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Naloxone-induced cortisol predicts mu opioid receptor binding potential in specific brain regions of healthy subjects

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Summary Investigators have administered the opioid receptor antagonist, naloxone, to interrogate the hypothalamic-pituitary-adrenal (HPA) axis response under the assumption that this technique provides a measure of endogenous opioid activity. However it has never been tested whether provocation of the HPA axis with naloxone provides a surrogate marker for direct measurement of endogenous opioid activity using PET imaging as the gold standard. To test this hypothesis, eighteen healthy subjects underwent a PET scan with the mu-opioid receptor (MOR) selective ligand [^{11}C]carfentanil (CFN). The following day ACTH and cortisol responses were assessed using a technique which allows administration of 5 incremental doses of naloxone (0, 25, 50, 100 and 250 μg/kg) in a single session. Relationships between ACTH and cortisol responses and [^{11}C]CFN binding potential (BP_{ND}) were examined in 5 brain regions involved in the regulation of the HPA axis and/or regions with high concentrations of MOR. All subjects mounted graded ACTH and cortisol responses to naloxone administrations. There were significant negative relationships between cortisol response to naloxone and [^{11}C]CFN BP_{ND} in ventral striatum, putamen and caudate. When sex and smoking were added as covariates to the model, these correlations were strengthened and there was a significant correlation with the hypothalamus. There were no significant correlations between ACTH and any volumes of interest. The opioid receptor antagonist naloxone is not merely a non-specific pharmacologic activator of the HPA axis; it provides information about individual differences in opioid receptor availability.

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Introduction

Endogenous opioid systems regulate myriad nociceptive and other homeostatic processes. Genetic and environmental factors modulate endogenous opioid systems, and may result in physical and behavioral symptoms as well as chronic neuropsychiatric disorders. For example, mu opioid receptor (MOR) expression is altered in several classes of disorders including substance use disorders, chronic pain and eating disorders (Bencherif et al., 2002, 2004; Heinz et al., 2005; Gorelick et al., 2008; Williams et al., 2009).

In the pursuit of understanding the pathophysiologic role of opioid systems in these and other neuropsychiatric illnesses, investigators have administered the opioid receptor antagonist, naloxone, to interrogate the HPA axis. The assumption has been that this challenge provides a measure of endogenous opioid activity (Russell et al., 2008; Adinoff et al., 2005; Wand et al., 1998; Alexander and Irvine, 1995; Torpy et al., 1993). Naloxone administration triggers HPA activity by blocking opioid inhibitory tone directed at hypothalamic regulators of ACTH secretion; ACTH, in turn, stimulates cortisol release. Using naloxone in this manner, studies have *presumed* to identify differences in opioid activity as a function of alcoholism, family history of alcoholism, gender, neuroticism and genetic variations in the mu opioid receptor (Adinoff et al., 2005; Wand et al., 1998, 1999, 2001, 2002; Mangold and Wand, 2006; Mangold et al., 2000; Oswald et al., 2004; Uhart et al., 2006).

The goal of this study was to examine whether naloxone is merely a non-specific pharmacologic activator of the HPA axis, providing information about ACTH and cortisol secretory capacity, or whether individual differences in hormone responses to naloxone are influenced by individual variations in opioid receptor availability. We suspected the latter explanation because we have previously shown that, within an individual, cortisol response to the biological provocator naloxone do not correlate with cortisol response to a psychological provocator, the Trier Psychosocial Stress Test (TSST) (Oswald and Wand, 2004). Additionally, we have shown that while men have a greater cortisol response to the TSST than women (Oswald and Wand, 2004), women have a greater cortisol response to naloxone administration than men (Uhart et al., 2006). Both observations suggest that naloxone activates the HPA axis through mechanisms independent from those activated by mental stress. Thus, the challenge procedure using naloxone may provide more specific information about the status of opioidergic systems than previously realized.

The assumption that studying ACTH and/or cortisol responses to a naloxone challenge provides a surrogate marker for direct measurement of endogenous opioid activity has never been empirically tested. Therefore, we conducted a study to examine the relationship between PET-derived measurements of mu opioid receptor availability and naloxone-induced ACTH and cortisol secretion in healthy subjects. We hypothesized that hormone responses to opioid receptor blockade by naloxone would be correlated with mu opioid receptor availability measured by PET using [^{11}C]carfentanil (CFN).

Methods

Subjects

Healthy male and female subjects (n = 18) between 25 and 58 years of age were recruited via advertisement and provided informed consent using an Institutional Review Board approved informed consent document. Subjects underwent a history and physical examination by a physician or nurse practitioner; screening labs were obtained including a pregnancy test in females. Subjects were interviewed by a Masters-level research assistant who utilized the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA-II) to rule out major DSM IV Axis 1 psychiatric disorders (Bucholz et al., 1994). Assessment results were reviewed and study eligibility determined by author MEM. Subjects were drinking within the NIAAA recommended guidelines (less than 8 drinks/wk for women and 15 drinks/week for men). Individuals were excluded from study participation based any of the following criteria: (1) if they met current or lifetime DSM-IV diagnostic criteria for any major Axis I disorder including alcohol, nicotine and other drug abuse/dependence, (2) if urine drug toxicology was positive at screening or on session days, (3) if they had other ongoing health problems or were taking prescription medication, (4) if screening CBC or liver studies were abnormal, (5) if pregnancy test was positive or if subjects were taking hormonal birth control. Two of the 18 subjects were occasional smokers, and were not nicotine dependent based on the SSAGA and The Fagerstrom Nicotine Dependence Test (Heatherton et al., 1991).

General procedures

Subjects were admitted to the Clinical Research Unit (CRU) the day before the PET scan for a 3-day inpatient stay. Participants were screened for recent alcohol and drug use and pregnancy status at the time of admission and were closely supervised throughout the inpatient stay. No smoking was permitted for the duration of the study. Prior to the CRU admission, subjects underwent magnetic resonance imaging (MRI) to allow anatomical localization and alignment of PET imaging planes within subjects (Meltzer et al., 1990).

PET procedures

On the morning of the PET scan, subjects were provided a calorie-controlled breakfast. A thermoplastic mask was individually fitted to each subject's face for immobilization and positioning during imaging. Subjects underwent a PET scan with the mu-opioid selective ligand [^{11}C]carfentanil (CFN) (Lever et al., 1992; Madar et al., 1996).

PET scans were acquired in 3D mode on a GE Advance PET scanner (GE Medical Systems, Milwaukee, WI). Before injection of the radiotracer a transmission scan of 10-min duration was obtained using rotating germanium-68 rods. After intravenous bolus administration of the radiotracer [^{11}C]CFN (19.9 $\pm$ 1.2 mCi SA: 17,298 $\pm$ 13,907 mCi/μmole), 25 images with variable time intervals (6 $\times$ 30 s, 5 $\times$ 60 s, 5 $\times$ 120 s, 9 $\times$ 480 s) were acquired during a 90-min period for each subject. The dose of carfentanil injected was less than