while activation of the noradrenergic system resulted in either increase or decrease of LH release depending on presence or absence of steroids, respectively (Taleisnik and Sawyer, 1986). Therefore, potentially "CRF could activate the noradrenergic system during stress", in turn acting "directly on GnRH neurons" (Rivier and Rivest, 1991). Specifically, the locus coeruleus was reported to be a site of direct stimulation of cathecholaminergic neurons by CRF (Rivier and Rivest, 1991; Butler et al., 1990). Additionally, biphasic feedback of HPG axis in response to stressful stimuli was documented as being stimulatory under acute circumstances and inhibitory under chronic/sufficient magnitude stress (Grey et al., 1978; Rivier and Rivest, 1991). Finally, evidence exists that the above-mentioned anti-reproductive effects of EOPs are mediated via monoaminergic-dependent pathways (Leadem et al., 1985, Gopalan et al., 1989; Johnson et al., 1986). For example, it was documented that systemic injections of mu-agonists such as morphine stimulated dopaminergic and serotonergic systems in hypothalamus, while inhibiting hypothalamic "norepinephrine concentrations and plasma LH levels" (Gopalan et al., 1989; Rivier and Rivest, 1991). In contrast, selective kappa-agonists such as tifluadom were shown to decrease LH levels but increase "norepinephrine and 5-HT turnover" in the hypothalamus (Gopalan et al., 1989; Rivier and Rivest, 1991). Furthermore, serotonergic influence on the hypothalamus from the dorsal raphe nucleus was documented to directly modulate 5-HT receptors on GnRH neurons, possibly exerting an inhibitory influence on GnRH secretion under acute stress (Assenmacher et al., 1987; Rivier and Rivest, 1991).

The role of the HPA and HPG axes in the effects of medications on cocaine's reinforcing effects is poorly understood. One approach to the medication-based treatment of cocaine abuse has been to study compounds that can modulate dopaminergic activity indirectly by acting on other receptor systems, for example opioid analgesics. Kappa-opioid agonists are one novel candidate medication for cocaine abuse treatment. Opioid analgesics are classified as full agonists, partial agonists, or mixed agonist–antagonists, depending on the specific receptors to which they bind and their intrinsic activity at that receptor. Full agonists do not have a ceiling to their analgesic efficacy and will not reverse or antagonize the effects of other opioids within this class given simultaneously. Partial agonists have relatively low intrinsic efficacy at the opioid receptor in comparison to full opioid agonists and display a ceiling effect to analgesia. Mixed agonist–antagonists have an analgesic ceiling and block opioid analgesia at one type of opioid receptor or are neutral at this receptor while simultaneously activating a different opioid receptor.

Furthermore, as Archer et al. (1996) reported, "since both mu-antagonists and kappa-agonists prevent dopamine release in nucleus accumbens, these properties should be additive if present in one compound". For example, mixed mu-antagonist/kappa-agonists such as L-cyclorphan and cyclazocine were suggested to be useful for