Decreased serum levels of proBDNF, but not mature BDNF during adolescent oxycodone intoxication preceding long-term social neglect and harsh environmental conditions.

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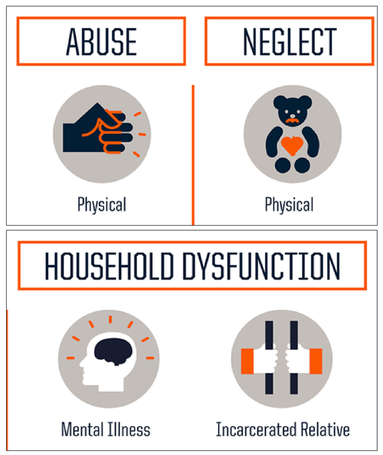
BACKGROUND

Adverse Childhood Experiences (ACEs) are stressful and traumatic experiences during early life (1). The early life stress (ELS) induced by social isolation model is one of the closest to resemble parental abuse and neglect within an adverse environment (2). Including various types of housing with different levels of social-cognitive stimulation (i.e., enriched environment paradigm vs. social isolation environment) is paramount for advancing a preclinical model of ACEs that can be applied to describe the underlying neurobiological mechanism.

More importantly, experiencing ACEs during impressionable periods of development, especially infancy and adolescence, is a predisposing factor for various psychopathology types, including depression, anxiety, and substance abuse disorders (3). Most of these studies focus on the effects of an enriched environment for reversing or counteracting drug effects, with the caveat that nearly all reports included only adult animals (4). The role of social interactions when working with adolescent animal models of addiction encourage one to consider the role of social interactions. Evidence suggests that morphine-induced CPP could be prevented by exposure to different social partners; more so, despite increasing morphine doses, those animals that are exposed to early and continuous social experiences did not develop a preference for the drug (5). This suggests that exposure to different peers and various social interactions can change the abuse potential of opioids (6).The neural mechanisms underlying the transition from a drug-nondependent to a drug-dependent state remain elusive. However, chronic exposure to drugs has been shown to increase brain-derived neurotrophic factor (BDNF) levels in the ventral tegmental area (VTA) neurons (7-8). BDNF is involved in the function and survival of dopaminergic neurons in brain-reward areas. BDNF has attracted attention as one of the biomarker candidates for opioid abuse and has been widely investigated. However, the roles of the mBDNF/proBDNF pathway during adolescent opioid use are not clearly understood. Brain-derived neurotrophic factor (BDNF) plays a role in synaptic plasticity and neuroprotection. Furthermore, BDNF has well-established pro-survival effects, whereas its precursor protein, proBDNF, induces apoptosis (9). Thus, it has been suggested that the proBDNF/BDNF ratio could indicate neuronal health. Meta-analyses have identified serum levels of brain-derived neurotrophic factor (BDNF) as a potential biomarker for psychiatric disorders in an adult population. However, the lack of information on baseline circulating levels of BDNF and its precursor during the adolescent onset is still unknown.

Long-term Social Neglect & Harsh Environmental Conditions

HUMANS



RODENTS

Isolated Environment

Enriched Environment

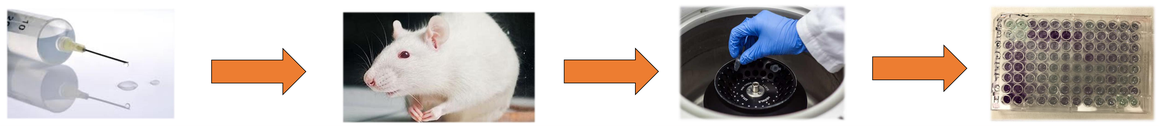
Likelihood to opioid addiction

OBJECTIVES

To determine blood (serum) levels of circulating proBDNF and matureBDNF in adolescent drug naïve adolescent rats compared to levels expressed in oxycodone-treated rats.

METHODS

Serum Collection: The rats were euthanized using the CO2 chamber. After decapitation by guillotine, truncal blood was collected. The serum samples were diluted with RIPA buffer and analyzed with a BCA Protein Assay kit. The immunoassay was performed with a 96 well plate and the Biosensis® mature BDNF and proBDNF Rapid™ ELISA kit. The resulting plate was read at 450 nm.



RESULTS

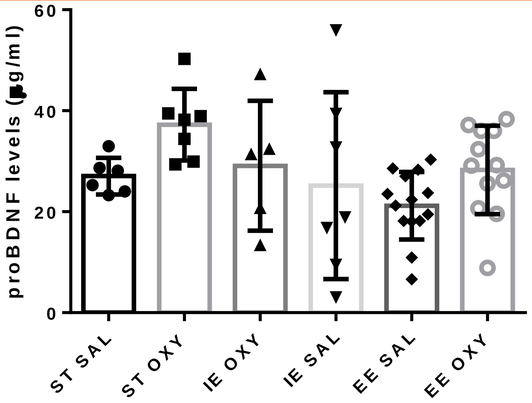


Fig1. 2X3 ANOVA showed significant differences for the environment {F 1,44= 56.78, p<0.05} and treatment {F 1,44= 198.90, p<0.001} and the interaction between factors {F 1,44= 98.78, p<0.05}. Post hoc comparisions demostrated that oxycodone increased significantly (p<0.05) proBDNF periphery levels, while enriched environment decreased those (p<0.05).

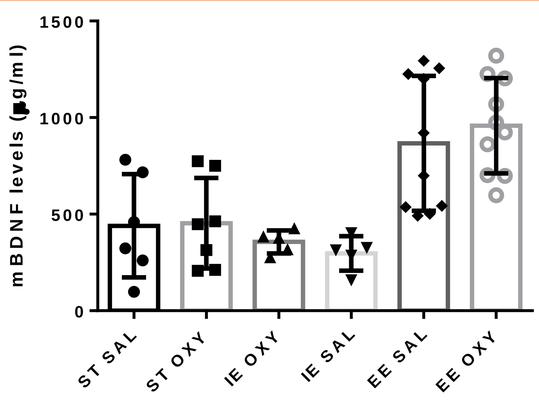


Fig2. 2X3 ANOVA showed only significant differences for the environment {F 1,52= 167.97, p<0.05} and the interaction between environment and treatment {F 1,52= 79.43, p<0.05}. Suggesting that environment but not chronic oxycodone increases mature BDNF levels in the blood (p<0.05).

CONCLUSIONS

- Oxycodone intoxication increased circulating proBDNF levels by 37%.
- There was negligible change in circulating mBDNF concentrations between saline-treated and oxycodone-treated groups
- Regardless of oxycodone treatment, long-term exposure to an enriched environment encouraged a 3-fold increase in mature BDNF levels; while continuous environmental enrichment reduced circulating proBDNF levels by 23.3%
- Our results suggested that the ratio of adolescent circulating proBDNF/mBDNF is significantly changed by oxycodone intoxication and environmental enrichment. More importantly, long-term exposure to social, cognitive, and visual stimulation shifts and increases circulating levels of matureBDNF in the adolescent rat

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