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A comparison of dexmedetomidine and placebo on the plasma concentrations of NGF, BDNF, GDNF, and epinephrine during severe alcohol withdrawal

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ABSTRACT

Alcohol withdrawal and therapies may affect nerve growth factor (NGF), brain-derived neurotrophic growth factor (BDNF), glial-derived neurotrophic growth factor (GDNF), and epinephrine (EPI). This study evaluated dexmedetomidine (DEX) on NGF, BDNF, GDNF, and EPI in severe alcohol withdrawal and related their plasma concentrations to DEX concentrations. Twenty-four subjects were randomized to DEX 1.2 mcg/kg/hour (high dose [HD]), 0.4 mcg/kg/hour (low dose [LD]), or placebo. Blood was collected at 0 (T0), 48 (T48), and 96–120 (T96) hours after starting the study drug, and concentrations of these transmitters and DEX were determined. Similar NGF suppression occurred at T48 and T96 across all groups. BDNF and GDNF levels increased insignificantly at T48 in the placebo group but steadily declined in both DEX groups, with a trend toward significance in the HD group at T48. EPI concentrations declined significantly in the HD group at T48, only to increase at T96. Median DEX concentrations during the study were insignificantly higher in HD than LD. T0 values of BDNF ($r = -0.47$, $p = 0.02$) and GDNF ($r = -0.37$, $p = 0.05$) were inversely associated with the need for mechanical ventilation before study enrollment. No other clinical parameter was associated with the plasma concentrations of these transmitters. Daily lorazepam requirements were associated with the severity of withdrawal ($r = 0.7$, $p < 0.0001$) and DEX concentrations were inversely related to daily lorazepam requirements ($r = -0.33$, $p = 0.008$). DEX utilization suppressed EPI ($r = -0.57$, $p = 0.004$). EPI concentrations were associated with BDNF values at T0 ($r = 0.55$, $p = 0.04$) and throughout the study ($r = 0.25$, $p = 0.04$). In summary, the plasma concentrations of NGF, BDNF, GDNF, and EPI during alcohol withdrawal are variable and the effects of DEX were marginal. DEX administration and higher DEX concentrations attenuated lorazepam administration in the short-term and suppressed EPI.

Introduction

Alcohol-associated dependence and subsequent withdrawal are complex physiological processes that involve a wide variety of altered neural pathways (Jung & Metzger, 2010). The role of neurotrophic growth factors in the physiology of alcohol dependence, neuronal plasticity, survival, and adaptation, and cellular remodeling during abstinence is evolving. Brain-derived neurotrophic growth factor (BDNF) is a member of the nerve growth factor (NGF)-related family of neurotrophic factors in the brain, whereas glial cell-derived neurotrophic factor (GDNF) belongs to the transforming growth factor (TGF-β) line of factors (Airaksinen & Saarma, 2002; Lewin & Barde, 1996). NGF, BDNF, and GDNF induce the activity of tyrosine kinase A (TrkA), tyrosine kinase B (TrkB), and tyrosine kinase RET, respectively (Airaksinen & Saarma, 2002; Blum & Konnerth, 2005). Upon initial exposure to alcohol, acute releases in protective BDNF are seen; however, this effect tends to degrade during chronic alcohol consumption, which may increase the severity of withdrawal symptoms (Jeanblanc et al., 2009; Logrip,

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Janak, & Ron, 2009; Ting-A-Kee et al., 2013). In recently abstinent individuals after chronic alcohol exposure, BDNF tone is increased and may represent relapse-free treatment success through its modulation of the dopaminergic reward pathway (Costa, Girard, Dalmay, & Malauzat, 2011; Köhler, Klimke, Hellweg, & Lang, 2013). Mixed evidence exists regarding the association between measured BDNF levels and acute withdrawal severity (Heberlein et al., 2010; Huang et al., 2008; Köhler et al., 2013). While GDNF suppresses self-administration of alcohol (Carnicella, Ahmadiantehrani, Janak, & Ron, 2009), it often is reduced during chronic alcohol intake and the withdrawal period (Heberlein et al., 2010).

The effects of withdrawal medications on the neurotrophic growth factors remain largely unknown. Benzodiazepines, positive allosteric modulators of the γ-aminobutyric acid A ($GABA_A$) receptor and agents of choice to manage alcohol withdrawal down-regulate the genetic expression of NGF and BDNF, and may suppress BDNF levels in patients receiving the drugs therapeutically (Huang & Hung, 2009; Huopaniemi, Keist, Randolph, Certa, & Rudolph, 2004; Vutskits et al., 2008). *In vitro* studies suggest the α_2 agonists, clonidine and dexmedetomidine (DEX), at physiological levels induce the astrocyte expression of BDNF and GDNF genes, which may promote cellular survival (Degos et al., 2013; Yan et al., 2011). Alternatively, α_2 agonists may suppress the generation of these neurotrophic growth factors by blunting the adrenergic stimulation of their synthesis (Juric, Loncar, & Carman-Krzan, 2008). Clinically, the anesthetic/sedative-sparing effects of DEX led to less sedative-induced suppression of BDNF in patients undergoing surgery (Yang et al., 2013). We showed that DEX (Precedex, Hospira Pharmaceuticals, Lake Forest, IL) reduces benzodiazepine requirements during acute alcohol withdrawal, but whether this alters the levels of these neurotrophic growth factors is unknown (Mueller et al., 2013). A plausible disadvantage of using DEX during acute alcohol withdrawal is that it may lower the seizure threshold by lessening the administration of benzodiazepines. Homocysteine, an endogenous amino acid, may modulate the seizure threshold through its agonism of the N-methyl-D-aspartate receptor, and has been shown to be an independent predictor of seizures during acute withdrawal (Bleich & Hillemacher, 2009; Karagülle et al., 2012). DEX also provides autonomic stability, but whether it reduces the level of epinephrine (EPI) during withdrawal has not been studied.

The purpose of this study was to evaluate the effects of the selective α_2 receptor agonist, DEX, and its possible benzodiazepine-sparing properties, on the plasma kinetics of NGF, BDNF, GDNF, homocysteine, and EPI in patients experiencing severe acute alcohol withdrawal, and to relate these concentrations to DEX levels.

Materials and methods

Subjects and study design

This study was planned *a priori* as an independent analysis of data generated from a previously published trial (Mueller et al., 2013). The original study was a randomized, double-blind trial that compared high dose DEX (1.2 mcg/kg/hour [HD]), low dose DEX (0.4 mcg/kg/hour [LD]), and placebo as adjunctive therapy to symptom-triggered treatment of severe alcohol withdrawal, defined by a Clinical Institute Withdrawal Assessment (CIWA) score of ≥15 despite ≥16 mg of lorazepam over a 4-h period, in 24 patients (8 subjects in each group). The primary efficacy outcomes were the change in total lorazepam requirements over the 24-h period after starting the study drug (post) compared with the 24-h period before starting the study drug (pre), and the cumulative lorazepam dose over the first 7 hospital days of alcohol withdrawal. Secondary efficacy outcomes included total and daily lorazepam requirements after starting the study drug; CIWA scores indicating severe (≥15), moderate (8–14), or minimal (≤7) withdrawal symptoms, and the occurrence of hypotension (SBP < 90 mm HG) or bradycardia (heart rate < 50 bpm). Study outcomes were analyzed as groups allocated to placebo or all subjects exposed to DEX (i.e., the combination of HD and LD groups) and according to HD and LD to explore the possibility of a dose–response effect. The study drug was administered for up to 5 days or until subjects were judged to no longer be in withdrawal by the primary care team. Temporary discontinuation of the study drug or rate adjustment was allowed for hypotension or bradycardia. This analysis was approved by the Institutional Review Board at the University of Colorado Anschutz Medical Center as a component of the original study, and consent was obtained from the patient's legally authorized next of kin. It must be stressed that the study evaluated the adjunctive use of DEX so subjects received benzodiazepines as clinically indicated, as they represent the standard of therapy to prevent severe withdrawal manifestations such as seizure or delirium tremens.

Laboratory analyses

Venous blood samples of 20 mL were collected from an indwelling catheter immediately before starting the study drug (T0) and 48 (T48) and 96–120 (T96) hours after the study drug was initiated. All blood samples were collected in test tubes without heparin and transported on ice. Plasma was immediately separated from the remaining cellular material by centrifugation at 3000 rpm for 15 min, placed in labeled polyethylene vials, frozen at −80 °C, and stored until assayed. Concentrations of NGF, BDNF, GDNF, homocysteine, EPI, and carbohydrate-deficient transferrin (CDT), a diagnostic biomarker of alcohol dependence, were measured in duplicate from the thawed samples using commercially available enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's instructions (BDNF, NGF, GDNF – Promega Corporation, Madison, WI; homocysteine – ALPCO LTD, Salem, NH; EPI – Abnova Corporation, Taipei, Taiwan; CDT – BIOTANG, Inc., Lexington, MA). Plasma DEX concentrations were determined in duplicate using high performance liquid chromatography-electrospray ionization-tandem mass spectrometry (Shimadzu Scientific Instruments, Inc., Columbia, MD) with medetomidine-d_3 hydrochloride (Toronto Research Chemicals, Inc., Toronto, ON, Canada) as the internal standard (Preslaski, Mueller, Wempe, & MacLaren, 2013).

Statistical analyses

The primary outcomes assessed plasma levels of NGF, BDNF, GDNF, and EPI over time according to study group and DEX concentrations. Secondary analyses explored relationships between plasma concentrations of these transmitters or DEX and the following clinical criteria: benzodiazepine administration, CIWA severity, hemodynamic parameters, and intubation during study period.

A power analysis was not conducted, as this was an exploratory assessment of existing data. Multiple comparisons of concentrations over time used repeated-measures analysis of variance. Pearson Product–Moment correlation for parametric data or Spearman Rank Order correlation for nonparametric data was used to determine if relationships existed between hormone or DEX concentrations and the other outcomes. Statistical analyses were performed using JMP®, version 10 (SAS Institute, Inc., Cary, NC, 2012). Statistical significance was defined as a two-sided p value of <0.05.