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# Stress-related neuropeptides and alcoholism: CRH, NPY and beyond

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## Abstract

This article summarizes the proceedings of a symposium held at the conference on “Alcoholism and Stress: A Framework for Future Treatment Strategies” in Volterra, Italy, May 6–9, 2008. Chaired by Markus Heilig and Roberto Ciccocioppo, this symposium offered a forum for the presentation of recent data linking neuropetidergic neurotransmission to the regulation of different alcohol related behaviours in animals and in humans. Dr. Donald Gehlert described the development of a new corticotrophin releasing factor (CRH) receptor 1 antagonist and showed its efficacy in reducing alcohol consumption and stress-induced relapse in different animal models of alcohol abuse. Dr. Andrey Ryabinin reviewed recent findings in his laboratory indicating a role of the urocortin 1 (Ucn) receptor system in the regulation of alcohol intake. Dr. Annika Thorsell showed data supporting the significance of the neuropetide Y (NPY) receptor system in the modulation of behaviours associated with a history of ethanol intoxication. Dr. Roberto Ciccocioppo focused his presentation on the nociceptin/orphanin FQ (N/OFQ) receptors as treatment targets for alcoholism. Finally, Dr. Markus Heilig showed recent preclinical and clinical evidence suggesting that neurokinin 1 (NK1) antagonism may represent a promising new treatment for alcoholism. Collectively, these investigators highlighted the significance of neuropeptidergic neurotransmission in the regulation of

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neurobiological mechanisms of alcohol addiction. Data also revealed the importance of these systems as treatment targets for the development of new medication for alcoholism.

**Keywords**

CRH; Nociceptin/Orphanin FQ; Neurokinins; Substance P; Neuropeptide Y; Urocortin

## Introduction

Alcoholism is an etiologically and clinically heterogeneous disorder in which compulsive alcohol seeking and use represent core symptoms (McLellan, et al., 1992). While inheritance plays a significant role in individual vulnerability to developing alcohol abuse (Sigvardsson, et al., 1996; Lovinger and Crabbe, 2005), chronic exposure to alcohol and alcohol intoxication is a necessary condition for the development of alcoholism. Genetic and environmental factors have long been recognized as playing a significant role in shaping alcohol abuse, though the interaction between these factors is still not well understood.

In recent years, several approaches have been investigated to help alcoholic patients to control not only alcohol drinking but also alcohol craving and relapse (Monti et al., 1993; O'Brien, 1997; Volpicelli et al., 1992). Medications tested for their potential therapeutic effect on alcohol abuse (i.e., naltrexone, acamprosate, ondansetron, disulfiram, gamma-hydroxybutyrate, topiramate) belong to several classes (Monti et al., 1993; O'Brien, 1997; Volpicelli et al., 1992). Despite some promising results, though, none of these medications is sufficiently effective in alcoholism and prognosis remains poor. Understanding the neurobiology of alcoholism will strongly contribute to the development of effective new pharmacotherapies for alcoholism.

Recently, a wealth of research has been focused on the identification of new targets for pharmacological treatments of alcohol addiction; among these are several peptidergic systems known for their established role in the regulation of stress response and anxiety (i.e., corticotropins, opioids, and tachykinins).

This symposium highlighted recent advances in our understanding of how these neuropeptidergic system activities may regulate responses to alcohol. The significance these systems as a treatment target for alcoholism was discussed.

## MTIP: a novel brain penetrant, orally available corticotrophin releasing hormone receptor 1 (CRH-R1) antagonist for treatment of alcoholism

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In clinical studies, stress is traditionally measured as the ability of external or internal stimuli to activate the hypothalamic-pituitary-adrenal (HPA) axis. Through activation of CRH-R1, CRH stimulates the synthesis and release of adrenocorticotropin (ACTH) by the anterior pituitary, which in turn stimulates the synthesis and release of cortisol by the adrenal cortex. Both enhanced and attenuated hormonal responses to stress are maladaptive. Chronic HPA axis dysregulation is associated with the development of mood disorders (Gold and Chrousos, 2002) and alcohol addiction (Sinha et al., 1999; Uhart et al., 2006). Studies in large cohorts of alcoholics demonstrated that 50–60% of patients simultaneously suffer from anxiety or depression disorders (Gratzer et al., 2004; Hettema et al., 2003). In approximately half of the patients, alcohol dependence preceded the manifestation of depressive or anxiety symptoms.

In the other half, depression or anxiety was the primary disorder (Hettema et al., 2003). Dysregulation of the brain CRH system (innate or resulting as a maladaptive response to drugs of abuse or stress) appears to be one of the major elements common to depression, anxiety and addiction (see for review Nemeroff et al., 2005). Preclinical studies have shown that physical, social, and emotional stress can facilitate acquisition or increase self-administration of ethanol in rodents and nonhuman primates (Mollenauer et al., 1993; Higley et al., 1991) and can elicit reinstatement of extinguished ethanol-seeking behavior in drug-free animals (Martin-Fardon et al., 2000; Le et al., 2000). These effects appear to be predominantly controlled by the extrahypothalamic CRH-R1 system. For example, it has been recently demonstrated that administration of various structurally-unrelated, selective CRH-R1 antagonists markedly reduces ethanol self-administration in animals with a history of alcohol dependence (Funk et al., 2006) and the central nucleus of the amygdala (CeA) has been shown to be the brain site of action of these compounds (Funk et al., 2006). The role of extrahypothalamic $CRH_1R$ in mediating the reinstatement of alcohol seeking behavior has also been demonstrated. For example, foot shock stress-induced reinstatement of extinguished ethanol responding is reversed by pretreatment with selective CRH antagonists but not by adrenalectomy (Le et al., 2000; Liu et al., 2002).

The present study described the development of a novel CRH-R1 antagonist with advantageous properties for clinical development, and its in vivo activity in preclinical alcoholism models. Experiments conducted in our laboratories showed that the newly synthesized CRH-1R antagonist 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (MTIP) inhibited 125I-sauvagine binding to rat pituitary membranes and cloned hCRH-R1 with sub-nanomolar affinities, with no detectable activity at the CRH-R2 receptor or other common drug targets. Following oral administration to rats, MTIP inhibited 125I-sauvagine binding to rat cerebellar membranes ex vivo with an ED50 of app. 1.3 mg/kg and an oral bioavailability of 91.1%. Compared to other well characterized CRH-1R antagonists, namely R121919 and CP154,526, MTIP had a markedly reduced volume of distribution and clearance. Neither open field activity nor baseline exploration of an elevated plus-maze was affected by MTIP (1–10mg/kg). In contrast, MTIP dose-dependently reversed anxiogenic effects of withdrawal from a 3 g/kg alcohol dose. Similarly, MTIP blocked excessive alcohol self-administration in Wistar rats with a history of dependence, and in a genetic model of high alcohol preference, the Marchigian Sardinian (msP) rat, at doses that had no effect in non-dependent Wistar rats. Also, MTIP blocked reinstatement of stress-induced alcohol seeking both in post-dependent, and in genetically selected msP animals, again at doses that were ineffective in non-dependent Wistar rats (Gehlert et al., 2007)

A large body of evidence indicates that up-regulated activity of the CRH system confers susceptibility for excessive self-administration of alcohol, and for relapse into alcohol seeking following abstinence. MTIP is a novel, orally available and brain penetrant CRH-R1 antagonist. Its activity in animal models predicts efficacy in alcohol dependence. Based on these findings, MTIP is a promising candidate for treatment of alcohol dependence.

## Urocortin 1 – a CRF-related peptide regulating alcohol intake

Andrey E. Ryabinin, Simranjit Kaur

The corticotrophin releasing hormone (CRH), also referred to as corticotrophin releasing factor (CRF), is a peptidergic system that has long been proposed to be involved in drug addiction and alcoholism (Dave and Eskay, 1986; Hawley et al., 1994; Inder et al., 1995; Koob, 1999; Rivier et al., 1984; Wand and Dobs, 1991; Wilkins and Gorelick, 1986). In mammals this system is composed of four endogenous ligands, namely, corticotropin–releasing factor, Urocortin (Ucn)1, Ucn 2, and Ucn 3 (Bale and Vale, 2004). CRF and Ucn 1 are known to act

on $CRF_1$ receptors, $CRF_2$ receptors, and/or the CRF-binding protein. CRF has greater affinity for the $CRF_1$ receptor than for the $CRF_2$ receptor whereas Ucn 1 acts at $CRF_1$ receptors and $CRF_2$ receptors with equal affinity. Ucn 2 and Ucn 3 act preferentially at $CRF_2$ receptors (Bale and Vale, 2004). Discovered first of the four ligands, CRF has attracted most attention in the addiction field. However, evidence is accumulating that Ucn 1 also may be important for addiction-related behaviors, specifically, for alcohol self-administration (Ryabinin and Weitemier, 2006).

In the brain, Ucn 1 is primarily synthesized in the perioculomotor Ucn 1-containing area (pIIIu), also known as the nonpreganglionic Edinger-Westphal nucleus, and to lesser extent, in the lateral superior olive (Bittencourt et al., 1999; Kozicz et al., 1998; May et al., 2008; Ryabinin et al., 2005; Vaughan et al., 1995; Weitemier and Ryabinin, 2005). The pIIIu exerts its actions via its projections to the lateral septum, dorsal raphe, spinal cord and other brain regions (Bachtell et al., 2003; Bittencourt et al., 1999; Weitemier et al., 2005).

Substantial evidence implicating Ucn 1 in alcohol self-administration has been obtained in mouse experimental models. First, various alcohol drinking paradigms in mice have demonstrated preferential induction of c-Fos expression in pIIIu (Bachtell et al., 1999; Ryabinin et al., 2001; Ryabinin et al., 2003; Sharpe et al., 2005). Second, higher levels of Ucn 1 immunoreactivity in pIIIu were found in ethanol-naïve, C57BL/6J mice, an inbred strain with spontaneously high alcohol preference, than in alcohol-avoiding DBA/2J mice, which show low ethanol preference (Bachtell et al., 2002; Weitemier et al., 2005). Moreover, HAP1 and HAP2 mice, selectively bred to prefer alcohol, also show higher pIIIu Ucn 1 immunostaining than LAP1 and LAP2 mice, selectively bred to avoid alcohol (Bachtell et al., 2003).

Evidence implicating Ucn 1 in alcohol self-administration in rats also exists. For example, it has been shown that ethanol dose-dependently increased c-Fos expression in the in pIIIu in genetically selected alcohol preferring AA (Alko alcohol) rats and in beer drinking Sprague-Dawley rats. No effects of saccharin on c-Fos expression were found (Weitemier et al., 2001)

In addition, genetic studies showed that Ucn 1 levels in the pIIIu were higher in 2 out of 5 rat lines selectively bred for high alcohol intake compared to lines showing low alcohol intake. A meta-analysis across five pairs of selectively-bred rat lines showed that alcohol-preferring lines had more Ucn 1 fibers in the lateral septum when compared to non-preferring lines (Turek et al., 2005).

Importantly, electrolytic lesions of the pIIIu block alcohol preference as well as ethanol-induced hypothermia in C57BL/6J mice (Bachtell et al., 2004), whereas bilateral injections of picomolar doses of Ucn 1, but not CRF, into the mouse lateral septum selectively attenuate alcohol self-administration during the expression phase as well as the acquisition phase of a limited access alcohol drinking procedure (Ryabinin et al., 2008). Taken together, these studies indicate that the Ucn 1-containing neurocircuit contributes to regulation of alcohol intake and should be strongly considered as a potential target in the pharmacotherapy of alcoholism.

## Neuropeptide Y in stress, anxiety, and alcoholism

Annika Thorsell, Andrea Cippitelli, Markus Heilig

Neuropeptide Y (Tatemoto et al 1982), a 36 amino acid peptide expressed at high levels within the mammalian nervous system, is an endogenous, anxiolytic neuropeptide that has been extensively examined in behavioral stress and anxiety paradigms. The effects of NPY are mediated by G-protein coupled receptors, 4 subtypes of which have been identified to date: Y1, Y2, Y4, and Y5 (review in Berglund et al., 2003). The Y1 and Y2 receptor subtypes are

found at significant levels with the central nervous system (CNS). Anti-anxiety effects of NPY have been shown to rely in part on activation of Y1 receptors in the amygdala (Heilig, 1995) and Y2 receptors may also play a role in the regulation of emotionality. NPY-Y2 receptors are located pre-synaptically on NPY-ergic neurons, and control the release of endogenous NPY (Wahlestedt et al., 1986). Here, we summarize our work looking at NPY in relation to stress, anxiety, and alcoholism.

NPY is an anxiolytic compound when admistered into the central nervous system. Furthermore, NPYs expression levels are affected by external stressors. When we examined the effect of a stressor on NPY expression within the amygdala we were able to show different effects following acute and repeated stress-exposure and to correlate this with anxiety-related behavior on the elevated plus-maze, leading to the conclusion that NPY-expression partakes in behavioral adaptation to stressors (Thorsell et al., 1998Thorsell et al., 1999). Furthermore, rats over-expressing NPY in the hippocampus lacked fear-linked suppression of behavior and demonstrated behavioral insensitivity to restraint stress measured on the elevated plus-maze (Thorsell et al., 2000).

NPY, being a potent, endogenous anxiolytic, is of interest in finding novel treatment targets for alcohol abuse and alcoholism. In a ground-breaking study published in 1998, the authors demonstrated, using genetically modified mice, that NPY levels are inversely related to ethanol intake (Thiele et al., 1998). Since NPY is exerting its anxiolytic effect primarily via the Y1-receptor (Heilig 1995, Karlsson et al 2008) compounds modifying would be of great interest. However, creating specific agonists to the NPY-Y1 receptor is chemically difficult. Following the theory that antagonism at the pre-synaptic Y2-receptor would mimic Y1-agonism, we instead used an Y2 antagonist, BIIE0246, and demonstrated that BIIE0246 does indeed suppress alcohol intake in both naïve (Thorsell et al 2002) and post-dependent animals (Rimondini et al., 2005). Studies of NPY-Y2 receptor knockout mice have supported this idea (Redrobe et al., 2003; Tschennett et al., 2003) and it is consistent with the anxiogenic-like effects of intra-amygdala treatment of Y2-preferring agonists in the rat social interaction test (Sajdyk et al., 1999). A novel brain-penetrant Y2-antagonist has been examined, however the results were negative (unpublished data) while the study reproduced previously published results (Rimondini et al., 2005). Also, intra-amygdala administration of a viral vector designed to over-express NPY was found to have anxiolytic-like properties and suppressed ethanol intake in the treated animals (Thorsell et al., 2007). As seen for the anxiolytic-like effects of NPY, the effects appear to be activity dependent. In summary, increasing NPY-levels or administering an antagonist to the presynaptic Y2-receptor, and thereby theoretically increasing the availability of NPY in the synaptic cleft, does decrease ethanol intake primarily in animals with a history of alcohol exposure. Thus, targeting the NPY system, possibly through antagonism at pre-synaptic Y2 auto-receptors, may still offer an attractive strategy for developing novel antidepressant and anti-anxiety treatments.

## The Nociceptin/Orphanin FQ as a target for the treatment of alcohol abuse

Roberto Ciccocioppo, Daina Economidou, Serena Stopponi, Nazzareno Cannella, Simone Braconi, Marsida Kallupi, Giordano de Gugliemo, Maurizio Massi.

Pharmacological, molecular, and genetic data generated at both the preclinical and clinical levels implicate numerous stress-related neuropetidergic systems in the regulation of aspects of alcohol abuse. Among these, substantial evidence indicates involvement of the Nociceptin/Orphain FQ N/OFQ system: several publications have demonstrated that N/OFQ regulates ethanol preference, ethanol reward, and ethanol-seeking behavior (Ciccocioppo et al., 2004; Economidou et al., 2006; Kuzmin, et al., 2007). Specifically, activation of NOP receptors by N/OFQ has been shown to inhibit home cage ethanol drinking as well as operant ethanol self-

administration (Ciccocioppo et al., 2004; Economidou et al., 2006). N/OFQ also reduces both ethanol-induced conditioned place preference and conditioned reinstatement of alcohol seeking (Ciccocioppo et al., 2004). Moreover, N/OFQ inhibits stress-induced ethanol-seeking and exerts general anti-stress effects by acting as a functional antagonist of extrahypothalamic corticotropin-releasing factor (CRH) transmission (Ciccocioppo et al., 2003; Martin-Fardon et al., 2000).

Previous studies have also shown that subchronic administration of N/OFQ or N/OFQ analogues significantly reduces ethanol self-administration in genetically selected alcohol preferring Marchigian Sardinian msP rats (Ciccocioppo et al., 2004; Economidou et al., 2006). In contrast, in nonselected Wistars tested under the same experimental conditions, N/OFQ did not alter ethanol consumption (Economidou et al., 2008). *In situ* hybridization studies revealed higher expression levels of N/OFQ and NOP receptor mRNA in numerous brain areas of msP compared to Wistar rats. In particular, significantly higher levels of N/OFQ mRNA have been found in the bed nucleus of the stria terminalis (BNST) and central amygdala (CeA) of msP rats; again, in these animals, the NOP receptor transcript was higher in the CeA and the basolateral amygdala (BLA). Receptor autoradiography revealed that these gene expression changes were accompanied by significant increases in NOP receptor binding within several brain areas, including the CeA, the BNST, the ventral tegmental area, and several cortical structures (Economidou et al., 2008).

These observations are indicative of an innate upregulation of the N/OFQ-NOP system in msP rats. However, while a consistent up-regulation of NOP receptor expression, binding and signaling was observed in msP rats in a majority of brain regions, a distinct and unexpected pattern of differences was found in the CeA. In this brain region, N/OFQ-stimulated [$^{35}$S] GTPγS binding was significantly lower in msP than in Wistars despite elevated NOP receptor expression and binding in the msP line. This finding suggests that although the N/OFQ system is generally upregulated in msP rats, “uncoupling” of the NOP receptor from G-protein-mediated signal transduction in CeA leads to a regionally-selective dysfunction of the N/OFQ system in the CeA. Consistent with the reduction of ethanol intake by N/OFQ in msP rats, the hypofunction of the system in the CeA may facilitate alcohol drinking in this line of rats. This hypothesis is supported by data showing that stimulation of NOP receptors in the CeA by site-specific microinjection of N/OFQ reduces alcohol self-administration in msP rat (Economidou et al., 2008).

Translation of neuropeptide-mediated effects into clinical treatments has typically proven difficult. However, recent data showing that the opioid agonist/partial agonist buprenorphine reduces alcohol intake in msP rats via activation of NOP receptors (Ciccocioppo et al., 2007) not only confirm a possible link between N/OFQ and excessive alcohol consumption, but suggest a possible path toward clinical applications. Buprenorphine has long been in clinical use for the treatment of pain (Picard et al., 1997) and management of heroin dependence (Johnson et al., 2000; Kakko et al., 2003). Our findings with buprenorphine provide “proof of concept” for the feasibility of targeting central NOP receptors via peripheral drug administration to suppress excessive alcohol intake. In addition, as reported in clinical studies, in heroin addicts, buprenorphine given at doses higher than those needed to occupy opioid receptors is beneficial in controlling cocaine addiction (Montoya et al., 2004): another study showed that in heroin addicts, it not only lowers opiate consumption, but also decreases alcohol intake (Kakko et al., 2003).

These findings point toward the possibility that these effects of buprenorphine are mediated by activation of NOP receptors. Altogether, these data provide strong rationale for the development of N/OFQ receptor agonists as new therapeutics for the treatment of alcohol addiction.

## Neurokinin 1 (NK1) receptor blockade: A novel anti-stress based mechanism for treatment of alcoholism

DT George, J Gilman, J Hersh, A Thorsell, DR Gehlert, JT Tauscher, SP Hunt, D Hommer and Markus Heilig

Behavioral sensitivity to stress increases as alcohol dependence evolves, and stress is a relapse trigger in alcoholism. Up-regulation of corticotropin-releasing hormone (CRH) signaling in extrahypothalamic brain sites contributes to these dependence-induced changes, but other stress-related neurotransmitters may also play a role. One such neurotransmittor is substance P (SP), which together with its preferred neurokinin 1 receptor (NK1R) is highly expressed in brain areas involved in stress responses and drug reward, including the hypothalamus, amygdala, and nucleus accumbens. In rodents, genetic deletion or pharmacological blockade of NK1R inhibits the associated behavioral responses, whereas psychological stressors induce release of SP in the amygdale (Holmes et al., 2003). In humans, the NK1 antagonist GR205171 reduces symptoms of social anxiety and suppresses brain responses to the Trier Social Stress Test (TSST) (Furmark et al., 2005). Together, these findings suggest that blockade of NK1Rs might modulate stress-related processes of importance for excessive alcohol use and relapse. To our knowledge, however, NK1 antagonism has not been examined in relation to alcoholism. In our recent studies we have therefore examined the role of the NK1 receptor system in the modulation of alcohol addiction. Specifically, we studied mice with disruption of the NK1 receptor gene, and found that these have markedly decreased voluntary alcohol consumption ($p=0.000001$; appr. 6 vs 10 g/kg/24 hrs at final alcohol concentration), and markedly higher alcohol sensitivity, shown as longer sleep-time following a sedative alcohol dose compared to wildtype littermates (186±14 min vs 104±16 min, $p<0.001$), despite unaltered alcohol metabolism. In anxious, recently detoxified alcoholic inpatients, a novel NK1 antagonist, LY686017, suppressed spontaneous cravings for alcohol (Alcohol Urge Questionnaire, AUQ 3; $p<0.05$) and improved overall well-being (Clinician Global Impression, CGI Severity 4; $p=0.001$) in the absence of effects on anxiety or depression. LY686017 also blunted craving induced by a combined social stress and alcohol cue challenge ($p=0.002$), and attenuated the concomitant cortisol response ($p=0.010$). Finally, brain fMRI BOLD responses to negative affective stimuli (IAPS) were attenuated in LY686017-treated subjects, while responses to positive stimuli were increased.

NK1 antagonism may thus offer another approach to alcoholism treatment based on attenuation of the stress that triggers craving and relapse; the consistent activity observed in studies indicates that this approach may prove clinically effective in treating alcoholism (George et al., 2008).

## Summary

The results of these investigations provide new insights into the correlation between alcohol abuse, the negative effects of stress and anxiety, and the function of different neuropetidergic systems. Of particular interest are data showing that progression of ethanol dependence can be facilitated by innate high sensitivity to stress or by recruitment of stress mechanisms by a history of ethanol intoxication. It has been shown, for example, that high ethanol drinking msP rats carry a mutation of the gene encoding for the CRH1R protein, conferring on these animals high sensitivity to stress and anxiety-like behavior that are attenuated by ethanol drinking. Interestingly, in these rats treatment with selective CRH1R antagonists like MTIP attenuates ethanol self-administration and relapse to ethanol seeking. Similar, but less robust effects of MTIP were observed in postdependent Wistar rats, while nondependent animals are less sensitive to inhibition of CRH neurotransmission.

Also of interest is the observation that Ucn 1, another peptide of the corticotrophin family, can modulate alcohol intake and preference. For example, it has been shown that this peptide system, primarily synthesized in the nonpreganglionic Edinger-Westphal nucleus, is overexpressed in mice and in rats with innate high ethanol preference and intake. In addition, it has been shown that alcohol but not saccharine exposure in mice induces preferential increase of c-Fos expression in this nucleus. Lastly, electrolytic lesions of the Edinger-Westphal nucleus block alcohol preference in high ethanol drinking mice (i.e., C57BL/6J); whereas Ucn 1 microinjection into the lateral septum selectively attenuates alcohol self-administration (Ryabinin et al., 2008).

Results of experiments with Neuropeptide Y, an endogenous anxiolytic neuropeptide also involved in behavioral adaptation to stressors, showed that when given ICV, it reduces alcohol intake in postdependent but not in nondependent rats. When a viral vector was used to over-express NPY in the amygdala, decreased alcohol intake and mild anxiolytic effect were observed in rats with a history of dependence. On the other hand, in animals with a history of ethanol exposure, administration of an antagonist to the presynaptic Y2-receptor, which theoretically increased the availability of NPY in the synaptic cleft, also decreased ethanol intake.

Results also point to the N/OFQ system as another important modulator of behaviors related to stress and alcohol abuse. For example, data showed that activation of NOP receptors by N/OFQ reduces home cage ethanol drinking and operant ethanol self-administration in msP rats. N/OFQ also reduces conditioned reinstatement and stress-induced reinstatement of ethanol-seeking in rats. These effects have been well documented in msP rats. In contrast, in nonselected Wistars, N/OFQ did not alter ethanol consumption. Neurochemical and molecular data demonstrated that N/OFQ function is upregulated in the brain of msP rats compared to nonselected Wistars, with the only exception of the CeA. In this area, in fact, due to "uncoupling" of the NOP receptor from G-protein-mediated signal transduction, the system is hypofunctional. It is noteworthy that stimulation of CeA NOP receptors by administration of the exogenous ligand potently and selectively reduces alcohol self-administration in msP rats.

Translation of neuropeptide-mediated effects into clinical treatments has typically proven difficult. However, recent data showing that the opioid agonist/partial agonist buprenorphine reduces alcohol intake in msP rats via activation of NOP receptors suggest a possible path toward rapid translation of these preclinical findings into clinical practice.

One example of successful translational research came from the study of the neurokinin NK1 system. In fact, starting from preclinical evidence indicating that NK1 receptors are highly expressed in brain areas involved in stress responses and drug reward and from findings showing that genetic deletion of these receptors in mice markedly decreases voluntary alcohol consumption and markedly higher alcohol sensitivity, a novel NK1 receptor antagonist, LY686017, was tested in anxious, recently detoxified alcoholics. Results showed that in these patients the drug significantly suppressed spontaneous cravings for alcohol and improved overall well-being. LY686017 also blunted craving induced by a combined social stress and alcohol cue challenge.

In conclusion, these studies demonstrate that several peptidic systems linked to stress regulation may also modulate alcohol addictive behaviors in laboratory animals and in humans. The study of these systems may provide new insights into the neurobiology of alcohol addiction. Moreover, drugs targeting these systems may have potential significance for the treatment of alcoholism.

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