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Emerging Pharmacotherapies for Alcohol Use Disorder

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Abstract

The identification of different stages within the alcohol use disorder (AUD) cycle that are linked to neurocircuitry changes in pathophysiology associated with the negative emotional states of abstinence has provided a view of medication development for AUD that emphasizes changes in the brain reward and stress systems. Alcohol use disorder can be defined as a chronic relapsing disorder that involves compulsive alcohol seeking and taking, loss of control over alcohol intake, and emergence of a negative emotional state during abstinence. The focus of early medications development was to block the motivation to seek alcohol in the *binge/intoxication* stage. More recent work has focused on reversing the motivational dysregulations associated with the *withdrawal/negative affect* and *preoccupation/anticipation* stages during protracted abstinence. Advances in our understanding of the neurocircuitry and neuropharmacological mechanisms that are involved in the development and maintenance of the *withdrawal/negative affect* stage using validated animal models have provided viable targets for future medications. Another major advance has been proof-of-concept testing of potential therapeutics and clinical validation of relevant pharmacological targets using human laboratory models of protracted abstinence. This review focuses on future targets for medication development associated with reversal of the loss of reward function and gain in brain stress function that drive negative reinforcement in the *withdrawal/negative affect* stage of addiction. Basic research has identified novel neurobiological targets associated with the *withdrawal/negative affect* stage and *preoccupation/anticipation* stage, with a focus on neuroadaptive changes within the extended amygdala that account for the transition to dependence and vulnerability to relapse.

Graphical Abstract

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Keywords

alcohol use disorder; alcoholism; medications development; neurobiology; stress

CONCEPTUAL FRAMEWORK FOR MEDICATIONS DEVELOPMENT IN ALCOHOL USE DISORDER

Alcohol Use Disorder (AUD) is a chronic, relapsing disorder that has been characterized by a compulsion to seek and take alcohol, the loss of control over alcohol intake, and the emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) that defines a motivational withdrawal syndrome when access to alcohol is prevented. Moderate to severe AUD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (American Psychiatric Association, 2013), can be considered to be operationally equivalent to the syndrome of alcoholism. Alcohol use disorder, like addiction, has been conceptualized as a three-stage cycle—*binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation*—that involves disruption in incentive salience, reward and stress, and executive function, respectively, mediated by changes in the corresponding neurocircuitry (for review, see Koob and Volkow, 2016). These neuroadaptations represent a break with homeostasis in the motivational domain and have been argued to represent a readjustment of parameters at a new set point but outside the homeostatic range, known as allostasis. In this context, both the loss of reward system function and the sensitization of stress systems lead to malaise, hypohedonia, anxiety, dysphoria, negative affect, pain, irritability, and sleep disturbances (defined as motivational withdrawal symptoms) which can drive alcohol seeking via negative reinforcement. Negative reinforcement is defined as the process by which removal of an aversive stimulus (or aversive state of abstinence from compulsive alcohol taking in the case of AUD) increases the probability of a response (relapse to drinking). Given the hypothesis that such negative reinforcement is one of the major driving factors for compulsivity in AUD, the reversal of reward deficits and stress surfeit in the *withdrawal/negative affect* stage of the AUD cycle becomes a compelling source of targets for medications for AUD.

CLINICAL TRIALS: CHALLENGES AND OPPORTUNITIES

Double-blind, placebo-controlled trials with random assignment to treatments are the accepted standard for determining drug efficacy in AUD. A primary challenge is obtaining access to an investigational compound with an approved Investigational New Drug (IND) application to the U.S. Food and Drug Administration (FDA) so that the drug can be tested in humans (see Koob et al., 2009, for further information regarding INDs for medications for the treatment of addiction), or identifying a drug already approved for another indication that could be repurposed for AUD.

There are then a number of unique features of clinical trials for medications for the treatment of AUD. These include challenges regarding the definition of clinically relevant outcome measures, admission criteria, and methods for detecting relapse to alcohol use between study visits. Issues related to adherence (formerly called “compliance”), placebo response, and drop-out rates continue to present challenges to the design and conduct of clinical trials in AUD. There are also AUD-specific safety and tolerability issues, particularly the potential pharmacokinetic and pharmacodynamic interactions between alcohol and the drug under study (for further details, see Koob et al., 2009).

HUMAN LABORATORY STUDIES: SCREENING DRUGS THAT TARGET THE WITHDRAWAL/NEGATIVE AFFECT STAGE IN ALCOHOL USE DISORDER

Human laboratory studies are a potentially powerful means of exploring treatment targets for specific components of the AUD cycle, independent of expensive and lengthy double-blind, placebo-controlled trials. Using the AUD cycle framework (Figure 1), human laboratory studies provide validated measures for each of the stages of AUD and have heuristic value for predicting potential treatment efficacy in these domains (Koob et al., 2009). In particular, accumulating data demonstrate the predictive validity of human laboratory models for medications that focus on the *withdrawal/negative affect* stage. Such models may include personalized stressful scripts and exposure to *in vivo* alcohol cues in abstinent alcoholics. The success of drugs for AUD in the real world will ultimately provide the proof-of-principle of the validity of animal models combined with human laboratory models as a springboard for the development of novel medications for AUD (Koob et al., 2009; Koob & Mason, 2016).

A model of stress-induced responsivity involves the playback of personalized stressful auditory scripts developed with the subject and recorded at the previous visit (Sinha, 2009). This method is based on the early work of Lang (1980) and elicits stress-related responses and stress-induced craving in individuals with AUD in a human laboratory setting. Here, individuals who used higher amounts of alcohol per week and subjects who were recovering from alcohol dependence showed greater craving and physiological responses to stressors compared with controls (i.e., social drinkers; Fox et al., 2007). From a validation perspective, stress-induced alcohol craving in the laboratory significantly predicted time to relapse (al’Absi et al., 2005) and showed positive results for prazosin (Fox et al., 2012). Studies that cross-reference pharmacological probes from animal and human studies can provide further support for the construct validity and predictive validity of pharmacological

targets for AUD and may provide an excellent basis for advancing compounds into the clinic.

A novel approach to screen potential therapeutics for reducing the risk of drinking relapse in protracted abstinence is the use of the cue reactivity model to evaluate the efficacy of medications (relative to placebo) in suppressing alcohol-induced craving in abstinent alcoholics (Mason et al., 2009). Non-treatment-seeking paid volunteers with current AUD are exposed to affective stimuli with positive or negative content and then to a beverage cue (their preferred alcohol beverage or bottled water control) but with no opportunity to self-administer alcohol. Exposing abstinent alcoholics to alcohol cues following the induction of affective states that are commonly linked to drinking relapse may serve as a powerful stressor in brain systems that are intrinsic to drinking relapse. Cue reactivity can be measured using subjective craving and psychophysiological measures (Mason et al., 2008), including heart rate, skin conductance, and facial electromyograms. Alcohol exposure and both positive and negative emotional cues are associated with significantly increased subjective craving, with confirmatory but less specific effects on psychophysiological measures (Mason et al., 2008). Gabapentin significantly decreased subjective alcohol-evoked craving in this model and also improved several measures of sleep quality in abstinent alcoholics (Mason et al., 2009). These outcomes were confirmed in independent clinical trials of gabapentin in AUD (Furieri et al., 2007; Brower et al., 2008; Mason et al., 2014). The convergence of human laboratory and clinical trial results suggest that cue reactivity, combined with an emotional overlay, may provide a powerful means of evaluating potential medications for the *withdrawal/negative affect* stage of protracted abstinence in AUD. Particularly compelling about this approach is that it reliably predicts efficacy in human double-blind, placebo-controlled trials. Positive results have been observed for three medications that showed efficacy in human laboratory studies and in double-blind, placebo-controlled trials: acamprosate, gabapentin, and pregabalin (Jonas et al., 2014; Mason et al., 2009; Mason et al., 2014; Mason 2015a; Mason 2015b). Additionally, the suppression of alcohol-induced craving in this model by administration of the glucocorticoid antagonist mifepristone, relative to placebo, predicted subsequent decreased drinking posttreatment (Vendruscolo et al., 2015). Particularly compelling is that these same medications also yielded positive results in animal models of withdrawal-induced drinking (see Koob and Mason, 2016).

NEUROBIOLOGICAL MECHANISMS IN ALCOHOL USE DISORDER THAT ARE RELEVANT TO NOVEL TARGETS FOR THE DEVELOPMENT OF MEDICATIONS ASSOCIATED WITH PROTRACTED ABSTINENCE

As noted above and previously reviewed, two processes are hypothesized to form the neurobiological basis for the *withdrawal/negative affect* stage: loss of function in the reward systems and recruitment of the brain stress systems in the extended amygdala (Koob and Mason, 2016; Tunstall et al., 2017). The extended amygdala has been conceptualized to be composed of several basal forebrain structures, including the bed nucleus of the stria terminalis (BNST), central nucleus of the amygdala (CeA), sublentiform substantia innominata, and a transition zone in the medial part of the nucleus accumbens (NAc; e.g.,

shell; Heimer and Alheid, 1991). As motivational withdrawal symptoms, defined above, develop, the brain reward systems become compromised. There are decreases in dopamine cell firing and dopamine D₂ receptors, both hypothesized to reflect hypodopaminergic states (Volkow et al., 2007), with additional changes in opioid transduction mechanisms that contribute to alcohol withdrawal (Chen and Lawrence, 2000). Brain stress systems, such as corticotropin-releasing factor (CRF), norepinephrine, dynorphin, hypocretin, and substance P, are also recruited, producing aversive or stress-like states, and brain anti-stress systems, such as neuropeptide Y (NPY), are downregulated (Koob and Le Moal, 2008; Carlezon et al., 2000). The thesis here is that the loss of reward systems and the recruitment of the central stress systems develop during the *withdrawal/negative affect* stage and persist into protracted abstinence (in the *preoccupation/anticipation* stage). Thus, the combination of decreases in reward neurotransmitter function and recruitment of brain stress systems provides a powerful motivation for relapse during both acute and protracted abstinence.

The global function of the prefrontal cortex is to engage executive function, and deficits in executive function are one of the hallmarks of AUD, particularly in the *preoccupation/anticipation* stage. However, superimposed on these deficits in executive function in the *preoccupation/anticipation* stage are residual deficits that carry over from the *withdrawal/negative affect* stage, termed protracted abstinence. Individuals with substance use disorders exhibit disruptions of executive function, such as impaired decision making and behavioral inhibition, which can contribute to craving, but the residual subcortical dysregulations associated with the *binge/intoxication* and *withdrawal/negative affect* stages probably are the driving force of relapse (Koob and Mason, 2016; Marlatt and Gordon, 1980).

A plethora of druggable targets can be derived from the basic neurobiology of AUD but remain a challenge for drug development because of the lack of INDs, lack of human laboratory testing, and the extraordinary expense of properly powered clinical trials. Briefly, the targets for each stage of the AUD cycle will be addressed but with a focus on neurobiological targets that are based on efficacy in models of the motivational components of the *withdrawal/negative affect* stage of the AUD cycle. Much early work focused on direct antagonism of the reinforcing effects of alcohol, representing the *binge/intoxication* stage, but such drugs can produce side effects that limit compliance (Mitchell et al., 2009). Thus, the following section will focus on two major domains—restoring reward system tone and decreasing brain stress system tone—as targets for medications development in AUD.

Reward Modulators: Partial Agonists

Two neurochemical systems in the basal forebrain have been implicated in alcohol reward: the mesocorticolimbic dopamine system and the opioid peptide system (Koob, 2014). The mesocorticolimbic dopamine system projects from the ventral tegmental area to basal ganglia forebrain sites, such as the NAc and CeA, and has been hypothesized to play a key role in incentive salience by directing behavior toward salient rewarding stimuli (Schultz, 2007). As such, activation of the mesocorticolimbic dopamine system appears to be involved in the incentive salience actions of alcohol. Opioid peptides in the basal ganglia and their transduction of activity via μ opioid receptors also play a key role in alcohol reward. They mediate affiliative behavior and hedonic responses and play a key role in the reinforcing

effects of opioids and alcohol (Le Merrer et al., 2009; Mitchell et al., 2012). The $\alpha 4\beta 2$ subunit of nicotinic acetylcholine receptors (nAChRs) has long been hypothesized to mediate rewarding effects via the phasic activation of signaling by dopamine and is intimately involved in the expression of nicotine reward and reinforcement and possibly alcohol reward (Tolu et al., 2013).

More importantly for the reward deficit contribution to the negative emotional state that drives compulsive alcohol seeking, both dopaminergic and opiodergic function are significantly compromised during acute withdrawal from alcohol (Weiss et al., 1992; Diana et al., 1993; Diana et al., 1995; Nestler, 1996). Animals that are sustained on an alcohol liquid diet during withdrawal show a decrease in extracellular levels of dopamine in the NAc (Weiss et al., 1996). Withdrawal from most major drugs of abuse is associated with decreases in the firing of dopaminergic neurons in the ventral tegmental area (Melis et al., 2005). Withdrawal from alcohol is accompanied by dramatic alterations in signal transduction mechanisms also associated with withdrawal from opioid peptides and opiates (Ron and Barak, 2016). Perhaps even more compelling, imaging studies have documented hypofunction in dopamine pathways during protracted withdrawal, reflected by a decrease in dopamine D₂ receptor expression and a decrease in dopamine release for alcohol (Koob and Volkow, 2016).

Partial agonists can be defined as drugs that bind to a receptor and have low efficacy, often with high affinity. As such, partial agonists will show antagonism when there is high agonist tone but agonism when there is low agonist tone. In terms of the AUD cycle outlined above, partial agonists could theoretically block the reinforcing effects of alcohol during the *binge/intoxication* stage but in addition block or blunt the negative motivational effects that characterize the *withdrawal/negative affect* stage. Two medications that are on the market for the treatment of addiction, buprenorphine and varenicline, have exactly such effects.

Buprenorphine is an oripavine derivative that is an opioid receptor partial agonist. It is an effective maintenance therapy for opioid addiction (Mello and Mendelson, 1980) and is widely used as a first-line treatment for addiction to opioids such as heroin and oxycodone, and to treat pain (Koob and Mason, 2016). Buprenorphine is functionally considered a partial agonist at μ and κ opioid receptors and at nociception/orphanin (NOP) receptors, and an antagonist at δ receptors. Differences in effects of buprenorphine depend on what opioid action is being measured. Buprenorphine has partial or full agonist properties in animal tests of analgesia, depending on the test employed. In humans, it is a full agonist for analgesia. Buprenorphine has a ceiling effect for producing respiratory depression, consistent with a partial agonist-like effect for this measure. However, use of buprenorphine with CNS depressants (e.g., alcohol or benzodiazepines) is contraindicated, as such combinations may lead to fatal respiratory depression (Center for Substance Abuse Treatment, 2004). Buprenorphine has been shown to have a dual action on alcohol consumption *per se* (Ciccocioppo et al., 2007). At low doses, it increased ethanol drinking in alcohol-preferring rats, an effect found with μ agonists and that was blocked by pretreatment with naltrexone. Conversely, at high doses, buprenorphine decreased ethanol intake, and this effect was not modified by naltrexone but was blocked by pretreatment with a selective NOP receptor

antagonist, suggesting the NOP against properties of buprenorphine may offer a target for medication development (Ciccocioppo et al., 2007).

Varenicline is a partial $\alpha 4\beta 2$ nAChR agonist that decreases relapse rates in smoking cessation in humans (Jorenby et al., 2006). Varenicline decreases nicotine-induced dopamine release in the NAc *in vivo* but also reverses the decrease in dopamine release of nicotine withdrawal (Rollema et al., 2007; Foulds et al., 2013) and decreases motivational measures of nicotine withdrawal (Igari et al., 2014; Foulds et al., 2006). Varenicline also has shown positive effects for the treatment of AUD in an multicenter, double-blind, placebo-controlled clinical trial, in which varenicline lowered weekly percent heavy drinking days, drinks per drinking day, and alcohol craving compared with the placebo group (Litten et al., 2013).

Given the role of dopamine in the acute reinforcing effects of drugs and its dysregulation during drug withdrawal, a reasonable hypothesis is that a more direct approach to re-regulating the reward deficit associated with the *withdrawal/negative affect* stage of the AUD cycle would be to develop a dopamine partial agonist. Indeed, dopamine D₂ partial agonists dose-dependently decreased the reinforcing effects of oral alcohol self-administration in nondependent rats (Pulvirenti and Koob, 2002). However, placebo-controlled studies with the partial agonist aripiprazole in the treatment of AUD have shown inconsistent results (Anton et al., 2008; Voronin et al., 2008), and dopamine-modulating drugs typically are associated with significant side effects. To date, no clinical studies have been performed with D₁ and D₃ partial agonists in AUD.

Glutamate Modulators

Glutamate has been hypothesized to play key roles in the neurobiology of craving in AUD, particularly alcohol-primed and cue-induced craving, and could provide potential targets for medications development. One hypothesis that may be compatible with subcortical changes involves glutamate dysregulation of the frontal cortex and the *preoccupation/anticipation* stage. Repeated self-administration of psychostimulants decreases the basal release of glutamate in key brain circuits that are associated with frontal cortex function, but an exaggerated glutamate response of activity in these circuits could convey sensitivity to relapse (Kalivas et al., 2003). For example, cue-induced reinstatement involves a glutamatergic projection to the NAc from both the basolateral amygdala and ventral subiculum (Everitt and Wolf, 2002; Vorel et al., 2001). α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists, *N*-methyl-D-aspartate (NMDA) receptor antagonists, metabotropic glutamate-2/3 receptor agonists, and metabotropic glutamate-5 receptor antagonists, all of which decrease glutamate function, have been shown to block cue-induced reinstatement (Backstrom and Hyttia, 2006).

Acute and protracted abstinence from alcohol that is described in preclinical models of AUD appears to involve overactive glutamatergic systems and is a target for the actions of acamprosate (de Witte et al., 2005; Littleton, 2007; Spanagel and Kiefer, 2008).

Acamprosate, approved by the FDA for the treatment of AUD, is clinically effective in maintaining abstinence in alcohol dependence (Jonas et al., 2014; Maisel et al., 2013) and is a functional antagonist of NMDA receptors, possibly via an action at regulatory polyamine

sites, and it may also act directly on metabotropic glutamate receptors to decrease glutamate activity (Littleton, 2007).

Studies with the anticonvulsant compound topiramate provide evidence of a potential AMPA/kainate target for glutamate modulation in AUD. Topiramate blocks AMPA/kainate receptors, in addition to allosterically modulating ion channel conductance (Shank et al., 2000). Double-blind, placebo-controlled clinical trials have reported decreases in drinking behavior in AUD and improvements in quality of life but with significant adverse effects on memory and concentration (Stringer et al., 2008; Olmsted and Kockler, 2008). Preclinical studies showed that topiramate decreased stress-induced increases in alcohol consumption and preference in mice (Farook et al., 2009). These results suggest that targeting the AMPA/kainate receptor system may be a strategy for restoring stress homeostasis. To date, however, side effects of topiramate itself appear to limit acceptability for routine clinical use in AUD.

CRF, Glucocorticoid, and Dynorphin- κ Opioid Receptor Antagonists: Brain Stress Systems as Targets for Medications for Alcohol Use Disorder

As noted above, brain neurochemical systems within the neurocircuitry of the brain stress systems mediate stress modulation and are activated during acute withdrawal from alcohol (Koob, 2008). Both the hypothalamic-pituitary-adrenal (HPA) axis and extrahypothalamic brain stress system that are mediated by CRF are dysregulated by chronic and/or compulsive administration of alcohol, with a common response of elevated adrenocorticotrophic hormone (ACTH), glucocorticoids, and amygdala CRF during acute withdrawal (Koob, 2013). Activation of the HPA response may also be an early dysregulation associated with excessive drinking that ultimately “sensitizes” the extrahypothalamic CRF systems (Koob and Kreek, 2007; Vendruscolo et al., 2012).

In rodent models, CRF receptor antagonists reverse anxiety-like and aversive-like responses during acute withdrawal and protracted abstinence from chronic and compulsive use of alcohol (Koob, 2013). CRF antagonists blocked the increased self-administration of alcohol in dependent rats during both acute withdrawal and protracted abstinence (Funk et al., 2007; Rimondini et al., 2002; Valdez et al., 2002; Gehlert et al., 2007). When administered directly into the CeA, a CRF₁/CRF₂ antagonist blocked alcohol self-administration in alcohol-dependent rats (Funk et al., 2006). CRF antagonists also reversed the elevation in reward thresholds produced by alcohol withdrawal (Bruijnzeel et al., 2010). All of these effects have been hypothesized to be mediated by actions in the extended amygdala (Koob, 2013). Human laboratory studies involving stress-induced craving methods (see above) evaluated the CRF₁ antagonists pexacerfont and verucerfont in treatment-seeking anxious alcoholics after 3 weeks of treatment in an inpatient unit (Kwako et al., 2015; Schwandt et al., 2016). Neither study found a drug effect on craving outcomes. The authors speculated that the effects of CRF₁ antagonists in preclinical models of AUD may not translate to humans with AUD. Alternatively, human laboratory studies typically test non-treatment-seeking outpatient alcoholics after a few days of abstinence, whereas the milieu effects of a 3-week inpatient stay in the treatment-seeking participants in these two studies may have blunted factors that underlie drug response.

Chronic alcohol use disrupts and dysregulates the HPA axis, and clinical reports have shown impaired stress responsivity in alcoholics (Lovallo et al., 2000; O'Malley et al., 2002; Adinoff et al., 2005). Although some individuals with AUD actually present symptomatology that mimics Cushing's syndrome (characterized by high glucocorticoids in blood), excessive HPA axis activation more commonly results in a blunted HPA axis response (for review, see Edwards et al., 2015). Drugs that are used to prevent relapse to heavy drinking, such as opioid receptor antagonists, activate the HPA axis, and sensitivity to this activation is most predominant in subjects with a strong family history of AUD (O'Malley et al., 2002; Wand et al., 1999; Kiefer et al., 2006). Animal models have shown similar effects, with a blunted corticosterone response in rats that were made dependent using the chronic intermittent alcohol vapor model (Richardson et al., 2008). Oral alcohol self-administration in rats stimulates the HPA axis to release ACTH and corticosterone but at the same time drives neuroadaptive changes in extrahypothalamic CRF systems in the extended amygdala. High corticosterone increases CRF mRNA in the CeA and lateral BNST, and decreases CRF mRNA in the paraventricular nucleus of the hypothalamus (Albeck et al., 1997; Makino et al., 1994a; Makino et al., 1994b; Shepard et al., 2000; Schulkin et al., 1998), thus contributing to both the blunted HPA response to chronic high-dose alcohol exposure and sensitization of the extrahypothalamic CRF responses. Thus, initial exposure to high corticosterone, stimulated by moderate to heavy drinking, may stimulate CRF expression in the CeA and lateral BNST, eventually leading to neuroadaptive changes, including further sensitization of CRF activation in the extended amygdala and decreased HPA function (Richardson et al., 2008). Glucocorticoid receptor signaling in the HPA axis and extrahypothalamic system may be a potential target for drug development because of a putative dual role, i.e., normalize reward function and desensitize stress systems (Vendruscolo et al., 2017).

Another neuropeptide that has long been hypothesized to contribute to negative emotional states is dynorphin. Hyperactivation of dopamine and opioid peptides has been hypothesized to produce subsequent activation of dynorphin systems, which in turn was hypothesized to decrease (via negative feedback) dopamine release and contribute to the dysphoric syndrome associated with drug withdrawal (Carlezon et al., 2000; Nestler, 2004). Dynorphins produce aversive dysphoric-like effects in animals and humans and have been hypothesized to mediate negative emotional states in general and more specifically to be associated with drug withdrawal (Koob, 2013; Shippenberg et al., 2007; Wee and Koob, 2010). The dynorphin- κ opioid system also mediates compulsive-like alcohol seeking associated with dependence in rodents. Excessive, compulsive-like alcohol self-administration can also be blocked by κ opioid receptor antagonists (Walker et al., 2010), and one site of action is hypothesized to be the shell of the NAc (Nealey et al., 2011).

Other pro-stress, pro-dysphoria-inducing brain neurotransmitter systems converge on the extended amygdala. In addition to CRF and dynorphin, evidence shows that norepinephrine, vasopressin, substance P, and hypocretin (orexin) may all contribute to negative emotional states associated with drug withdrawal, particularly alcohol withdrawal (Koob, 2008; Edwards et al., 2012; Koob, 2013; Barbier et al., 2013; Edwards et al., 2015; Schmeichel et al., 2015). Indeed, a recent multi-site, randomized controlled clinical trial showed that participants who received ABT-436, a novel vasopressin 1b antagonist that blocks a key

receptor of the stress neurotransmitter, vasopressin, experienced more days of alcohol abstinence. Furthermore, participants who reported high levels of stress responded better to ABT-436 as evidenced by decreases in both the frequency of drinking and the number of heavy drinking days (Ryan et al., 2016). Again, a likely target for these actions is the extended amygdala, suggesting that multiple distributed systems from the brainstem and hypothalamus converge in the extended amygdala to contribute to negative emotional states.

Neuropeptide Y, Nociceptin, Endocannabinoids and Oxytocin: Emotional Buffer Systems as Targets for Medications for Alcohol Use Disorder

Activation of the pro-stress systems promotes the negative emotional states that drive negative reinforcement during acute withdrawal and protracted abstinence and is multi-determined. However, a multi-determined anti-stress buffering system that may help return the organism to homeostasis when activated has also been hypothesized (Koob, 2008). Preclinical studies have identified four prominent neurotransmitter/neuromodulator systems that play a role in buffering the actions of pro-stress neurotransmitter systems: NPY, nociceptin, and endocannabinoids and oxytocin.

Neuropeptide Y is a neuropeptide that is hypothesized to exert effects that are opposite to CRF in the negative motivational state of withdrawal from drugs of abuse (Heilig and Koob, 2007). Neuropeptide Y has significant anxiolytic-like properties and is localized to multiple brain regions but also innervates the amygdala, a site hypothesized to be involved in its anxiolytic-like effects in rodents (Koob, 2013; Heilig and Koob, 2007). The hypothesis is that NPY acts as a buffer or homeostatic response to between-system neuroadaptations that can homeostatically regulate emotional systems in the brain (Heilig and Koob, 2007; Valdez and Koob, 2004).

Two other neurotransmitter systems, nociceptin and endocannabinoids, may have effects that buffer activation of the brain stress systems. Nociceptin (also known as orphanin FQ), is the endogenous ligand for the NOP receptor (formerly referred to as opioid receptor-like-1; Meunier et al., 1995; Reinscheid et al., 1995). Nociceptin generally attenuates stress-like responses and has a broad anxiolytic-like profile that extends to animal models of AUD (Ciccocioppo et al., 2003; Martin-Fardon et al., 2010). Substantial evidence shows increases in endocannabinoid production in response to stress and as such can regulate negative emotional states (Patel et al., 2005). The elevation of brain extracellular levels of endocannabinoids through the inhibition of endocannabinoid metabolism or reuptake mechanisms produces anxiolytic-like effects in various animal models of anxiety, particularly under stressful or aversive conditions, and a reduction of cannabinoid CB₁ receptor signaling can produce anxiogenic-like behavioral effects (Parsons and Hurd, 2015). Evidence also shows that drug-seeking behavior can be blocked by inhibiting endocannabinoid clearance (Parsons and Hurd, 2015; Serrano and Parsons, 2011). As with the other stress buffers discussed above, one could hypothesize that endocannabinoids play a protective role in preventing drug dependence by buffering stress activation associated with withdrawal, and thus, dysregulations in endocannabinoid function may also contribute to the negative affective disturbances associated with drug dependence and protracted withdrawal.

Oxytocin is a neuropeptide that is an emerging candidate as a stress buffer, which may have a role in modulating susceptibility to the development of dependence. Preclinical studies have shown that oxytocin inhibits the development of tolerance to multiple abused drugs, including alcohol, and may impact the development of dependence through its interactions with multiple systems, including dopamine, HPA axis and immune systems (Kovács et al., 1998).

Oxytocin is currently under investigation for the treatment of alcohol use disorder and withdrawal. Preliminary work has shown that intranasal oxytocin was superior to placebo in reducing symptoms of relatively mild alcohol withdrawal (Pedersen et al., 2013), and had a dual effect on alcohol craving in a human lab study: more socially anxious subjects with alcohol abuse showed decreased craving, and less socially anxious subjects showed increased craving, with oxytocin relative to placebo (Mitchell 2016). A survey of clinicaltrials.gov indicates a number of studies are currently investigating the therapeutic potential of oxytocin in alcohol use disorder.

Molecular-Cellular Correlates Predict Medication Targets

Molecular-cellular changes load the neurocircuits that drive the motivational set points described above that contribute to compulsive alcohol seeking. Such molecular targets become potential medication targets and range from molecules involved in the transduction of receptor-mediated events to growth factors that are involved in the regulation of growth, maintenance, proliferation, and survival of target neurons to transcription factors that activate specific genes. For example, it has long been known that chronic alcohol alters the function of cyclic adenosine monophosphate (cAMP)-dependent protein kinases, and the inhibition of protein kinases decreases alcohol consumption (Ron and Barak, 2016).

Targeting ubiquitous growth factors, such as brain-derived neurotrophic factor, in specific neurocircuits provides a means of more specifically accessing molecular targets of stress systems in specific brain regions to reverse the negative emotional states that drive compulsive alcohol seeking (Moonat et al., 2011). There are dynamic, short-term, and long-lasting changes that occur in the transcription factors FosB, cAMP response element binding protein (CREB), and nuclear factor κ B after chronic alcohol administration that modulate the synthesis of proteins that are involved in key aspects of synaptic plasticity associated with the AUD phenotype (Nestler, 2012). Such molecular targets also mediate cellular actions in the neurocircuitry discussed above; the actions of alcohol in the extended amygdala provide a representative example. Alcohol enhances the release of γ -aminobutyric acid (GABA) from GABAergic afferents or interneurons via either release from the same terminal, such as CRF, which then acts on CRF₁ receptors on the terminal to elicit the release of more GABA via a protein kinase C-mediated mechanism, or direct activation of CRF₁ receptors to elicit the release of more GABA (Bajo et al., 2008). CRF₁ antagonists and the drug gabapentin decrease presynaptic GABA release in dependent animals (Roberto et al., 2008; Roberto et al., 2010), and both CRF₁ antagonists and gabapentin block dependence-induced drinking in animal models. Gabapentin has also been shown to have efficacy in clinical trials (Brower et al., 2008; Furieri et al., 2007; Mason et al., 2014;). κ -Opioid antagonists may have similar effects as CRF₁ antagonists on cellular activity in the

CeA (Gilpin et al., 2014). Thus, CRF, dynorphin, and alcohol have been hypothesized to augment the inhibition of CeA projection interneurons (co-containing CRF, opioids, or NPY), leading to the excitation of downstream neurons through disinhibition (see Roberto review, this issue). Thus, the cellular actions parallel the neuropharmacological effects in animal models of compulsive drug taking and seeking, leading to a powerful preclinical framework for future drug development (Roberto and Gilpin, 2014). A focus on restoring motivational homeostasis by reversing acute withdrawal and protracted abstinence associated with the *withdrawal/negative affect* and *preoccupation/anticipation* (craving) stages of the addiction cycle reveals numerous preclinical targets for medications development for addiction.

Future Molecular-Genetic Approaches to Predict Medication Targets

The advent of “big data” in science has highlighted other approaches that capitalize on new information regarding molecular-genetic components involved in the neurocircuitry of brain development/plasticity and consequently have promise for identifying targets for interventions in addiction, some of which may not require a drug. From a molecular perspective, the National Institutes of Health Library of Integrated Network-based Cellular Signatures (LINCS) program (<http://www.lincsproject.org/>; accessed January 20, 2017) aims to create a network-based understanding of biology by cataloging changes in gene expression and other cellular processes that occur when cells are exposed to a variety of perturbing agents. Additionally, computational tools are being developed to integrate this diverse information into a comprehensive view of normal and disease states that can be applied to the development of new biomarkers and therapeutics. The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative in the United States (<http://braininitiative.nih.gov>; access January 20, 2017) and other initiatives abroad (<https://www.humanbrainproject.eu/>; accessed January 20, 2017) are developing new tools for assessing brain function *in vivo*. Such advances in new types of imaging techniques, including higher resolution functional magnetic resonance imaging, optogenetics, and a cutting-edge technique called CLARITY for assessing brain function *in vivo* (Chung and Deisseroth, 2013), will provide insights into new targets related to means of modulating neurocircuitry (Nussinov and Tsai, 2015; Day et al., 2015). Another National Institutes of Health initiative aims at “Illuminating the Druggable Genome” (<https://commonfund.nih.gov/idg/index>; accessed January 20, 2017) to improve our understanding of the properties and functions of proteins that are currently unannotated within the four most commonly drug-targeted protein families: G-protein-coupled receptors, nuclear receptors, ion channels, and protein kinases. Collectively, these innovative programs provide the scientific community with the resources and knowledge to propel and enable major discoveries in drug development to improve health and combat complex diseases.

Multiple genetic markers have been identified through classic genome-wide association studies (see Reilly review, this issue), and attempts are now being made to identify specific single-nucleotide polymorphisms (SNPs) in the human population that may predict not only vulnerability to endophenotypes associated with specific stages of the addiction cycle but also ultimately responses to medications. Work on genetic association studies that have

focused on the dysregulated stress systems outlined above are limited, but there are some preliminary studies with CRF and NPY.

A number of polymorphisms in human CRF system molecules have been associated with excessive alcohol use phenotypes, particularly in interactions with stress history. An association was found between binge drinking in adolescents and alcohol-dependent adults and SNPs of the CRF₁ receptor gene (Treutlein et al., 2006), and one of the SNPs could potentially influence transcription of the CRF₁ receptor gene. Furthermore, a stress history was shown to produce greater increases in future alcohol intake (Blomeyer et al., 2008; Schmid et al., 2010) and an earlier onset of drinking (Schmid et al., 2010) in adolescents who were homozygous for a SNP of the *Crhr1* gene. *Crhr1* SNPs also predicted greater alcohol consumption in individuals who were already dependent (Treutlein et al., 2006), and significant associations were found between P3 amplitude and alcohol dependence and multiple SNPs in the *Crhr1* gene (Chen et al., 2010).

Associations were also found between SNPs in the *NPY2R* gene and alcohol dependence, alcohol withdrawal symptoms, and comorbid alcohol and cocaine dependence (Wetherill et al., 2008). The specific polymorphism of the NPY gene has been linked to alcohol dependence (Bhaskar et al., 2013). Thus, should a medication become available that blocks CRF or facilitates NPY neurotransmission, one could speculate that some specific human genetic subgroups might be more responsive. Indeed, observations in a clinical study of AUD treatment with acamprosate that baseline serum glutamate levels are significantly higher in responders compared with non-responders and that serum glutamate levels of responders are normalized after acamprosate treatment, whereas there was no significant glutamate change in non-responders, suggest that there is a genetic predisposition that can predict responsiveness to acamprosate, suggesting ultimately a means of predicting which patients are likely to respond to which medication (Nam et al., 2015).

SUMMARY AND CONCLUSIONS

The thesis of this review is that medications development for AUD can benefit from use of a heuristic framework for stages of the AUD cycle linked to neurocircuitry and that dysregulation in the brain reward and stress systems that result in the symptoms of acute and protracted abstinence during the *withdrawal/negative affect* and *preoccupation/anticipation* stages of the AUD cycle are a neglected focus for drug development for AUD. Much previous work on medications for AUD focused on blocking the rewarding effects of drugs in the *binge/intoxication* stage of the AUD cycle, but identification of a clear role for the motivational signs of withdrawal as reflected by negative emotional states in the *withdrawal/negative affect* stage represent a compelling rationale for focusing on neurobiological targets in this domain. The dramatic surge in our understanding of the neurocircuitry and neuropharmacological mechanisms that are involved in the development and maintenance of the *withdrawal/negative affect* stage have provided numerous unique and viable targets for future drug development. Human laboratory models of the *withdrawal/negative affect* stage permit proof-of-concept testing of potential therapeutics, as well as preclinical and clinical validation of relevant pharmacological targets. Such a domain approach rather than

syndrome approach (Kwako et al., 2016) to drug development has the potential to reveal novel targets for drug development for AUD.

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References

- Abulseoud OA, Camsari UM, Ruby CL, Kasasbeh A, Choi S, Choi DS. Attenuation of ethanol withdrawal by ceftriaxone-induced upregulation of glutamate transporter EAAT2. *Neuropsychopharmacology*. 2014; 39:1674–1684. [PubMed: 24452391]
- al'Absi M, Hatsukami D, Davis GL. Attenuated adrenocorticotrophic responses to psychological stress are associated with early smoking relapse. *Psychopharmacology*. 2005; 181:107–117. [PubMed: 15834539]
- Adinoff B, Junghanns K, Kiefer F, Krishnan-Sarin S. Suppression of the HPA axis stress-response: implications for relapse. *Alcohol Clin Exp Res*. 2005; 29:1351–5. Erratum: 30(3):585. [PubMed: 16088999]
- Alaux-Cantin S, Buttollo R, Houchi H, Jeanblanc J, Naassila M. Memantine reduces alcohol drinking but not relapse in alcohol-dependent rats. *Addict Biol*. 2015; 20:890–901. [PubMed: 25138717]
- Albeck DS, McKittrick CR, Blanchard DC, Blanchard RJ, Nikulina J, McEwen BS, Sakai RR. Chronic social stress alters levels of corticotropin-releasing factor and arginine vasopressin mRNA in rat brain. *J Neurosci*. 1997; 17:4895–903. [PubMed: 9169547]
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5. Washington DC: American Psychiatric Publishing; 2013.
- Anton RF, Kranzler H, Breder C, Marcus RN, Carson WH, Han J. A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. *J Clin Psychopharmacol*. 2008; 28:5–12. [PubMed: 18204334]
- Backstrom P, Hyttia P. Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology*. 2006; 31:778–786. [PubMed: 16123768]
- Bajo M, Cruz MT, Siggins GR, Messing R, Roberto M. Protein kinase C ϵ mediation of CRF- and ethanol-induced GABA release in central amygdala. *Proc Natl Acad Sci U S A*. 2008; 105:8410–8415. [PubMed: 18541912]
- Barbier E, Vendruscolo LF, Schlosburg JE, Edwards S, Juergens N, Park PE, Misra KK, Cheng K, Rice KC, Schank J, Schulteis G, Koob GF, Heilig M. The NK1 receptor antagonist L822429 reduces heroin reinforcement. *Neuropsychopharmacology*. 2013; 38:976–984. [PubMed: 23303056]
- Bhaskar LV, Thangaraj K, Kumar KP, Pardhasaradhi G, Singh L, Rao VR. Association between neuropeptide Y gene polymorphisms and alcohol dependence: a case-control study in two independent populations. *Eur Addict Res*. 2013; 19:307–313. [PubMed: 23652361]
- Blomeyer D, Treutlein J, Esser G, Schmidt MH, Schumann G, Laucht M. Interaction between *CRHR1* gene and stressful life events predicts adolescent heavy alcohol use. *Biol Psychiatry*. 2008; 63:146–151. [PubMed: 17597588]
- Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. *Alcohol Clin Exp Res*. 2008; 32:1429–1438. [PubMed: 18540923]
- Bruijnzeel AW, Small E, Pasek TM, Yamada H. Corticotropin-releasing factor mediates the dysphoria-like state associated with alcohol withdrawal in rats. *Behav Brain Res*. 2010; 210:288–291. [PubMed: 20193713]
- Carlezon WA Jr, Nestler EJ, Neve RL. Herpes simplex virus-mediated gene transfer as a tool for neuropsychiatric research. *Crit Rev Neurobiol*. 2000; 14:47–67. [PubMed: 11253955]

- Center for Substance Abuse Treatment (US). DHHS publication No. (SMA) 04-3939. Rockville: Substance Abuse and Mental Health Services Administration; 2004. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) series 40.
- Chen AC, Manz N, Tang Y, Rangaswamy M, Almasy L, Kuperman S, Nurnberger J Jr, O'Connor SJ, Edenberg HJ, Schuckit MA, Tischfield J, Foroud T, Bierut LJ, Rohrbaugh J, Rice JP, Goate A, Hesselbrock V, Porjesz B. Single-nucleotide polymorphisms in corticotropin releasing hormone receptor 1 gene (*CRHR1*) are associated with quantitative trait of event-related potential and alcohol dependence. *Alcohol Clin Exp Res*. 2010; 34:988–996. [PubMed: 20374216]
- Chen F, Lawrence AJ. Effect of chronic ethanol and withdrawal on the mu-opioid receptor- and 5-Hydroxytryptamine_{1A} receptor-stimulated binding of [³⁵S]guanosine-5'-O-(3-thio)triphosphate in the fawn-hooded rat brain: a quantitative autoradiography study. *J Pharmacol Exp Ther*. 2000; 293:159–165. [PubMed: 10734165]
- Chu K, Koob GF, Cole M, Zorrilla EP, Roberts AJ. Dependence-induced increases in ethanol self-administration in mice are blocked by the CRF₁ receptor antagonist antalarmin and by CRF₁ receptor knockout. *Pharmacol Biochem Behav*. 2007; 86:813–821. [PubMed: 17482248]
- Chung K, Deisseroth K. CLARITY for mapping the nervous system. *Nat Methods*. 2013; 10:508–513. Erratum 2013;10:1035. [PubMed: 23722210]
- Ciccocioppo R, Economidou D, Fedeli A, Massi M. The nociceptin/orphanin FQ/NOP receptor system as a target for treatment of alcohol abuse: a review of recent work in alcohol-preferring rats. *Physiol Behav*. 2003; 79:121–128. [PubMed: 12818717]
- Ciccocioppo R, Economidou D, Rimondini R, Sommer W, Massi M, Heilig M. Buprenorphine reduces alcohol drinking through activation of the nociception/orphanin FQ-NOP receptor system. *Biol Psychiatry*. 2007; 61(1):4–12. [PubMed: 16533497]
- Day JJ, Kennedy AJ, Sweatt JD. DNA methylation and its implications and accessibility for neuropsychiatric therapeutics. *Annu Rev Pharmacol Toxicol*. 2015; 55:591–611. [PubMed: 25340930]
- de Witte P, Littleton J, Parot P, Koob G. Neuroprotective and abstinence-promoting effects of acamprostate: elucidating the mechanism of action. *CNS Drugs*. 2005; 19:517–537. [PubMed: 15963001]
- Diana M, Pistis M, Carboni S, Gessa GL, Rossetti ZL. Profound decrement of mesolimbic dopaminergic neuronal activity during ethanol withdrawal syndrome in rats: electrophysiological and biochemical evidence. *Proc Natl Acad Sci U S A*. 1993; 90:7966–7969. [PubMed: 8367449]
- Diana M, Pistis M, Muntoni A, Gessa G. Profound decrease of mesolimbic dopaminergic neuronal activity in morphine withdrawn rats. *J Pharmacol Exp Ther*. 1995; 272:781–785. [PubMed: 7853194]
- Edwards S, Guerrero M, Ghoneim OM, Roberts E, Koob GF. Evidence that vasopressin V1b receptors mediate the transition to excessive drinking in ethanol-dependent rats. *Addict Biol*. 2012; 17:76–85. [PubMed: 21309953]
- Edwards S, Little HJ, Richardson HN, Vendruscolo LF. Divergent regulation of distinct glucocorticoid systems in alcohol dependence. *Alcohol*. 2015; 49:811–6. [PubMed: 26003866]
- Everitt BJ, Wolf ME. Psychomotor stimulant addiction: a neural systems perspective. *J Neurosci*. 2002; 22:3312–3320. Erratum 2002;22(16):1a. [PubMed: 11978805]
- Farook JM, Lewis B, Littleton JM, Barron S. Topiramate attenuates the stress-induced increase in alcohol consumption and preference in male C57BL/6J mice. *Physiol Behav*. 2009; 96:189–193. [PubMed: 18786555]
- Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. *Int J Clin Pract*. 2006; 60:571–576. [PubMed: 16700857]
- Foulds J, Russ C, Yu CR, Zou KH, Galaznik A, Franzon M, Berg A, Hughes JR. Effect of varenicline on individual nicotine withdrawal symptoms: a combined analysis of eight randomized, placebo-controlled trials. *Nicotine Tob Res*. 2013; 15:1849–1857. [PubMed: 23694782]
- Fox HC, Anderson GM, Tuit K, Hansen J, Kimmerling A, Siedlarz KM, Morgan PT, Sinha R. Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. *Alcohol Clin Exp Res*. 2012; 36:351–360. [PubMed: 21919922]

- Fox HC, Bergquist KL, Hong KI, Sinha R. Stress-induced and alcohol cue-induced craving in recently abstinent alcohol-dependent individuals. *Alcohol Clin Exp Res*. 2007; 31:395–403. [PubMed: 17295723]
- Funk CK, O'Dell LE, Crawford EF, Koob GF. Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. *J Neurosci*. 2006; 26:11324–11332. [PubMed: 17079660]
- Funk CK, Zorrilla EP, Lee MJ, Rice KC, Koob GF. Corticotropin-releasing factor 1 antagonists selectively reduce ethanol self-administration in ethanol-dependent rats. *Biol Psychiatry*. 2007; 61:78–86. [PubMed: 16876134]
- Furieri FA, Nakamura-Palacios EM. Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2007; 68:1691–1700. [PubMed: 18052562]
- Gehlert DR, Cippitelli A, Thorsell A, Le AD, Hipskind PA, Hamdouchi C, Lu J, Hembre EJ, Cramer J, Song M, McKinzie D, Morin M, Ciccocioppo R, Heilig M. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine: a novel brain-penetrant, orally available corticotropin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism. *J Neurosci*. 2007; 27:2718–2726. [PubMed: 17344409]
- Gilpin NW. Neuropeptide Y (NPY) in the extended amygdala is recruited during the transition to alcohol dependence. *Neuropeptides*. 2012; 46:253–259. [PubMed: 22938859]
- Gilpin NW, Koob GF. Effects of β -adrenoceptor antagonists on alcohol drinking by alcohol-dependent rats. *Psychopharmacology*. 2010; 212:431–439. [PubMed: 20676608]
- Gilpin NW, Misra K, Koob GF. Neuropeptide Y in the central nucleus of the amygdala suppresses dependence-induced increases in alcohol drinking. *Pharmacol Biochem Behav*. 2008a; 90:475–480. [PubMed: 18501411]
- Gilpin NW, Richardson HN, Koob GF. Effects of CRF₁-receptor and opioid-receptor antagonists on dependence-induced increases in alcohol drinking by alcohol-preferring (P) rats. *Alcohol Clin Exp Res*. 2008b; 32:1535–1542. [PubMed: 18631323]
- Gilpin NW, Roberto M, Koob GF, Schweitzer P. Kappa opioid receptor activation decreases inhibitory transmission and antagonizes alcohol effects in rat central amygdala. *Neuropharmacology*. 2014; 77:294–302. [PubMed: 24157490]
- Heilig M, Koob GF. A key role for corticotropin-releasing factor in alcohol dependence. *Trends Neurosci*. 2007; 30:399–406. [PubMed: 17629579]
- Heimer, L., Alheid, G. Piecing together the puzzle of basal forebrain anatomy. In: Napier, TC, Kalivas, PW., Hanin, I., editors. *The Basal Forebrain: Anatomy to Function* (series title: *Advances in Experimental Medicine and Biology*. Vol. 295. New York: Plenum Press; 1991. p. 1-42.
- Hinton DJ, Lee MR, Jacobson TL, Mishra PK, Frye MA, Mrazek DA, Macura SI, Choi DS. Ethanol withdrawal-induced brain metabolites and the pharmacological effects of acamprosate in mice lacking ENT1. *Neuropharmacology*. 2012; 62:2480–2488. [PubMed: 22616110]
- Igari M, Alexander JC, Ji Y, Qi X, Papke RL, Buijnzeel AW. Varenicline and cytosine diminish the dysphoric-like state associated with spontaneous nicotine withdrawal in rats. *Neuropsychopharmacology*. 2014; 39:455–465. [PubMed: 23966067]
- Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA*. 2014; 311:1889–1900. [PubMed: 24825644]
- Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR. Efficacy of varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006; 296:56–63. Erratum 2006;296:1355. [PubMed: 16820547]
- Kalivas, PW., McFarland, K., Bowers, S., Szumlanski, K., Xi, ZX., Baker, D. Glutamate transmission and addiction to cocaine. In: Moghaddam, B., Wolf, ME., editors. *Glutamate and Disorders of Cognition and Motivation* (series title: *Annals of the New York Academy of Sciences*). Vol. 1003. New York: New York Academy of Sciences; 2003. p. 169-175.

- Kiefer F, Jahn H, Otte C, Naber D, Wiedemann K. Hypothalamic-pituitary-adrenocortical axis activity: a target of pharmacological anticraving treatment? *Biol Psychiatry*. 2006; 60:74–6. [PubMed: 16483549]
- Koob GF. A role for brain stress systems in addiction. *Neuron*. 2008; 59:11–34. [PubMed: 18614026]
- Koob GF. Addiction is a reward deficit and stress surfeit disorder. *Front Psychiatry*. 2013; 4:72. [PubMed: 23914176]
- Koob GF. Neurocircuitry of alcohol addiction: synthesis from animal models. In: Sullivan, EV., Pfefferbaum, A., editors. *Alcohol and the Nervous System* (series title: Handbook of Clinical Neurology). Vol. 125. Amsterdam: Elsevier; 2014. p. 33–54.
- Koob GF, Kreek MJ. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *Am J Psychiatry*. 2007; 164:1149–1159. [PubMed: 17671276]
- Koob GF, Le Moal M. Addiction and the brain antireward system. *Annu Rev Psychol*. 2008; 59:29–53. [PubMed: 18154498]
- Koob GF, Lloyd GK, Mason BJ. Development of pharmacotherapies for drug addiction: a Rosetta Stone approach. *Nat Rev Drug Discov*. 2009; 8:500–515. [PubMed: 19483710]
- Koob GF, Mason BJ. Existing and future drugs for the treatment of the dark side of addiction. *Annu Rev Pharmacol Toxicol*. 2016; 56:299–322. [PubMed: 26514207]
- Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016; 3:760–773. [PubMed: 27475769]
- Kovács GL, Sarnyai Z, Szabó G. Oxytocin and addiction: a review. *Psychoneuroendocrinology*. 1998; 23(8):945–62. [PubMed: 9924746]
- Kwako LE, Momenan R, Litten RZ, Koob GF, Goldman D. Addictions neuroclinical assessment: a neuroscience-based framework for addictive disorders. *Biol Psychiatry*. 2016; 80:179–189. [PubMed: 26772405]
- Kwako LE, Spagnolo PA, Schwandt ML, Thorsell A, George DT, Momenan R, Rio DE, Huestis M, Anizan S, Concheiro M, Sinha R, Heilig M. The corticotropin releasing hormone-1 (CRH1) receptor antagonist pexacerfont in alcohol dependence: a randomized controlled experimental medicine study. *Neuropsychopharmacology*. 2015; 40:1053–1063. [PubMed: 25409596]
- Lang, PJ. Behavioral treatment and bio behavioral assessment: computer applications. In: Sidowski, JB., Johnson, JH., editors. *Technology in Mental Health Care Delivery Systems*. Norwood: Ablex; 1980. p. 119–137.
- Le Merrer J, Becker JA, Befort K, Kieffer BL. Reward processing by the opioid system in the brain. *Physiol Rev*. 2009; 89:1379–1412. [PubMed: 19789384]
- Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, Green AI, Pettinati HM, Ciraulo DA, Sarid-Segal O, Kampman K, Brunette MF, Strain EC, Tiouririne NA, Ransom J, Scott C, Stout R. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. *J Addict Med*. 2013; 7:277–286. [PubMed: 23728065]
- Littleton JM. Acamprosate in alcohol dependence: implications of a unique mechanism of action. *J Addict Med*. 2007; 1:115–125. [PubMed: 21768946]
- Lovallo WR, Dickensheets SL, Myers DA, Thomas TL, Nixon SJ. Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. *Alcohol Clin Exp Res*. 2000; 24:651–8. [PubMed: 10832906]
- Makino S, Gold PW, Schulkin J. Corticosterone effects on corticotropin-releasing hormone mRNA in the central nucleus of the amygdala and the parvocellular region of the paraventricular nucleus of the hypothalamus. *Brain Res*. 1994a; 640:105–112. [PubMed: 8004437]
- Makino S, Gold PW, Schulkin J. Effects of corticosterone on CRH mRNA and content in the bed nucleus of the stria terminalis: comparison with the effects in the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus. *Brain Res*. 1994b; 657:141–9. [PubMed: 7820612]
- Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction*. 2013; 108:275–293. [PubMed: 23075288]

- Marlatt, G., Gordon, J. Determinants of relapse: implications for the maintenance of behavioral change. In: Davidson, P., Davidson, S., editors. *Behavioral Medicine: Changing Health Lifestyles*. New York: Brunner/Mazel; 1980. p. 410-452.
- Martin-Fardon R, Zorrilla EP, Ciccocioppo R, Weiss F. Role of innate and drug-induced dysregulation of brain stress and arousal systems in addiction: focus on corticotropin-releasing factor, nociceptin/orphanin FQ, and orexin/hypocretin. *Brain Res*. 2010; 1314:145–161. [PubMed: 20026088]
- Mason, BJ. Innovative Pharmacological Strategies to Treat Alcohol Use Disorder. 168th American Psychiatric Association (APA) Annual Meeting; Toronto, Ontario, Canada. 2015a;
- Mason, BJ. Identifying Potential Clinical Predictors of Acamprosate Response with a Human Laboratory Model of Protracted Withdrawal. 38th Annual Research Society on Alcoholism (RSA) Scientific Meeting; San Antonio, TX. 2015b;
- Mason BJ, Light JM, Williams LD, Drobos DJ. Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. *Addict Biol*. 2009; 14:73–83. [PubMed: 18855801]
- Mason BJ, Light JM, Escher T, Drobos DJ. Effect of positive and negative affective stimuli and beverage cues on measures of craving in non treatment-seeking alcoholics. *Psychopharmacology*. 2008; 200:141–150. [PubMed: 18604601]
- Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Intern Med*. 2014; 174:70–77. [PubMed: 24190578]
- Melis M, Spiga S, Diana M. The dopamine hypothesis of drug addiction: hypodopaminergic state. *Int Rev Neurobiol*. 2005; 63:101–154. [PubMed: 15797467]
- Mello NK, Mendelson JH. Buprenorphine suppresses heroin use by heroin addicts. *Science*. 1980; 207:657–659. [PubMed: 7352279]
- Meunier JC, Mollereau C, Toll L, Suaudeau C, Moisand C, Alvinerie P, Butour JL, Guillemot JC, Ferrara P, Monsarrat B, Mazarguil H, Vassart G, Parmentier M, Costentin J. Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. *Nature*. 1995; 377:532–535. [PubMed: 7566152]
- Mitchell JM, Bergren LJ, Chen KS, Rowbotham MC, Fields HL. Naltrexone aversion and treatment efficacy are greatest in humans and rats that actively consume high levels of alcohol. *Neurobiol Dis*. 2009; 33:72–80. [PubMed: 18955144]
- Mitchell JM, O'Neil JP, Janabi M, Marks SM, Jagust WJ, Fields HL. Alcohol consumption induces endogenous opioid release in the human orbitofrontal cortex and nucleus accumbens. *Sci Trans Med*. 2012; 4:116ra6.
- Mitchell JM, Arcuni PA, Weinstein D, Woolley JD. Intranasal oxytocin selectively modulates social perception, craving, and approach behavior in subjects with alcohol use disorder. *J Addict Med*. 2016; 10(3):182–9. [PubMed: 27159342]
- Moonat S, Sakharkar AJ, Zhang H, Pandey SC. The role of amygdaloid brain-derived neurotrophic factor, activity-regulated cytoskeleton-associated protein and dendritic spines in anxiety and alcoholism. *Addict Biol*. 2011; 16:238–250. [PubMed: 21182574]
- Mutschler J, Abbruzzese E, von der Goltz C, Dinter C, Mobascher A, Thiele H, Diaz-Lacava A, Dahmen N, Gallinat J, Majic T, Petrovsky N, Kornhuber J, Thuerauf N, Gründer G, Brinkmeyer J, Wienker T, Wagner M, Winterer G, Kiefer F. Genetic variation in the neuropeptide Y gene promoter is associated with increased risk of tobacco smoking. *Eur Addict Res*. 2012; 18:246–252. [PubMed: 22584873]
- Nam HW, Karpyak VM, Hinton DJ, Geske JR, Ho AM, Prieto ML, Biernacka JM, Frye MA, Weinshilboum RM, Choi DS. Elevated baseline serum glutamate as a pharmacometabolomic biomarker for acamprosate treatment outcome in alcohol-dependent subjects. *Transl Psychiatry*. 2015; 5:e621. [PubMed: 26285131]
- Nealey KA, Smith AW, Davis SM, Smith DG, Walker BM. κ -Opioid receptors are implicated in the increased potency of intra-accumbens nalmefene in ethanol-dependent rats. *Neuropharmacology*. 2011; 61:35–42. [PubMed: 21338616]
- Nestler EJ. Under siege: the brain on opiates. *Neuron*. 1996; 16:897–900. [PubMed: 8630245]

- Nestler EJ. Historical review: molecular and cellular mechanisms of opiate and cocaine addiction. *Trends Pharmacol Sci.* 2004; 25:210–218. [PubMed: 15063085]
- Nestler EJ. Transcriptional mechanisms of drug addiction. *Clin Psychopharmacol Neurosci.* 2012; 10:136–143. [PubMed: 23430970]
- Nussinov R, Tsai CJ. The design of covalent allosteric drugs. *Annu Rev Pharmacol Toxicol.* 2015; 55:249–267. [PubMed: 25149918]
- Okahisa Y, Ujike H, Kotaka T, Morita Y, Kodama M, Inada T, Yamada M, Iwata N, Iyo M, Sora I, Ozaki N, Kuroda S. Association between neuropeptide Y gene and its receptor Y1 gene and methamphetamine dependence. *Psychiatry Clin Neurosci.* 2009; 63:417–422. [PubMed: 19566775]
- Olmsted CL, Kockler DR. Topiramate for alcohol dependence. *Ann Pharmacother.* 2008; 42:1475–1480. [PubMed: 18698008]
- O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. *Psychopharmacology.* 2002; 160:19–29. [PubMed: 11862370]
- Overstreet DH, Knapp DJ, Breese GR. Drug challenges reveal differences in mediation of stress facilitation of voluntary alcohol drinking and withdrawal-induced anxiety in alcohol-preferring P rats. *Alcohol Clin Exp Res.* 2007; 31:1473–1481. [PubMed: 17624999]
- Parsons LH, Hurd YL. Endocannabinoid signalling in reward and addiction. *Nat Rev Neurosci.* 2015; 16:579–594. [PubMed: 26373473]
- Patel S, Roelke CT, Rademacher DJ, Hillard CJ. Inhibition of restraint stress-induced neural and behavioural activation by endogenous cannabinoid signaling. *Eur J Neurosci.* 2005; 21:1057–1069. [PubMed: 15787710]
- Pedersen CA, Smedley KL, Leserman J, Jarskog LF, Rau SW, Kampov-Polevoi A, Casey RL, Fender T, Garbutt JC. Intranasal oxytocin blocks alcohol withdrawal in human subjects. *Alcohol Clin Exp Res.* 2013; 37(3):484–9. [PubMed: 23025690]
- Pulvirenti L, Koob GF. Being partial to psychostimulant addiction therapy. *Trends Pharmacol Sci.* 2002; 23:151–153. [PubMed: 11931978]
- Qiang M, Li JG, Denny AD, Yao JM, Lieu M, Zhang K, Carreon S. Epigenetic mechanisms are involved in the regulation of ethanol consumption in mice. *Int J Neuropsychopharmacol.* 2014; 18(2) pii: pyu072.
- Reinseheid RK, Nothacker HP, Bourson A, Ardati A, Henningsen RA, Bunzow JR, Grandy DK, Langen H, Monsma FJ Jr, Civelli O, Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor. *Science.* 1995; 270:792–794. [PubMed: 7481766]
- Richardson HN, Zhao Y, Fekete EM, Funk CK, Wirsching P, Janda KD, Zorrilla EP, Koob GF. MPZP: a novel small molecule corticotropin-releasing factor type 1 receptor (CRF1) antagonist. *Pharmacol Biochem Behav.* 2008; 88:497–510. [PubMed: 18031798]
- Rimondini R, Arlind C, Sommer W, Heilig M. Long-lasting increase in voluntary ethanol consumption and transcriptional regulation in the rat brain after intermittent exposure to alcohol. *FASEB J.* 2002; 16:27–35. [PubMed: 11772933]
- Rimondini R, Thorsell A, Heilig M. Suppression of ethanol self-administration by the neuropeptide Y (NPY) Y2 receptor antagonist BIIE0246: evidence for sensitization in rats with a history of dependence. *Neurosci Lett.* 2005; 375:129–133. [PubMed: 15670655]
- Roberto M, Cruz MT, Gilpin NW, Sabino V, Schweitzer P, Bajo M, Cottone P, Madamba SG, Stouffer DG, Zorrilla EP, Koob GF, Siggins GR, Parsons LH. Corticotropin releasing factor-induced amygdala gamma-aminobutyric acid release plays a key role in alcohol dependence. *Biol Psychiatry.* 2010; 67:831–839. [PubMed: 20060104]
- Roberto M, Gilpin NW, O'Dell LE, Cruz MT, Morse AC, Siggins GR, Koob GF. Cellular and behavioral interactions of gabapentin with alcohol dependence. *J Neurosci.* 2008; 28:5762–5771. [PubMed: 18509038]
- Roberto, M., Gilpin, NW. Central amygdala neuroplasticity in alcohol dependence. In: Noronha, A.Cui, C.Harris, A., Crabbe, J., editors. *Neurobiology of Alcohol Dependence*. New York: Elsevier; 2014. p. 207-220.

- Rollema H, Chambers LK, Coe JW, Glowa J, Hurst RS, Lebel LA, Lu Y, Mansbach RS, Mather RJ, Rovetti CC, Sands SB, Schaeffer E, Schulz DW, Tingley FD 3rd, Williams KE. Pharmacological profile of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology*. 2007; 52:985–994. [PubMed: 17157884]
- Ron D, Barak S. Molecular mechanisms underlying alcohol-drinking behaviours. *Nat Rev Neurosci*. 2016; 17:576–591. [PubMed: 27444358]
- Ryan ML, Falk DE, Fertig JB, Rendenbach-Mueller B, Katz DA, Tracy KA, Strain EC, Dunn KE, Kampman K, Mahoney E, Ciraulo DA, Sickles-Colaneri L, Ait-Daoud N, Johnson BA, Ransom J, Scott C, Koob GF, Litten RZ. A phase 2, double-blind, placebo-controlled randomized trial assessing the efficacy of ABT-436, a novel V1b receptor antagonist, for alcohol dependence. *Neuropsychopharmacology*. 2016; in press. doi: 10.1038/npp.2016.214
- Sabino V, Cottone P, Koob GF, Steardo L, Lee MJ, Rice KC, Zorrilla EP. Dissociation between opioid and CRF1 antagonist sensitive drinking in Sardinian alcohol-preferring rats. *Psychopharmacology*. 2006; 189:175–186. [PubMed: 17047935]
- Schmeichel BE, Barbier E, Misra KK, Contet C, Schlosburg JE, Grigoriadis D, Williams JP, Karlsson C, Pitcairn C, Heilig M, Koob GF, Vendruscolo LF. Hypocretin receptor 2 antagonism dose-dependently reduces escalated heroin self-administration in rats. *Neuropsychopharmacology*. 2015; 40:1123–1129. [PubMed: 25367502]
- Schmid B, Blomeyer D, Treutlein J, Zimmermann US, Buchmann AF, Schmidt MH, Esser G, Rietschel M, Banaschewski T, Schumann G, Laucht M. Interacting effects of CRHR1 gene and stressful life events on drinking initiation and progression among 19-year-olds. *Int J Neuropsychopharmacol*. 2010; 13:703–714. [PubMed: 19607758]
- Schulkin J, Gold PW, McEwen BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. *Psychoneuroendocrinology*. 1998; 23:219–43. [PubMed: 9695128]
- Schultz W. Multiple dopamine functions at different time courses. *Annu Rev Neurosci*. 2007; 30:259–288. [PubMed: 17600522]
- Schwandt ML, Cortes CR, Kwako LE, George DT, Momenan R, Sinha R, Grigoriadis DE, Pich EM, Leggio L, Heilig M. The CRF1 antagonist verucerfont in anxious alcohol-dependent women: translation of neuroendocrine, but not of anti-craving effects. *Neuropsychopharmacology*. 2016; 41:2818–2829. [PubMed: 27109623]
- Serrano A, Parsons LH. Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. *Pharmacol Ther*. 2011; 132:215–241. [PubMed: 21798285]
- Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia*. 2000; 41(Suppl 1):S3–S9.
- Shepard JD, Barron KW, Myers DA. Corticosterone delivery to the amygdala increases corticotropin-releasing factor mRNA in the central amygdaloid nucleus and anxiety-like behavior. *Brain Res*. 2000; 861:288–95. [PubMed: 10760490]
- Shippenberg TS, Zapata A, Chefer VI. Dynorphin and the pathophysiology of drug addiction. *Pharmacol Ther*. 2007; 116:306–321. [PubMed: 17868902]
- Sinha R. Modeling stress and drug craving in the laboratory: implications for addiction treatment development. *Addict Biol*. 2009; 14:84–98. [PubMed: 18945295]
- Skelly MJ, Weiner JL. Chronic treatment with prazosin or duloxetine lessens concurrent anxiety-like behavior and alcohol intake: evidence of disrupted noradrenergic signaling in anxiety-related alcohol use. *Brain Behav*. 2014; 4:468–483. [PubMed: 25161814]
- Smith AW, Nealey KA, Wright JW, Walker BM. Plasticity associated with escalated operant ethanol self-administration during acute withdrawal in ethanol-dependent rats requires intact matrix metalloproteinase systems. *Neurobiol Learn Mem*. 2011; 96:199–206. [PubMed: 21530666]
- Spanagel R, Kiefer F. Drugs for relapse prevention of alcoholism: ten years of progress. *Trends Pharmacol Sci*. 2008; 29:109–115. [PubMed: 18262663]
- Stringer S, Rueve M, Mossman D. Topiramate as treatment for alcohol dependence. *JAMA*. 2008; 299:405–406.

- Tolu S, Eddine R, Marti F, David V, Graupner M, Pons S, Baudonnat M, Husson M, Besson M, Reperant C, Zemdegs J, Pagès C, Hay YA, Lambolez B, Caboche J, Gutkin B, Gardier AM, Changeux JP, Faure P, Maskos U. Co-activation of VTA DA and GABA neurons mediates nicotine reinforcement. *Mol Psychiatry*. 2013; 18:382–393. [PubMed: 22751493]
- Treutlein J, Kissling C, Frank J, Wiemann S, Dong L, Depner M, Saam C, Lascorz J, Soyka M, Preuss UW, Rujescu D, Skowronek MH, Rietschel M, Spanagel R, Heinz A, Laucht M, Mann K, Schumann G. Genetic association of the human corticotropin releasing hormone receptor 1 (CRHR1) with binge drinking and alcohol intake patterns in two independent samples. *Mol Psychiatry*. 2006; 11:594–602. [PubMed: 16550213]
- Tunstall BJ, Carmack SA, Koob GF, Vendruscolo LF. Dysregulation of brain stress systems mediates compulsive alcohol drinking. *Current Opinion in Behavioral Sciences*. 2017; 13:85–90. [PubMed: 28603755]
- Valdez GR, Koob GF. Allostasis and dysregulation of corticotropin-releasing factor and neuropeptide Y systems: implications for the development of alcoholism. *Pharmacol Biochem Behav*. 2004; 79:671–689. [PubMed: 15582675]
- Valdez GR, Roberts AJ, Chan K, Davis H, Brennan M, Zorrilla EP, Koob GF. Increased ethanol self-administration and anxiety-like behavior during acute withdrawal and protracted abstinence: regulation by corticotropin-releasing factor. *Alcohol Clin Exp Res*. 2002; 26:1494–1501. [PubMed: 12394282]
- Vendruscolo LF, Barbier E, Schlosburg JE, Misra KK, Whitfield T Jr, Logrip ML, Rivier CL, Repunte-Canonigo V, Zorrilla EP, Sanna PP, Heilig M, Koob GF. Corticosteroid-dependent plasticity mediates compulsive alcohol drinking in rats. *J Neurosci*. 2012; 32:7563–7571. [PubMed: 22649234]
- Vendruscolo LF, Estey D, Goodell V, Macshane LG, Logrip ML, Schlosburg JE, McGinn MA, Zamora-Martinez ER, Belanoff JK, Hunt HJ, Sanna PP, George O, Koob GF, Edwards S, Mason BJ. Glucocorticoid receptor antagonism decreases alcohol seeking in alcohol-dependent individuals. *J Clin Invest*. 2015; 125:3193–3197. [PubMed: 26121746]
- Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Jayne M, Ma Y, Pradhan K, Wong C. Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. *J Neurosci*. 2007; 27:12700–12706. [PubMed: 18003850]
- Vorel SR, Liu X, Hayes RJ, Spector JA, Gardner EL. Relapse to cocaine-seeking after hippocampal theta burst stimulation. *Science*. 2001; 292:1175–1178. [PubMed: 11349151]
- Voronin K, Randall P, Myrick H, Anton R. Aripiprazole effects on alcohol consumption and subjective reports in a clinical laboratory paradigm: possible influence of self-control. *Alcohol Clin Exp Res*. 2008; 32:1954–1961. [PubMed: 18782344]
- Walker BM, Koob GF. The γ -aminobutyric acid-B receptor agonist baclofen attenuates responding for ethanol in ethanol-dependent rats. *Alcohol Clin Exp Res*. 2007; 31:11–18. [PubMed: 17207096]
- Walker BM, Koob GF. Pharmacological evidence for a motivational role of κ -opioid systems in ethanol dependence. *Neuropsychopharmacology*. 2008; 33:643–652. [PubMed: 17473837]
- Walker BM, Rasmussen DD, Raskind MA, Koob GF. α 1-Noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. *Alcohol*. 2008; 42:91–97. [PubMed: 18358987]
- Walker BM, Zorrilla EP, Koob GF. Systemic κ -opioid receptor antagonism by nor-binaltorphimine reduces dependence-induced excessive alcohol self-administration in rats. *Addict Biol*. 2010; 16:116–119.
- Wand GS, Mangold D, Ali M. Adrenocorticotropin responses to naloxone in sons of alcohol-dependent men. *J Clin Endocrinol Metab*. 1999; 84:64–8. [PubMed: 9920063]
- Wee S, Koob GF. The role of the dynorphin- κ opioid system in the reinforcing effects of drugs of abuse. *Psychopharmacology*. 2010; 210:121–135. [PubMed: 20352414]
- Weiss F, Markou A, Lorang MT, Koob GF. Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. *Brain Res*. 1992; 593:314–318. [PubMed: 1450939]
- Weiss F, Parsons LH, Schulteis G, Hyttia P, Lorang MT, Bloom FE, Koob GF. Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-

hydroxytryptamine release in dependent rats. J Neurosci. 1996; 16:3474–3485. [PubMed: 8627380]

Wetherill L, Schuckit MA, Hesselbrock V, Xuei X, Liang T, Dick DM, Kramer J, Nurnberger JI Jr, Tischfield JA, Porjesz B, Edenberg HJ, Foroud T. Neuropeptide Y receptor genes are associated with alcohol dependence, alcohol withdrawal phenotypes, and cocaine dependence. Alcohol Clin Exp Res. 2008; 32:2031–2040. [PubMed: 18828811]

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Highlights

Early drug development for AUD focused on blocking the motivation to seek alcohol

A new focus is reversing motivational dysregulation associated with protracted abstinence

Validated animal models provide targets to normalize brain stress/reward systems in AUD

Human lab models of protracted abstinence provide POC screening of potential drugs for AUD

Figure 1.

Novel targets by stage of the alcohol use disorder cycle with corresponding clinical states.

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