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Kappa opioid regulation of depressive-like behavior during protracted withdrawal from ethanol

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Introduction

Alcoholism is a social and public health problem leading to approximately 79,000 deaths and approximately $220 billion lost annually in the United States alone (Bouchery, Harwood, Sacks, Simon, & Brewer, 2011). The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 2013) characterizes alcoholism as including the following: withdrawal; tolerance; consumption of alcohol to avoid or ameliorate withdrawal symptoms; and repeated yet unsuccessful attempts at controlling alcohol consumption (1994). Because negative affects tend to accompany withdrawal, periods of abstinence commonly result in relapse, thus making it difficult to manage alcoholism during longer periods of time (Cloninger, 1987). One study found that over 80% of recovering alcoholics experienced relapse due to feelings of depression (Hershon, 1977). Furthermore, another study reported that recovering alcoholics who were experiencing depression had a 75% chance of relapse, despite the fact that they were receiving treatment for their depression (Greenfield, Weiss, Muenz, & Vagge, 1998). However, the mechanisms in the brain underlying these depressive responses have not been fully characterized. Having an understanding of the behaviors and underlying brain mechanisms associated with alcohol dependence may offer information on how to treat alcoholism more effectively in the future.

One neurobiological system recently implicated as mediating an interaction between alcohol dependence, withdrawal, and depressive-like behaviors is the dynorphin/kappa opioid receptor (DYN/KOR) system (Walker, Valdez, McLauglin, & Bakalkin, 2012). For example, administration of the KOR antagonist nor-binaltorphimine (nor-BNI) has been shown to decrease dependence-induced ethanol self-administration without affecting ethanol consumption in non-dependent rats (Walker & Koob, 2008) and reduces stress-induced increases in ethanol intake caused by forced swim stress (Sperling, Gomes, Sypek, Carey, & McLaughlin, 2010). In addition, nor-BNI attenuates the usual decrease in open arm exploration of the elevated plus maze (EPM), which is putatively indicative of an anxiety-like state (Pellow, Chopin, File, & Briley, 1985), in rats experiencing acute ethanol withdrawal (Valdez & Harshberger, 2012) and protracted abstinence from ethanol (Gillett, Harshberger, & Valdez, 2013). Administration of JDTic, another KOR antagonist, has demonstrated a decrease in alcohol self-administration and cue-induced reinstatement of alcohol seeking (Schank et al., 2012). By contrast, the KOR agonist U50,488 potentiates ethanol drinking and ethanol-conditioned place preference (Sperling et al., 2010). Similar increases in stress-related behavior are observed following administration of U50,488, an effect which is reversed following pretreatment of nor-BNI (Valdez & Harshberger, 2012). Taken together, these results suggest similar mechanisms may be involved in regulating ethanol withdrawal and KOR agonist-induced changes in anxiogenic-like behavior.

The objective of the current study was to investigate the influence of the KOR antagonist nor-BNI on depressive-like behavior in ethanol dependent rats. Such behavior was characterized using the forced swim test (FST), an animal model of depression that is highly predictive of antidepressant effects in humans (Porsolt, Le Pichon, & Jalfre, 1977). Increased time spent immobile in the FST has been thought to be indicative of a depressive-like state, and this immobility has been observed following acute withdrawal from ethanol (Jarman, Haney, & Valdez, 2013). However, because the adverse mood effects of withdrawal can last long after the acute physiological symptoms subside, the present study looked at the influence of nor-BNI during protracted withdrawal from ethanol. Based on the previous literature, we hypothesized that we would observe more time spent immobile in the FST, and this effect would be reversed following administration of nor-BNI.

Methods

Animals and Housing

Male Wistar rats (Charles River, Portage, MI, USA) weighing 150-200 g upon arrival were used in this experiment. Animals were group housed (3 per cage) with food and water available ad libitum. Lights were on a 12-hour reverse light/dark cycle (lights...
on at 8:00 p.m.). Animals were allowed to habituate to colony housing 7 days prior to administration of the ethanol liquid diet and were handled and weighed at least 3 times a week.

**Induced Ethanol Dependence**

Animals were placed on a liquid diet composed of 10% ethanol, a commercially available liquid nutritional supplement, and vitamins and minerals (Macey et al., 1996). Control animals were placed on an analogous diet with sucrose isocalorically substituted for ethanol. Animals in the ethanol condition were allowed unlimited access to the diet, and the animals in the control condition were given the average intake of the ethanol condition animals on the previous day. This diet was administered for 28 days and has been shown to induce physical signs of dependence (Macey et al., 1996).

**Forced Swim Test**

A 65 cm tall x 25 cm diameter Plexiglas cylinder (Braintree Scientific, Braintree, MA) filled to 48 cm with 25°C water was used. Three weeks following completion of the liquid diet, animals were exposed to a 2 day forced swim test procedure modified from that described by Porsolt et al. (1977), in which the rats did not have the opportunity to escape. On the first day, the rats were placed in the cylinder for 10 minutes. On the second day, animals were exposed to forced swim stress for 5 minutes, and a video camera was used to record the animals’ behavior. Following each test, rats were dried off with a towel and were placed in a heated, ventilated chamber prior to being returned to their cages.

**Drug Administration**

Immediately following the initial 10 minute forced swim exposure and 24 hours prior to the 5 minute forced swim test, half of the animals were injected with saline, and half were injected with nor-BNI (20 mg/kg i.p.).

**Data Analysis**

The videos of the forced swim test sessions were analyzed to determine the animals’ levels of immobility versus swimming. A trained observer measured the total amount of time the animals spent immobile. Immobility is defined as floating to maintain the head above water with only minor paw movement. The statistical reliability of the results were analyzed using an analysis of variance (ANOVA), with liquid diet condition and nor-BNI dose as the between subjects factors.

**Results**

Rats given the ethanol liquid diet consumed an average of 11.62 g/kg of alcohol per day (SD = 3.44, range = 3.11-17.96) over the course of the liquid diet administration. These levels of ethanol consumption have previously been shown to induce pharmacologically relevant blood alcohol levels, which induce physical symptoms of dependence and withdrawal (Macey et al., 1996). Although the average intake per animal was determined by the total consumption of fluid per cage, the average body weights of each animal did not significantly differ from each other. This result suggests that significant differences in the amount of fluid intake between animals housed together are not likely. In addition, no significant differences were observed in body weight between animals exposed to the ethanol diet versus similarly housed animals exposed to a control diet (ethanol mean = 284.68, SD = 15.73; control mean = 291.86, SD = 26.60). Likewise, there were no significant differences between the amount of fluid consumed between the two groups during the entirety of the liquid diet (ethanol mean = 38.30 ml, SD = 11.72; control mean = 38.19 ml, SD = 12.45).

No significant differences were observed between ethanol dependent versus non-dependent animals who received either saline or 20 mg/kg nor-BNI (Figure 1).

**Discussion**

No significant differences were observed in animals that received saline versus nor-BNI in either the ethanol dependent or the non-dependent animals (Figure 1). One limitation of this study involved the small amount of nor-BNI available at the time of testing due to a supplier shortage, and this factor led to a small sample size in the current study, previous data obtained in our laboratory have suggested that administration of nor-BNI during the acute withdrawal phase attenuates depressive-like behavior (Jarman et al., 2013). Additionally, pilot data taken in this laboratory have found that depressive-like symptoms may last up to 6 weeks or more. These data tentatively lend credence to the idea that the KOR system may play a role in depressive-like behavior, and future research will aim to continue the work of the present study.
References


Figure 1. Time spent immobile in the forced swim test. Rats were placed on an ethanol liquid diet and were tested three weeks following removal of the liquid diet. No significant differences were observed between either ethanol dependent or non-dependent groups who were given either saline or 20 mg/kg nor-BNI.