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Neuroendocrine effects of naltrexone versus nalmefene in humans

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Abstract

Objective: Naltrexone and nalmefene are approved for the treatment of alcohol use disorders, in different countries. Naltrexone is also approved for the treatment for opioid use disorders, most recently in a depot formulation. These compounds target primarily μ(mu)- and κ(kappa)-opioid receptor systems, which are involved in the downstream neurobiological effects of alcohol and in the modulation of neuroendocrine Stress systems. The objective was to compare the neuroendocrine effects of naltrexone and nalmefene on adrenocorticotropic hormone (ACTH), cortisol, and prolactin, in normal volunteers.

Method: Adult normal volunteers (n = 11 male and n = 9 female) were studied in a stress-minimized inpatient setting on three consecutive days, after intravenous saline, naltrexone HCl (10 mg), or nalmefene HCl (10 mg), in fixed order. ACTH, cortisol, and prolactin were analyzed pre-injection and up to 180 min post-injection.

Results: Naltrexone and nalmefene caused elevations in ACTH and cortisol compared with saline. Nalmefene had a greater effect on ACTH and cortisol, compared with naltrexone. Both compounds also caused elevations in prolactin in males (females were not examined, due to the influence of menstrual cycle on prolactin).

Conclusions: This study suggests that both nalmefene and naltrexone have effects potentially due to κ-partial agonism in humans, as well as antagonist effects at μ-receptors.

Keywords

ACTH; cortisol; nalmefene; naltrexone; neuroendocrine; prolactin

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STATEMENT OF ETHICS

Subjects have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

INTRODUCTION

Naltrexone and nalmefene are pharmacotherapies approved for the treatment of alcohol use disorders (AUD), in different countries (Castera et al., 2018; Mann, Bladstrom, Torup, Gual, & van den Brink, 2013; Soyka, Friede, & Schnitker, 2016). Naltrexone is also approved for the treatment of opioid use disorders, most recently as an intramuscular depot formulation (Lee et al., 2017; Woody & Metzger, 2011). Very recent studies have also examined whether novel formulations of naltrexone or nalmefene could be useful as potent and long-lasting medications against overdose caused by μ-agonists such as fentanyl (Krieter, Chiang, Gyaw, Skolnick, & Snyder, 2019; Krieter, Gyaw, Crystal, & Skolnick, 2019). Studies have detected changes in μ-receptor systems in the brain of humans with AUD (Hermann et al., 2017; Nestor et al., 2018). Exposure to either alcohol or other drugs of abuse can also result in upregulation in transcription of the gene coding for κ-receptors (OPRK1), and for the endogenous κ-agonist neuropeptides, the dynorphins (prodynorphin gene; Daunais, Roberts, & McGinty, 1993; Fagergren et al., 2003; Karkhanis, Holleran, & Jones, 2017; Mash & Staley, 1999; Spangler, Unterwald, & Kreek, 1993; Wee & Koob, 2010).

Naltrexone and nalmefene are potent μ-antagonists, in vitro and in vivo (Bart et al., 2005; Kaplan & Marx, 1993; Ko, Butelman, Traynor, & Woods, 1998; Wang, Sun, & Sadee, 2007; Wentland et al., 2009). Naltrexone and nalmefene also have considerable affinity at κ-receptors, where they can exert partial agonist effects in vitro (e.g., in GTPgammaS assays; Bart et al., 2005; Glass, Jhaveri, & Smith, 1994; Gual, He, Torup, van den Brink, & Mann, 2013; Remmers et al., 1999; Wentland et al., 2009). Studies in cloned human receptors indicate that the affinity of naltrexone is greater at μ- versus κ-receptors, although this finding is not as robust for nalmefene (Bart et al., 2005; Bidlack, 2014; Ghirmai, Azar, Polgar, Berzetei-Gurske, & Cashman, 2008; Wang et al., 2007). By comparison, both naltrexone and nalmefene have lower affinity at δ(delta)-opioid receptors (Bart et al., 2005; Wang et al., 2007; Wentland et al., 2009). Neuroendocrine effects are useful biomarkers for the investigation of pharmacotherapies which target opioid receptor systems. Hypothalamic–pituitary–adrenal (HPA) stress axis hormones (e.g., adrenocorticotropic hormone [ACTH] and cortisol in humans) are modulated by both μ and κ systems. Thus, μ-antagonists cause ACTH and cortisol release (Schluger et al., 1998). Selective κ-agonists also cause increases in HPA axis hormones (Maqueda et al., 2016; Pascoe et al., 2008). HPA axis hormones are associated with neurobehavioral aspects of both AUD and opioid use disorders (Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006; Stephens & Wand, 2012). A prior study also shows that oral naltrexone administration results in an increase of ACTH and cortisol levels in humans with alcohol dependence (O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002). Furthermore, these cortisol levels were negatively correlated with alcohol craving (O'Malley et al., 2002). A very recent positron emission tomography neuroimaging study also showed that naltrexone-induced reduction in alcohol intake in heavy drinkers was negatively correlated with baseline κ-receptor availability in the striatum (de Laat et al., 2019). κ-agonists also cause dose-dependent increases in serum prolactin levels in vivo in humans and animals, and the potency and maximal effects of κ-receptor ligands on this neuroendocrine biomarker correlate with those observed in other assays (Butelman, Harris, & Kreek, 1999; Chang et al., 2011; Kreek, Schluger, Borg, Gunduz, & Ho, 1999).

For example, partial κ-agonists cause smaller maximal prolactin release than high efficacy κ-agonists (Butelman et al., 1999). μ-agonists also cause dose-dependent increases in serum prolactin in humans (Hoehe, Duka, Doenicke, & Matussek, 1984; Kreek, 1978). However, comparative data on the effects of naltrexone and nalmefene in humans are extremely limited (Soyka et al., 2016). To our knowledge, there has been only one study that directly compared an effect of nalmefene and naltrexone in humans (Drobes, Anton, Thomas, & Voronin, 2004; Soyka et al., 2016). This is the first study to compare neuroendocrine effects of naltrexone and nalmefene in humans, using an intravenous (IV) route of administration. This route of administration should minimize difficulties in interpretation caused by differential oral pharmacokinetic and bioavailability profiles of these medications.

METHODS

Volunteers

This protocol, informed consent forms, and advertisements for the study were approved by the local Institutional Review Board, and in accordance with the Declaration of Helsinki. Male and female volunteers were recruited from the New York City area through Institutional Review Board-approved newspaper advertisements and flyers. The group studied herein was composed of n = 20 adult volunteers (n = 9 female), without any lifetime diagnosis of any substance use disorder, by DSM-IV criteria. Volunteers were examined in the hospital clinic on at least two occasions before participating in this inpatient study. Volunteers received medical and psychiatric evaluations by a clinician and included clinical interviews, a physical exam, and electrocardiogram. Laboratory testing included a complete blood count, blood chemistries, hepatitis serology, liver function, thyroid function testing, and an HIV antibody test. HIV-positive persons were excluded from this study, because HIV infection is known to alter endocrine function. Urine for toxicology from each clinic visit, as well as 24-hr urine samples while inpatient, were used to examine for illicit substances. Nicotine replacement therapy (e.g., nicotine patch) was offered to the volunteers while in study, because smoking was not allowed in the unit. A breathalyzer test was carried out on the night of admission, to confirm no recent ingestion of alcohol.

Diagnostic criteria

Volunteers were initially categorized with the structured clinical interview for DSM-IV criteria (SCID-I), by a clinician (e.g., nurse practitioner). Alcohol and tobacco use were also characterized with Kreek–McHugh–Schluger–Kellogg scales (measuring maximum lifetime exposure to drugs), a dimensional measure of maximal self-exposure to specific substances (Butelman et al., 2018; Kellogg et al., 2003; Tang et al., 2011).

PROCEDURES

Volunteers were admitted to a smoke-free private room, the night prior to the first study day. All study procedures took place in the volunteer's room, and no passes were allowed. On each of the three following mornings, an indwelling 20 Gauge IV catheter (BD Angiocath, Becton-Dickinson, NJ) was inserted at least an hour prior to testing. The catheter was used for injection of saline, naltrexone, or nalmefene solutions and for blood sampling. The

volunteers were studied under three conditions on consecutive days, in fixed order (Day 1: IV isotonic saline; Day 2: IV naltrexone HCl 10 mg; and Day 3: IV nalmefene HCl 10 mg). This fixed order design was justified by the expected greater duration of action of IV nalmefene versus IV naltrexone (Dixon et al., 1986; Wall, Brine, & Perez-Reyes, 1981) and was selected in order to minimize the risk of "carryover" from one experimental day to the next. Naltrexone HCl and nalmefene HCl were compounded by Greenpark Pharmacy (Houston, TX). All solutions were injected IV over 2 min, at 10:00 (±30 min). Blood samples for neuroendocrine biomarker (ACTH, cortisol, and prolactin) analysis were obtained at specific time points: −10 min and immediately prior to IV injection (time "0"), and at 10, 20, 30, 40, 60, 75, 90, 120, and 180 min post-injection. Blood for plasma samples was placed in EDTA-coated vacutainer tubes and centrifuged within 30 min. Blood for serum samples was placed in a plain vacutainer and centrifuged. Plasma and serum samples were then immediately stored frozen at −40_C until neuroendocrine biomarker analysis (see below). Intra-assay and inter-assay coefficients of variation were recently reported (Reed, Butelman, Fry, Kimani, & Kreek, 2017).

Plasma ACTH was quantified by our laboratory with a radioimmunoassay kit (DiaSorin; Saluggia, Italy), following manufacturer's instructions, on Packard/COBRA Gamma Counters. Cortisol Serum cortisol was quantified by the Clinical Chemistry Service at the Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA. Measurements were obtained with an automated immunoassay analyzer (AIA 360, Tosoh Bioscience, South San Francisco, CA). Serum prolactin was quantified in duplicate in our laboratory, using human prolactin immunoradiometric kits (MP Biomedicals, Santa Ana, CA), following manufacturer's instructions, on Packard/COBRA Gamma Counters.

Visual analog scales for subjective mood effects

Visual analog scales (10 cm length, unmarked) were provided for scoring by the volunteers, 20 min prior to injection and at specific time points after injection (i.e., 30, 60, 90, 120, 150, 240, and 360 min). The scales were marked for "mood" self-report (marked "terrible" on the left to "terrific" on the right). This acute study was designed to focus principally on the aforementioned neuroendocrine measures rather than on potential subjective effects of these compounds on mood scores.

Statistical analysis

Neuroendocrine data are presented graphically as full time courses and also as area under the time-effect curve (0–180 min after injection), calculated with the trapezoidal rule (Graphpad Prism). The hormone level at time "0" was used as the baseline for these area under the curve (AUC) calculations. Time course data were analyzed with two-way repeated measures analyses of variance (ANOVAs; treatment day × time). AUC data were analyzed with one-way repeated measures ANOVA. Time course data for mood scores were analyzed with a two-way repeated measures ANOVA (treatment day × time). Post hoc comparisons were used as applicable. The level for significance (α) was set at the p 0.05 level.

Missing data

For situations in which a missing value occurred at post-injection time points, the whole data set was excluded from analysis (i.e., case-wise deletion).

RESULTS

Adverse events

There were no serious adverse events in any of these studies, and none required volunteer exiting from study. Reported events included experiencing a hot flash, flushing and/or sweating, or change of mood (both positive and negative), as well as headache, dizziness, and drowsiness.

Demographic data

Summary demographic details are in Table 1. This group of normal volunteers reported a normative range of alcohol and tobacco exposure, as expected.

Neuroendocrine data

ACTH—Both naltrexone and nalmefene caused time-dependent increases in ACTH, compared with saline. ACTH data from male and female volunteers were compared and did not differ from each other (not shown); therefore, we present results for males and females combined. Figure 1a shows the time course of ACTH levels. A two-way repeated measures ANOVA (treatment day × time) was significant for treatment day, $F(2, 30) = 14.12$, $p < .001$, and time, $F(12, 180) = 4.25$, $p < .001$ main effects, and for their interaction, $F(24, 360) = 5.19$, $p < .001$. Tukey's tests show that nalmefene had greater effects than both naltrexone and saline and that naltrexone had greater effects than saline. More specifically, nalmefene was different from saline at all time points from 10 to 120 min after injection. Naltrexone was different from saline for a shorter period, 20 to 90 min after injection. Nalmefene was different from naltrexone for the time points 10 to 60 min after injection. These ACTH data were then analyzed as AUC for the period 0 to 180 min (see Figure 1b). A one-way repeated measures ANOVA for ACTH AUC data was significant for the effect of treatment day, $F(2, 30) = 12.33$, $p < .001$. Tukey's tests for AUC data revealed that nalmefene was greater than both naltrexone and saline.

Cortisol—Cortisol data from male and female volunteers were compared and did not differ from each other (not shown); therefore, we present results for males and females combined. Both naltrexone and nalmefene caused time-dependent increases in cortisol, compared with saline (Figure 2a). A two-way repeated measures ANOVA was significant for treatment, $F(2, 34) = 21.73$, $p < .0001$, and time, $F(12, 204) = 4.30$, $p < .0001$ main effects and for their interaction, $F(24, 408) = 7.71$, $p < .0001$. Tukey's tests show that the effects of nalmefene were greater than saline for all time points from 20–180 min. Naltrexone had greater effects than saline for a shorter period, 30–90 min. Also, nalmefene had greater effects compared with naltrexone, for time points 20–150 min after injection. An AUC analysis of cortisol data was completed for the 0–180 min period (Figure 2b). A one-way repeated measures ANOVA for cortisol AUC data was significant for the effect of treatment day, $F(2, 34) =$

23.79, p < .0001. Tukey's tests for AUC data revealed that each treatment day was different from each other.

Prolactin—Due to the well-known sexually dimorphic effects of opioids on prolactin levels and because of potential changes in prolactin across the menstrual cycle (Kreek et al., 1999; Roche & King, 2015), we analyzed only prolactin data for males (Figure 3a). Data from one male was excluded from analysis, because it was an outlier (i.e., pre-injection prolactin values were >2 standard deviations above the group mean). Another male was removed from analysis due to missing data. Overall, both naltrexone and nalmefene caused time-dependent increases in prolactin, compared with saline.

A two-way repeated measures ANOVA was significant for main effects of treatment day, $F(2, 16) = 9.37$, $p = .003$, and time, $F(12, 96) = 2.10$, $p < .03$ main effects, and their interaction, $F(24, 192) = 3.94$, $p < .0001$. Tukey's tests show that the effects of nalmefene were greater than saline for all time points in 10–90 min after injection. Naltrexone had greater effects than saline for a slightly shorter period, 20–90 min after injection. Nalmefene did not differ significantly from naltrexone at any time point. Prolactin data were then recalculated as AUC for the 0- to 180-min period and analyzed with a one-way repeated measures ANOVA (Figure 3b). This ANOVA was significant, $F(2, 16) = 5.44$, $p = .016$. Tukey's tests indicate that naltrexone was significantly different from saline.

Effects of naltrexone and nalmefene effects on the "mood" visual analog scale—There were no robust effects of saline, naltrexone, or nalmefene injection in the visual analog scales for mood (Table 2). In a two-way repeated measures ANOVA (treatment day × time), there were no significant main effects of treatment day, $F(2, 36) = 1.14$, $p = .33$, time, $F(7, 126) = 0.66$, $p = .55$, or their interaction, $F(14, 252) = 0.72$, $p = .93$.

DISCUSSION

To our knowledge, this is the first study in which naltrexone and nalmefene have been directly compared for their neuroendocrine effects in humans (Soyka et al., 2016).

Neuroendocrine effects

ACTH and cortisol—In the time course analyses, naltrexone and nalmefene caused increases in the HPA axis hormone ACTH and cortisol. The effects of nalmefene on ACTH and cortisol were of greater magnitude and duration than those of naltrexone. Also, based on the AUC analyses for both ACTH and cortisol, nalmefene caused greater HPA axis activation than naltrexone. We previously also observed that the effects of nalmefene on these hormones were greater than those of another shorter acting antagonist, naloxone (Schluger et al., 1998). It is known that both κ-agonism and μ-antagonism can cause activation of the HPA axis in humans and nonhuman primates (Maqueda et al., 2016; Pascoe et al., 2008; Schluger et al., 1998). The IV dose of both naltrexone and nalmefene administered here (10 mg) is expected to cause maximal occupancy of μ-receptor populations (Broksoe Kyhl et al., 2016; Ingman et al., 2005; Webster, Johnson, Stauffer, Setnik, & Ciric, 2011). The pharmacokinetic half-life of IV nalmefene in humans is thought to be longer than that of naltrexone (Dixon et al., 1986; Webster et al., 2011), although they

have never been compared in the same study, to our knowledge. Such a difference in IV half-life could potentially influence neuroendocrine effects observed in a time course design, such as that used here. Overall, the greater HPA axis-activating effects of nalmefene versus naltrexone may be due to differences in their pharmacodynamics at κ- or μ-receptors, but we cannot fully exclude the potential influence of differences in IV pharmacokinetics.

Prolactin—Both μ-agonists and κ-agonists cause dose-dependent increases in prolactin levels in humans and other mammals, and therefore, this can be used as a neuroendocrine biomarker to interrogate ligand effects at these receptor systems (Bowen, Negus, Kelly, & Mello, 2002; Butelman et al., 1999; Chang et al., 2011; Hoehe, Duka, & Doenicke, 1988; Kreek et al., 1999). δ-agonists appear not to share this neuroendocrine effect (Butelman, Ball, & Kreek, 2002), and δ-receptor affinity of naltrexone and nalmefene is relatively low (Bart et al., 2005; Butelman et al., 2002; Wentland et al., 2009). Maximal prolactin-releasing effects of high efficacy κ-agonists are greater than those of partial κ-agonists (Butelman et al., 1999), and we have recently shown that a novel selective κ-antagonist (Rorick-Kehn et al., 2014) does not cause prolactin release in normal volunteers (Reed et al., 2017). In this study, prolactin levels were increased by both naltrexone and nalmefene. We have previously shown that nalmefene can increase prolactin levels in humans (Bart et al., 2005). These data show that IV naltrexone shares this neuroendocrine effect of nalmefene, consistent with a partial agonist signaling profile at κ-receptors, observed in vitro (Ghirmai, Azar, & Cashman, 2009; Wang et al., 2007; Wentland et al., 2009). However, other mechanisms for this effect, including actions at μ-receptors, cannot be fully excluded.

Subjective effects—In this stress-minimized inpatient setting, we did not observe robust subjective effects of acute IV naltrexone or nalmefene administration, in a “mood” scale. This is generally consistent with prior studies (Fudala, Heishman, Henningfield, & Johnson, 1991). It is possible that studies with behavioral or other stressors, or studies in other clinical populations may result in more robust subjective effects of acute naltrexone or nalmefene (Back et al., 2010; Sinha et al., 2006). 5.1.4 | Design considerations and limitations This study was designed with a fixed order of injections on consecutive days (Day 1: saline; Day 2: naltrexone; and Day 3: nalmefene), because nalmefene is thought to have a longer duration of action than naltrexone (Dixon et al., 1986; Wall et al., 1981), although this has never been directly compared in humans. However, it cannot be fully excluded that naltrexone administered on Day 2 may have caused some “carryover” on Day 3 (i.e., the nalmefene test day; Lee et al., 1988). It should be noted that ACTH, cortisol, and prolactin levels had returned to normal levels, in the pre-injection values on Day 3. Also, when administered on Day 3, IV nalmefene caused a rapid effect on the presently studied hormones, as had been observed in studies without prior naltrexone administration (Bart et al., 2005; Schluger et al., 1998). Therefore, it does not appear likely that such potential carryover effects substantially affected nalmefene data in this study. Future studies with different designs may further clarify this issue. The use of the IV route allowed for a comparison of the pharmacodynamics effects of naltrexone and nalmefene, decreasing the potential impact of different oral pharmacokinetics and bioavailability of these two compounds. Oral or IV pharmacokinetics and bioavailability of naltrexone and nalmefene have never been directly compared, to our knowledge (Broksoe Kyhl et al., 2016; Kogan,

Verebey, & Mule, 1977). The selection of the 10-mg IV dose was guided by the goal of achieving comparability with prior studies (Bart et al., 2005; Schluger et al., 1998) and is substantially greater than IV doses of either naltrexone or nalmefene, which are needed to cause μ-receptor antagonism in humans (Moore, Bikhazi, Tuttle, & Weidler, 1990; Webster et al., 2011). Therefore, it can be expected that there would be a maximal blockade of μ-receptors by both naltrexone and nalmefene, with the IV dose used herein.

CONCLUSIONS

To our knowledge, this is the first direct comparison of the neuroendocrine effects of naltrexone and nalmefene in humans. Nalmefene produced greater HPA axis activation than naltrexone. One interpretation of this finding is a greater κ-partial agonist effect by nalmefene versus naltrexone, based on the in vitro profile of these compounds in major signaling assays (Bart et al., 2005; Ghirmai et al., 2009). Nalmefene and naltrexone also caused a time-dependent increase in prolactin levels, in male normal volunteers. This finding is also consistent with partial agonist effects of these compounds, because neither μ-antagonist not κ-antagonist actions are thought to result in prolactin release (Bowen et al., 2002; Reed et al., 2017). The μ-antagonist effects of naltrexone and nalmefene have received much attention in human research (Comer et al., 2002; Gal & DiFazio, 1986; Webster et al., 2011). The potential importance of κ-receptor mediated effects of these compounds in the treatment of AUD is the focus of more recent studies (de Laat et al., 2019). Overall, these data provide further insight into the neuroendocrine biomarker profile of these two pharmacotherapies. These data also provide a basis for design and interpretation of future studies with novel ligands with μ- and κ-receptor-mediated effects in humans, and of novel formulations.

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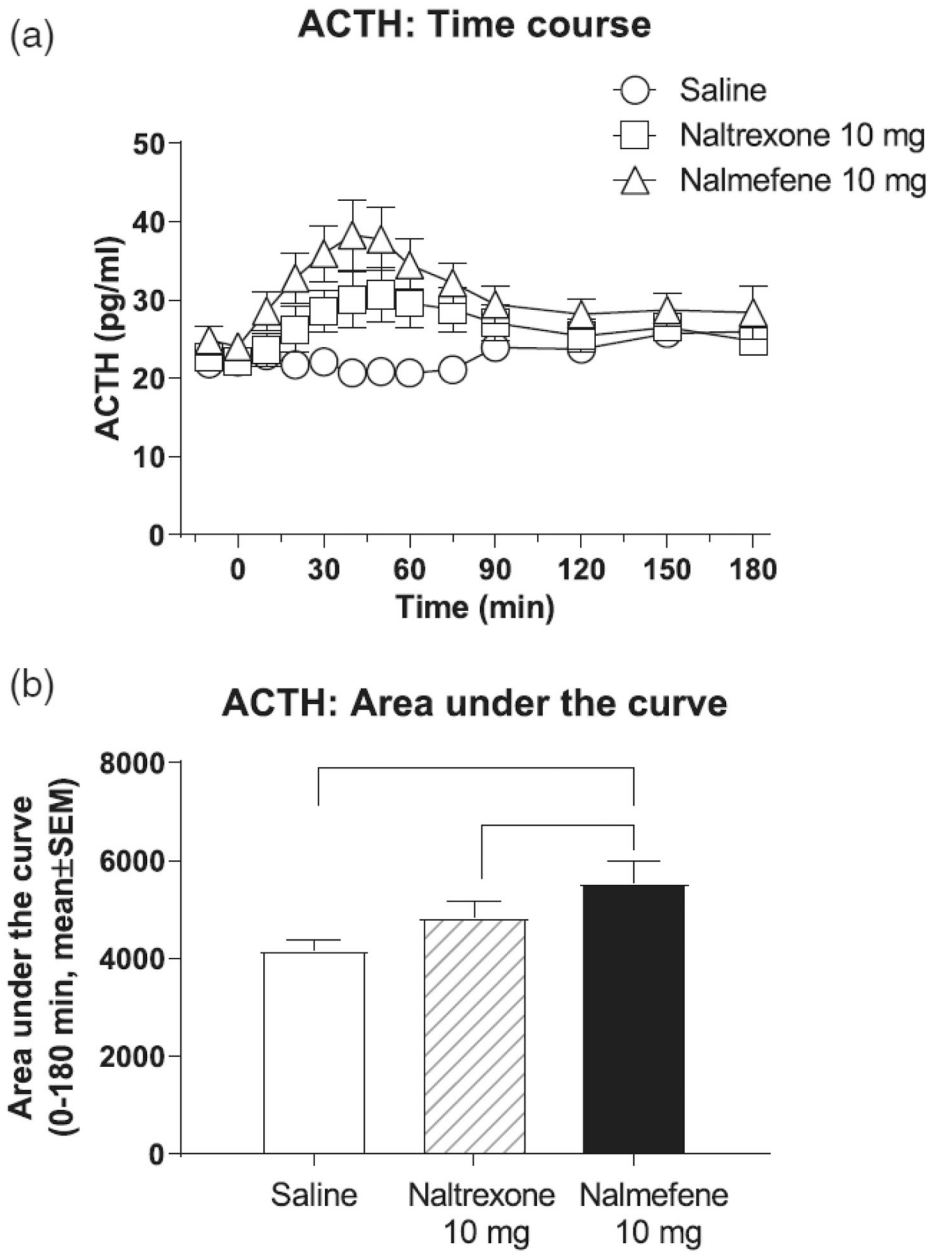

FIGURE 1:

Effects of intravenous saline, naltrexone, and nalmefene on adrenocorticotropic hormone (ACTH), in male and female volunteers. Data (n = 16) are presented as mean ± standard error of the mean. Time course data (a): A two-way repeated measures ANOVA was significant for treatment day, $F(2, 30) = 14.12$, $p < .001$, and time, $F(12, 180) = 4.25$, $p < .001$, main effects, and for their interaction, $F(24, 360) = 5.19$, $p < .001$. Area under the curve (AUC) data for the period 0 to 180 min (b): A one-way repeated measures ANOVA was significant for treatment day, $F(2, 30) = 12.33$, $p < .001$. Black lines in panel (b) show significant Tukey post hoc tests.

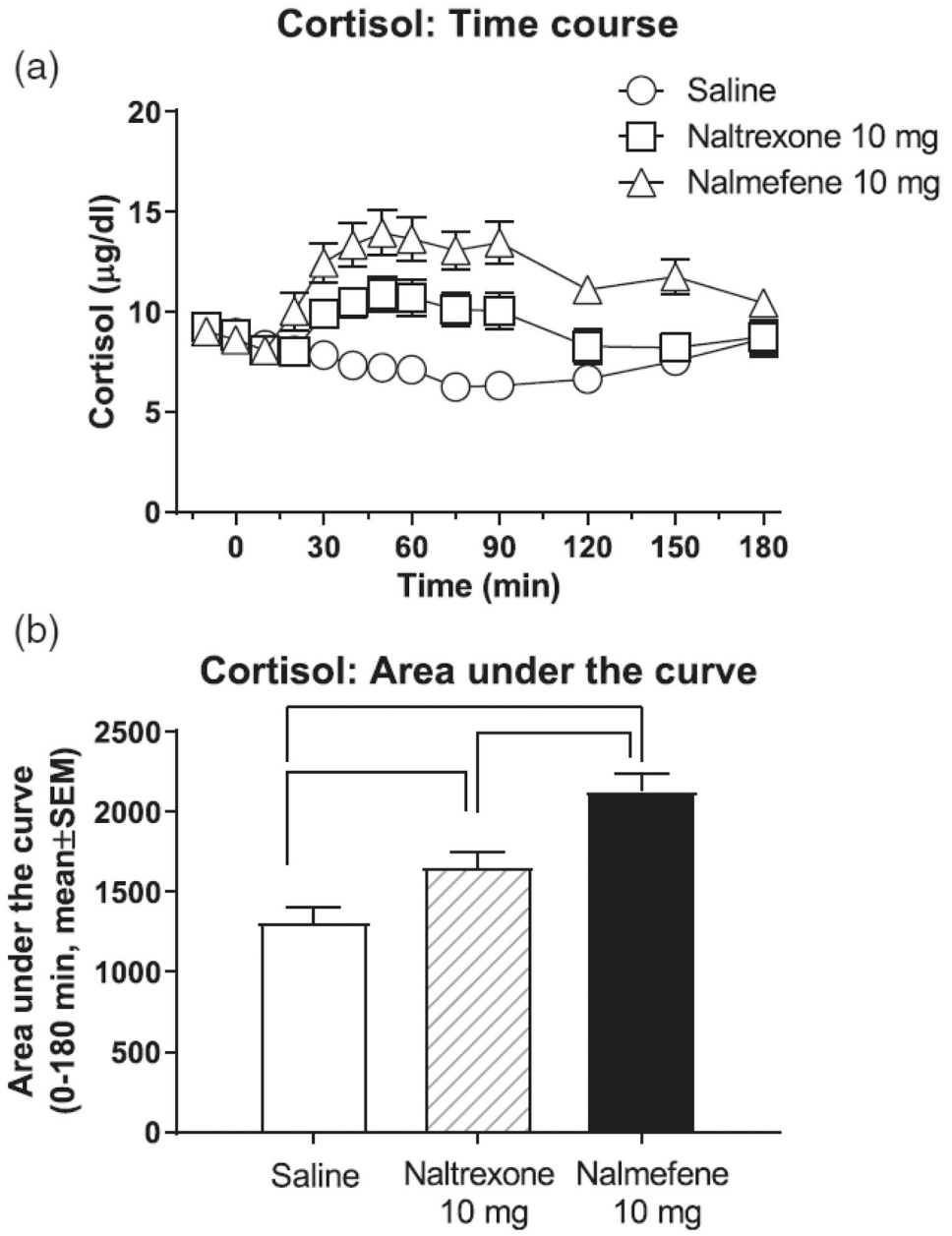

FIGURE 2:

Effects of intravenous saline, naltrexone, and nalmefene on cortisol, in male and female volunteers (time course: panel a; area under the curve: panel b). Data (n = 18) are presented as mean ± standard error of the mean. Time course data (a): A two-way repeated measures ANOVA was significant for treatment, $F(2, 34) = 21.73$, $p < .0001$, and time, $F(12, 204) = 4.30$, $p < .0001$, main effects and for their interaction, $F(24, 408) = 7.71$, $p < .0001$. Area under the curve (AUC) data for the period 0 to 180 min (b): A one-way repeated measures ANOVA was significant for treatment day, $F(2, 34) = 23.79$, $p < .0001$. Black lines in panel (b) show significant Tukey post hoc tests.

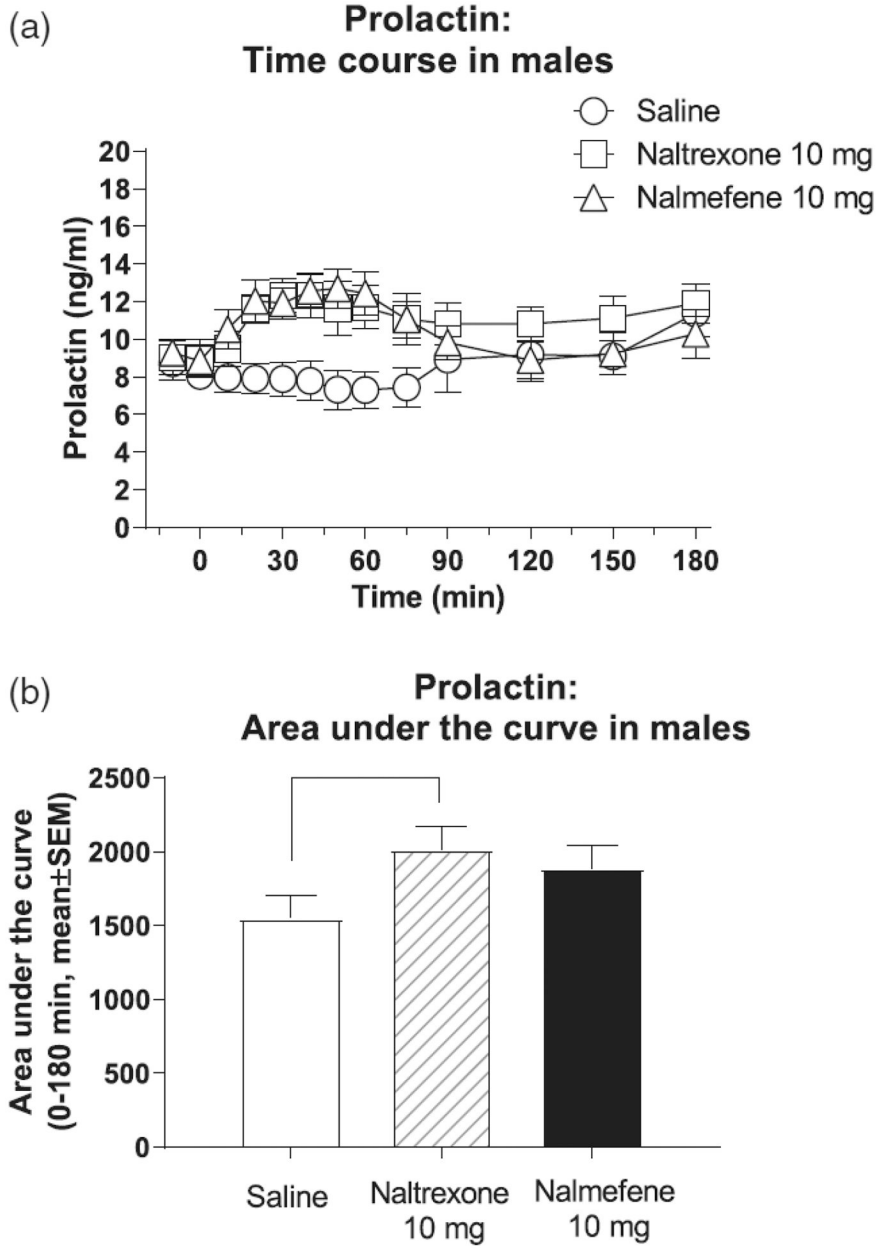

FIGURE 3:

Effects of intravenous saline, naltrexone, and nalmefene on prolactin, in male volunteers only (time course: panel a; area under the curve: panel b). Data (n = 9) are presented as mean ± standard error of the mean. Time course data (a): A two-way repeated measures ANOVA was significant for main effects of treatment day, $F(2, 16) = 9.37$, $p = .003$, and time, $F(12, 96) = 2.10$, $p < .03$, and their interaction, $F(24, 192) = 3.94$, $p < .0001$. Area under the curve (AUC) data for the period 0 to 180 min (b): A one-way repeated measures ANOVA was significant, $F(2, 16) = 5.44$, $p = .016$. Black lines in the lower panel show significant Tukey post hoc tests.

TABLE 1

Demographics[a]

Normal volunteers (n = 20)
Sex Male (n = 11)
Female (n = 9)
Ethnicity Black non-Hispanic (n = 9)
Black Hispanic (n = 5)
White non-Hispanic (n = 2)
White Hispanic (n = 1)
Asian (n = 1)
Mixed/other (n = 2)
Mean age (SEM) 41 (2.3)
Alcohol KMSK score[b]: median (IQR) 4 (2–8.5)
Tobacco KMSK score[b]: median (IQR) 0 (0–4.5)

Abbreviations:

IQR: interquartile range; KMSK: Kreek–McHugh–Schluger–Kellogg scale (measuring maximum lifetime exposure to drugs); SEM, standard error of the mean.

[a]Missing KMSK scores for n = 3.

[b]KMSK scales are ordinal integer measures of maximal self-exposure to each drug, for the period in a persons' life when use was the heaviest. A score of "0" indicates no lifetime use of the drug; the maximum scores for alcohol and tobacco is 13 (Butelman et al., 2018; Kellogg et al., 2003; Tang et al., 2011).

TABLE 2

Visual analog scale (VAS) data for mood[a,b]

Treatment day	Time from injection (min)							
	−20	+30	+60	+90	+ 120	+ 150	+240	+360
Saline								
Mean	7.1	7.1	7.0	7.0	6.9	7.0	7.2	7.1
SEM	0.5	0.4	0.4	0.5	0.4	0.4	0.4	0.5
Naltrexone 10 mg								
Mean	6.8	6.6	6.7	6.6	6.8	6.6	6.9	7.0
SEM	0.5	0.4	0.4	0.5	0.4	0.4	0.4	0.5
Nalmefene 10 mg								
Mean	6.9	6.6	6.9	6.9	6.7	6.7	7.0	7.1
SEM	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.4

Abbreviations: ANOVA, analysis of variance; SEM, standard error of the mean.

[a] VAS scale was 10 cm long, labelled as “terrible” on the left and “terrific” on the right. Data are presented in cm.

[b] A two-way repeated measures ANOVA (treatment day × time from injection) was non-significant (see Results).