Upregulated dynorphin opioid peptides mediate alcohol-induced learning and memory impairment

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The dynorphin opioid peptides control glutamate neurotransmission in the hippocampus. Alcohol-induced dysregulation of this circuit may lead to impairments in spatial learning and memory. This study examines whether changes in the hippocampal dynorphin and glutamate systems are related, and contribute to impairment of spatial learning and memory in a rat model of cognitive deficit associated with alcohol binge drinking. Hippocampal dynorphins (radioimmunoassay) and glutamate (in vivo microdialysis) were analyzed in Wistar rats exposed to repeated moderate-dose ethanol bouts that impair spatial learning and memory in the Water Maze Task (WMT). The highly selective, long-acting κ-opioid receptor (KOR) antagonist nor-Binaltorphimine (nor-BNI) was administered systemically or into the hippocampal CA3 region to test a role of dynorphins in alcohol-induced dysregulations in glutamate neurotransmission and behavior in the WMT. The ethanol treatment impaired learning and memory, upregulated dynorphins and increased glutamate overflow in the CA3 region. Administration of nor-BNI after cessation of ethanol exposure reversed ethanol-induced changes in glutamate neurotransmission in animals exposed to ethanol and normalized their performance in the WMT. The findings suggest that impairments of spatial learning and memory by binge-like ethanol exposure are mediated through the KOR activation by upregulated dynorphins resulting in elevation in glutamate levels. Selective KOR antagonists may correct alcohol-induced pathological processes, thus representing a novel pharmacotherapy for treating of ethanol-related cognitive deficits.

INTRODUCTION

A substantial part of the population in western countries consumes moderate to large amounts of alcohol, which can result in acute and delayed impairments in cognitive and executive functions—operations that guide complex behavior over time through planning, decision-making and response control. These impairments lead to medical and social problems including dementia, violence and decreased work productivity. Total alcohol consumption and binge drinking pattern, characterized by consumption of large amount of alcohol within a limited time, are risk factors for dementia later in life. Binge drinking during adolescence causes impairment in a spatial working memory and other cognitive tasks. Alcohol-induced deficits in cognition are critical factors underlying the habitual drug seeking and taking that characterize addiction and dependence.

The mechanisms of alcohol-induced cognitive impairments remain unknown but they may involve neurodegeneration and/ or aberrant neurotransmission. Several studies indicate that cognitive effects of alcohol are mediated through the dysregulation of the glutamate system in the hippocampus and prefrontal cortex (PFC). Glutamate neurotransmission in the hippocampus is tonically controlled by the dynorphin opioid peptides that have been implicated in cognitive decline. Administration of synthetic dynorphin into the dorsal hippocampus impairs spatial learning in rats. Dynorphins contribute to age-related and stress-induced deficits in learning and memory. In elderly humans, prodynorphin (PDYN) gene polymorphisms have a role in memory function. In individuals with Alzheimer’s disease, dynorphins are elevated in the PFC and this increase correlates with neuropathological lesions. In human alcohol-dependent subjects, dynorphins are upregulated in the hippocampus and PFC that may underlie, in part, cognitive impairments including the dysfunctions in cognitive control of addictive behavior and disrupted inhibitory control.

In this study, we investigated whether dynorphin levels are altered in the rat model of cognitive deficits induced by binge-like ethanol exposure and whether blockade of κ-opioid receptor (KOR), a target for dynorphins, prevents alcohol-induced cognitive impairments. In this model, repeated, intermittent intragastric administration of moderate dose of ethanol (3.4 g kg⁻¹; once daily by gavage for 6 days) produces blood alcohol concentrations (that is, between 110 and 150 mg dl⁻¹) similar to those produced by binge ethanol intoxications in humans (that is, between 80 and 200 mg dl⁻¹), and impairs spatial learning and memory in the Barnes maze task. Administration of nor-BNI after cessation of ethanol exposure reversed ethanol-induced changes in glutamate overflow (nor-BNI) was administered systemically or into the hippocampal CA3 region to test a role of dynorphins in alcohol-induced dysregulations in glutamate neurotransmission and behavior in the WMT. The ethanol treatment impaired learning and memory, upregulated dynorphins and increased glutamate overflow in the CA3 region. Administration of nor-BNI after cessation of ethanol exposure reversed ethanol-induced changes in glutamate neurotransmission in animals exposed to ethanol and normalized their performance in the WMT. The findings suggest that impairments of spatial learning and memory by binge-like ethanol exposure are mediated through the KOR activation by upregulated dynorphins resulting in elevation in glutamate levels. Selective KOR antagonists may correct alcohol-induced pathological processes, thus representing a novel pharmacotherapy for treating of ethanol-related cognitive deficits.

Keywords: alcohol; dynorphin; glutamate; κ-opioid receptor; learning; memory

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Methods and Materials

Drugs
Nor-Binaltorphimine (nor-BNI; 17,17-(dicyclopropylmethyl)-6,6,7,7-, 6,6'-imino-7,7'-bimorphinan-3,4',14,14'-tetrol) was obtained from Tocris Bioscience, Bristol, UK.

Behavioral experiments
Animals. Male, Wistar rats (B&K Universal, Sollentuna, Sweden), 12–14 weeks old (300–420 g) were housed at a 12-h light/dark cycle (lights on at 0800 hours) with food and water available ad libitum. Experiments took place between 1000 and 1500 hours. The experimental procedures followed the recommendations of the Swedish animal protection legislation and were approved by the local Animal Ethics Committee.

Surgery and cannulation. Rats were anaesthetised with a combination of Ketalar (ketamine hydrochloride 50 mg ml⁻¹, 0.2 ml, scubutaneously, Parke Davis, Barcelona, Spain) and Hypnorm (fluanisone 10 mg ml⁻¹ and fentanyl 0.2 mg ml⁻¹; 0.2 ml, intraperitoneally, Janssen, Beerse, Belgium).

The animals were implanted with steel guide cannulae (custom made, outside diameter = 0.4 mm) aimed at the CA3 region of the dorsal hippocampus (coordinates based on Paxinos and Watson atlas: 35 anterior–3.3 mm from bregma, lateral–3.2 mm to the midsagittal suture line and ventral–3.5 mm from the skull surface). During surgery, the body temperature of the animal was maintained at 37°C using a temperature controller (CMA/105, CMA/Microdialysis, Stockholm, Sweden). After surgery, a dummy cannula was put into the guide cannula and the rats were allowed at least 5 days of recovery. Animals with intracranial cannulae were individually housed in standard Macrolon (type 3, Sweden). The position of the cannula was verified histologically after the experiments following an intrahippocampal infusion of 0.3 μl methylene blue.

Forced intragastric ethanol administration. Rats were treated with ethanol (40% v/v; 10 ml kg⁻¹) or tap water once per day for 6 days intragastrically through gavages. In the acutely treated naive rats (3.4 g kg⁻¹ of ethanol), and after the last ethanol treatment in animals exposed to ethanol binge for 6 days, blood alcohol concentrations reached the peak values of 112 ± 27 mg dl⁻¹ and 153 ± 27 mg dl⁻¹, respectively, in 3–4 h and then decreased to the basal levels by 8 h in both animal groups.26,27 No significant differences in weight gain between the ethanol- and water-treated groups were assessed.26,27

The water maze task. A circular water tank, 180 cm in diameter and 45 cm high (AB Lomma Plastprodukt, Arlöv, Sweden), was used in the water maze task (WMT) procedure. The water tank was filled with tap water (22°C) and the transparent plexiglas escape platform invisible in clean water was submerged 1 cm below the water surface. The water tank was located in a room with several visual cues that were kept constant throughout the experiment.36

Acquisition test. During training, the submerged escape platform was located in the center of the southeast quadrant. The rats were given four trials per day for five consecutive days. In each trial, the rat was placed in the water facing the pool wall at one of four selected starting points (north, south, east or west).36 After each trial, the rat was placed at a different starting point, thus eliminating the use of a simple response strategy. Latency to escape to the platform in seconds, swim path in centimeters, average swim speed in cm s⁻¹, percent of time spent in near board zone, percent of time spent in quadrant with platform, proximity to the platform (mean distance to the platform in cm during the trial) and percent of swimming time with slow swim speed (less than 5 cm s⁻¹) were analyzed.

Probe tests. Four hours after the last trial, spatial memory was examined. For this purpose, the platform was removed from the pool and the animals were allowed to swim freely for 60 s. The rat was released into the water tank from a position opposite to that of the quadrant where the platform had been during the training sessions. The latency to the first crossing and the time spent in the different quadrants and zones were analyzed.

Experiment 1. The objective was to assess if repeated administration of ethanol (3.4 g kg⁻¹, intragastrically, daily for 6 days) affects spatial learning. Animals were treated with water (n = 27) or ethanol (n = 42) as described above. The WMT training was initiated 2 days after the last ethanol treatment.

Experiment 2. To investigate whether the effects of repeated ethanol administration are mediated through the KOR, animals were treated with the KOR-antagonist nor-BNI.35,37–41 Rats treated with either water or ethanol solution (see Experiment 1) for 6 days, were randomly assigned to two groups, treated once with saline (5 ml kg⁻¹, s.c.) or nor-BNI (6 mg kg⁻¹, dissolved in saline; s.c.) 2 h after the last ethanol administration. The WMT training was initiated 2 days after the last ethanol treatment.

Experiment 3. To examine if impairment produced by ethanol is mediated through the activation of the KOR in the hippocampus, artificial CSF (aCSF; 0.3 μl per side) or nor-BNI (10 nmol per side in 0.3 μl of aCSF) was injected once into the hippocampal CA3 region. Nor-BNI was infused bilaterally over 30 s using a microinfusion pump (CMA 100). The injection needles (0.2 mm outside diameter) were left in the guide cannula for an additional 30 s after infusion. The WMT training was initiated 2 days after the last ethanol treatment.

Microdialysis experiments

Animals. Male, Wistar rats (Charles River Laboratories, Germantown, MD, USA) (250–300 g at the beginning of the experiment) were housed in facilities accredited by the American Association for the Accreditation of Laboratory Animal Care and experiments were reviewed by the National Institute on Drug Abuse Intramural Research Program Institutional Care and Use Committee under National Institute on Drug Abuse (National Institutes of Health) guidelines.

Surgical procedures. Standard stereotaxic procedures were used to implant unilateral microdialysis guide cannulae (CMA/11; CMA/Microdialysis, Acton, MA, USA) in the CA3 region of the dorsal hippocampus (for coordinates see above) of animals anesthetized intraperitoneally with 3 ml kg⁻¹ Equithesin.

Treatment. Following 5 days of recovery, rats were treated via gastric gavage with either 3.4 g kg⁻¹ dose of ethanol or water for 6 days as described above. Animals were injected with either saline or nor-BNI (6 mg kg⁻¹, s.c.) 2 h after last ethanol administration.

Microdialysis procedures. Microdialysis experiments were commenced 2 days after treatment with ethanol. Before measurements, each probe was flushed overnight with 0.3 μl min⁻¹ aCSF containing 145 mM NaCl, 2.8 mM KCl, 1.2 mM MgCl₂, 1.2 mM CaCl₂, 0.25 mM ascorbic acid and 5.4 mM D-glucose, adjusted to pH 7.2 with high-performance liquid chromatography-grade NaOH or H₃PO₄. During the experiment, fresh aCSF was perfused at 1 μl min⁻¹. After 60 min of equilibration, 5-min dialysate sample collection commenced. After baseline determination (30 min), the aCSF was changed to that containing 60 mM KCl, and after 30 min of equilibration, six consecutive samples were collected. The perfusion solution was then changed to regular aCSF and six additional baseline samples were collected following a 30 min equilibration period.

Probe location confirmation. For anatomical confirmation, animals were euthanized by Equithesin and probe placement was assessed on 25-μm serial coronal cryostat sections. Only data obtained from animals with histologically correct placements were used for subsequent analysis.

Glutamate determination. Amino acid content was quantified using a capillary electrophoresis P/ACE MDQ system (Beckman, Fullerton, CA, USA) coupled to an external ZETALIF laser-induced fluorescence detector.
The intake of ethanol-induced cognitive impairment is related to the retrieval deficit. Experiment with the visible platform revealed no differences between ethanol- (n = 6) and water- (n = 6) treated rats (ANOVA: time × treatment interaction, P = 0.7) in the latency to navigate to the platform. Thus, the ethanol treatment did not affect the sensory and motor systems (abilities to navigate using local and distal cues and swim) or the motivation to escape from water.
Ethanol effects on the hippocampal dynorphins
To evaluate whether ethanol exposure affects dynorphin neurotransmission, we analyzed the levels of these peptides in the hippocampus. Analysis was conducted on day 3 and day 7 after cessation of ethanol exposure that corresponded to the first and last day of learning and memory trials (Figure 2). Dynorphin A was significantly increased in the day and remained elevated on day 7 (for both points, \( P < 0.05 \)), whereas the increase in dynorphin B reached significance on day 7 (\( P < 0.05 \)).

Effects of KOR antagonist nor-BNI on learning and memory impairment induced by ethanol administration
To examine whether KOR activation mediates ethanol effects on spatial learning and memory, we blocked KOR using nor-BNI, the highly selective KOR antagonist that exerts effects lasting for at least 1 month.\(^{37–39,41}\)

In the control rats (received water, intragastrically), nor-BNI (6 mg kg\(^{-1}\); s.c.) administered 2 days before the WMT training failed to modify their performance in the WMT (Figure 3). Virtually identical data were obtained after intrahippocampal administration of aCSF (\( n = 6 \)) or nor-BNI (10 nmol per 0.3 \( \mu \)l per side bilaterally; \( n = 6 \)). Thus, endogenous dynorphins are not likely involved in spatial learning and memory formation under physiological conditions.

Experiment 2. The ethanol-treated rats administered s.c. with nor-BNI 2 days before the WMT training were superior in spatial learning performance compared with the ethanol-saline group; the latencies to locate the platform were markedly shortened in the ethanol-nor-BNI group (Figure 4a). The differences in the latencies were significant on day 3 to day 5 of training. No effects of nor-BNI on swim speed were evident (Figure 4b). Quadrant selectivity returned to normal in nor-BNI-treated rats but not in saline-treated rats (Figure 4c). In the probe test, the latency to reach the position of the platform and the percentage of time spent in the correct quadrant were normalized in the ethanol-treated rats by nor-BNI administration (Figures 4a and c).

Experiment 3. The dorsal CA3 area 2 days before the first WMT training block. Intra-hippocampal nor-BNI significantly improved learning in ethanol-treated rats as was evident from the decrease in latencies to locate the platform compared with aCSF-treated rats on day 3 and day 5 (Figure 4d). No effects of nor-BNI on swim speed were found (Figure 4e). Nor-BNI-treated rats also displayed enhanced quadrant selectivity on day 4 and day 5 (Figure 4f) and a significant improvement in memory function in a probe test manifested as a normalization of both percentage time in correct quadrant and latency to reach the position of the platform (Figures 4d and f). The nor-BNI effects were significant on day 3 to and day 5 of training, that is in 5–7 days after the last ethanol administration, suggesting that they were not mediated through ethanol withdrawal.

Nor-BNI effects on ethanol-evoked alterations in hippocampal glutamate transmission
We previously demonstrated that ethanol treatment regimen used in the present study augments basal and depolarization-induced dialysate glutamate levels in the CA3 area due to elevated glutamate release.\(^{27}\) To evaluate whether KOR is involved in ethanol-induced alterations in glutamate neurotransmission, we examined the effects of nor-BNI pretreatment on these alterations. Ethanol treatment increased both basal and potassium-induced glutamate overflow in the CA3 region (Figures 5a and b) in average by 400% compared with controls, from 388 ± 97 nM to 1576 ± 770 nM and from 683 ± 120 nM to 2748 ± 869 nM for basal and stimulated overflow, respectively. Two-way ANOVA revealed a significant ethanol treatment effect (\( F(3,24) = 5.58, P < 0.05 \)) and ethanol × nor-BNI treatment interaction (\( F(3,24) = 4.31, P = 0.05 \)) for stimulated glutamate levels, whereas for basal levels they were not significant (\( F(3,24) = 1.01, P > 0.05 \) and \( F(3,24) = 1.51, P > 0.05 \), respectively). Analysis of stimulated glutamate levels revealed a significant effect of ethanol in saline-treated (\( F(1,13) = 9.85, P < 0.01 \)), but not in nor-BNI-treated animals (\( F(1,10) = 0.04, P > 0.05 \)). Correspondingly, effect of nor-BNI pretreatment was significant in ethanol-treated animals (\( F(1,14) = 5.54, P < 0.05 \)), but not in controls (\( F(1,9) = 0.52, P > 0.05 \)). There were no differences between pretreatment groups in basal or depolarization-induced GABA overflow (data not shown). Thus, ethanol treatment...
augmented potassium-induced glutamate release, whereas pretreatment with nor-BNI blocked this increase.

DISCUSSION
Postmortem analysis of human alcohol-dependent subjects identified upregulation of the dynorphin opioid peptides in the hippocampus and dl-PFC.25,48 These changes may be caused by many years of alcohol drinking and withdrawal, and may contribute to alcohol-associated impairments of cognitive and executive functions. Consistently, the present study found that dynorphins are upregulated in the hippocampus of rats exposed to ethanol that produced spatial memory impairment. The critical finding was that the highly selective long-acting KOR-antagonist nor-BNI,37–41 administered after cessation of ethanol exposure reversed cognitive deficits and normalized elevated glutamate levels in ethanol-treated rats. Nor-BNI was effective under both systemic and intrahippocampal administration suggesting that ethanol actions on glutamate overflow and spatial memory were mediated through the hippocampal dynorphin-KOR-dependent mechanism. No effects of nor-BNI on learning and memory and glutamate levels were evident in naïve animals, suggesting that this mechanism is not activated under normal conditions.

In the hippocampus, synthetic dynorphins act through presynaptic KOR to inhibit Ca\(^{2+}\)-dependent glutamate secretion thereby inhibiting synaptic transmission and reducing neural plasticity.17,18,49,50 These effects may potentially underlie inhibitory actions of KOR agonists on spatial memory.17–21 Dialysis studies, however, do not support this hypothesis. Thus, synthetic dynorphin increased glutamate levels in the hippocampus51 and spinal cord,52 and dynorphin upregulation followed by ethanol treatment resulted in elevation of hippocampal glutamate concentrations (the present study).

Under normal conditions endogenous dynorphins may control glutamate release in the hippocampus via two processes, by acting through KOR localized to glutamate terminals and by inhibiting GABA interneurons thereby disinhibiting glutamate release from dentate granule cells.18,49,50 At least two factors are critical for the maintenance of the balance between these two processes: (a) local dynorphin concentrations in the vicinity of the KOR localized to glutamate terminals or to GABA interneurons, and (b) status of KOR-activated signal transduction pathways in the two neuronal types. Ethanol intake may differentially alter...
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Figure 5. The nor-BNI (nBNI) pretreatment reverses the effects of ethanol on the basal- and potassium-induced dialysate concentrations of glutamate in the CA3 area of the hippocampus. (a) The time pattern of the basal- and potassium-stimulated extracellular glutamate concentration in the CA3 area of the hippocampus of the water- and ethanol-treated rats. The left panel shows the effects of vehicle (n = 6) or nor-BNI (n = 4) treatment on the water-exposed rats, and the right panel shows the effects of vehicle (n = 7) or nor-BNI (n = 7) treatment on the ethanol-exposed rats. The nor-BNI treatment normalized the glutamate concentrations in the ethanol-exposed rats but failed to influence those of the water-exposed rats. (b) The bar graphs of the area under the curve (AUC) values for the stimulated glutamate levels. *P < 0.05; the significance of the differences between the water-vehicle and ethanol-vehicle treatment group; and between the ethanol-nor-BNI and ethanol-vehicle treatment group.

This study suggests that both dynorphin and glutamate systems mediate effects of alcohol on learning and memory impairment. Although KOR activation has been identified as a critical event, the molecular mechanism of alcohol-induced dynorphin upregulation and causal relationships between dynorphin upregulation, increased glutamate overflow and learning and memory impairment have not been established, which is a limitation of the work. In the future studies, it would be important to address these issues and examine whether dysregulated interaction of the two neurotransmitter systems may contribute to decline in spatial memory in other neuropathological conditions including acute and chronic stress in which dynorphins may also be involved.

Activation of the dynorphin system in the hippocampus and dl-PFC in human alcoholics may be a part of the functional mechanism of cognitive deficits that may include the loss of cognitive control over alcohol drinking and seeking behavior. Indeed, these brain areas are implicated in the encoding and retrieval of drug-related memories that lead to drug craving and drug use, whereas variations in the PDYN and/or KOR genes are associated with the risk for alcohol dependence. Negative craving for alcohol and memory in the elderly. Importantly, nor-BNI decreases ethanol self-administration in ethanol-dependent but not in nondependent rats supporting the hypothesis that dynorphins and KOR are dysregulated in alcohol addiction and contribute to the increased drinking in dependent rats. Furthermore, KOR activation was found to induce an impulsive phenotype that may contribute to the initiation of alcohol abuse and relapse in dependent individuals.

In summary, our findings propose the functional mechanism of spatial learning and memory impairment induced by binge-like alcohol exposure. This mechanism involves the dynorphin/KOR system, whose activation augments glutamate neurotransmission and hence produces cognitive deficits. Selective KOR antagonists may correct alcohol-dysregulated neurotransmission, thus representing a novel pharmacotherapy for treating alcohol-related cognitive deficits.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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This article is dedicated to the memory of Tony Shippenberg.
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