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NEUROCHEMICAL MECHANISMS OF ALCOHOL WITHDRAWAL

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Abstract

Alcohol dependence encompasses a serious medical and societal problem that constitutes a major public health concern. A serious consequence of dependence is the emergence of symptoms associated with the alcohol withdrawal syndrome when drinking is abruptly terminated or substantially reduced. Clinical features of alcohol withdrawal include signs of central nervous system hyperexcitability, heightened autonomic nervous system activation, and a constellation of symptoms contributing to psychologic discomfort and negative affect. The development of alcohol dependence is a complex and dynamic process that ultimately reflects a maladaptive neurophysiologic state. Perturbations in a wide range of neurochemical systems, including glutamate, γ-aminobutyric acid, monoamines, a host of neuropeptide systems, and various ion channels produced by the chronic presence of alcohol ultimately compromise the functional integrity of the brain. These neuroadaptations not only underlie the emergence and expression of many alcohol withdrawal symptoms, but also contribute to enhanced relapse vulnerability as well as perpetuation of uncontrolled excessive drinking. This chapter highlights the hallmark features of the alcohol withdrawal syndrome, and describes neuroadaptations in a wide array of neurotransmitter and neuromodulator systems (amino acid and monoamine neurotransmitter, neuropeptide systems, and various ion channels) as they relate to the expression of various signs and symptoms of alcohol withdrawal, as well as their relationship to the significant clinical problem of relapse and uncontrolled dangerous drinking.

Keywords

alcohol dependence; alcohol withdrawal syndrome; neuroadaptations; neurochemical adaptations; glutamate; GABA; monoamines; neuropeptides; ion channels

INTRODUCTION

Alcohol abuse and alcoholism are significant public health concerns that continue to exact enormous burdens on the healthcare industry as well as producing a broad range of societal

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problems, including judicial (e.g., crime), economic (e.g., damage/loss of property, reduced productivity in the workplace) and, most tragically, collateral damage to personal/family relationships. While many individuals abuse alcohol without being dependent on the drug, continued excessive alcohol consumption can lead to the development of dependence.

A serious consequence of dependence is the emergence of symptoms associated with the alcohol withdrawal syndrome. When drinking is abruptly terminated or substantially reduced in the dependent individual, a characteristic withdrawal syndrome ensues. Clinical features of alcohol withdrawal include signs of central nervous system (CNS) hyperexcitability, heightened autonomic nervous system activation and, in its most severe form, hallucinosis and delirium tremens (Saitz, 1998; Becker, 2000). In addition to physical signs of withdrawal, a constellation of symptoms contributing to psychologic discomfort and negative affect constitutes a prominent component of the withdrawal syndrome (Becker, 2008; Koob, 2013). While many of the signs and symptoms of withdrawal abate within 5–7 days, some symptoms (primarily those related to mood and emotional disturbances) have been reported to linger on for a protracted period of time (Heilig et al., 2010). Moreover, it has been suggested that the negative affective or emotional components of withdrawal, while more subtle in nature, may constitute significant motivational factors that lead to resumption of alcohol-seeking behavior (relapse) (Becker, 2012, 2013; Koob, 2013). The high rate of recidivism in alcoholism underscores the relapsing nature of the disease. Thus, it is not uncommon for alcohol-dependent individuals to experience multiple episodes of withdrawal, with repeated attempts at abstinence tragically failing and individuals reverting back to excessive, unhealthy drinking habits.

The development of alcohol dependence is a complex and dynamic process that ultimately reflects a maladaptive neurophysiologic state. Perturbations in a wide range of neurochemical systems produced by the chronic presence of alcohol contribute to significant changes in neural activity (neuroadaptations) that ultimately compromise the functional integrity of the brain. Indeed, the development of alcohol dependence is thought to reflect an allostatic state fueled by progressive dysregulation of neurophysiologic systems beyond normal homeostatic limits (Koob and Le Moal, 2001). Many of these neuroadaptive changes associated with dependence are integral to brain reward and stress systems (e.g., Hansson et al., 2008; Koob and Le Moal, 2008). Indeed, manifestations of this allostatic state not only underlie the emergence and expression of many alcohol withdrawal symptoms, but also contribute to persistent vulnerability to relapse. Additionally, the potential for alcohol to alleviate discomfort associated with withdrawal-related stress/dysphoria may serve as a powerful motivational force that not only enhances relapse vulnerability, but also favors escalation of alcohol drinking to even higher levels. This chapter highlights the hallmark features of the alcohol withdrawal syndrome, and describes neuroadaptations in a wide array of neurotransmitter and neuromodulator systems as they relate to the expression of various signs and symptoms of alcohol withdrawal, as well as their relationship to the significant clinical problem of relapse and uncontrolled dangerous drinking.

SIGNS AND SYMPTOMS OF THE ALCOHOL WITHDRAWAL SYNDROME

CNS Hyperexcitability

A hallmark feature of the alcohol withdrawal syndrome is general CNS hyperexcitability. This is thought to reflect compensatory neural activity, induced by the depressant effects of alcohol, that is unmasked when the drug is withdrawn from the brain (Finn and Crabbe, 1997; Littleton, 1998; Becker, 2000). Both electrographic and behavioral measures of withdrawal-related seizure activity have been extensively documented in animals and humans (Victor, 1970; Deitrich et al., 1996; Porjesz and Begleiter, 1996; Becker, 2000). Electrographic measures include increased frequency of spontaneous as well as evoked perturbations in electroencephalogram (EEG) activity that include spike and sharp-wave epileptiform activity and more global synchronized high-voltage spindling activity. In animal studies, motor convulsions may occur spontaneously, but can be more readily elicited by exposure to sensory stimuli (e.g., audiogenic), handling manipulation, electroconvulsive stimulation, and various chemoconvulsant agents. Both electrographic and behavioral measures of withdrawal-related seizure activity in animals are highly sensitive to clinically effective anticonvulsants (Crabbe, 1992; Becker, 1996; Watson et al., 1997; Becker and Veatch, 2002; Veatch and Becker, 2005). In humans, sophisticated quantitative frequency analysis of EEG (power spectral analysis) has revealed more subtle and long-lasting functional CNS alterations resulting from chronic alcohol exposure and withdrawal (Sand et al., 2010). Detecting subtle (subclinical) indices of seizure-like activity may be particularly important in light of evidence indicating that repeated withdrawal experience (even relatively mild such episodes) may result in sensitization or a “kindling” effect of withdrawal (Ballenger and Post, 1978; Becker, 1996, 1998).

Kindling of alcohol withdrawal is thought to reflect a process whereby seizure activity (and other withdrawal symptoms) progressively worsens with repeated detoxification experiences. It has been postulated that such a process may underlie the commonly observed progression of withdrawal symptoms from relatively mild responses (e.g., irritability, tremors) characteristic of initial withdrawal episodes to more severe symptoms (e.g., seizures) associated with subsequent withdrawal episodes (Ballenger and Post, 1978). Indeed, a number of clinical studies involving retrospective analyses have reported a positive relationship between the likelihood of seizures occurring during a given withdrawal episode and a history of previous detoxifications (Brown et al., 1988; Lechtenberg and Worner, 1991; Moak and Anton, 1996). An increased risk of seizures in alcoholics with a history of multiple detoxifications is of clinical significance since poorer prognosis and a higher mortality rate have been reported for patients presenting with alcohol withdrawal-related seizures in contrast to individuals with seizures of unknown etiology (Pieninkeroinen et al., 1992). Further, a history of multiple previous detoxifications was reported to be associated with more severe and medically complicated withdrawal syndromes, as well as an increased likelihood of hospital readmission for alcohol-related problems (Booth and Blow, 1993). Preclinical studies have provided critical support and validation of these findings, demonstrating progressive intensification of withdrawal symptoms over repeated withdrawal experiences (Becker, 1998, 1999). From a treatment perspective, detecting withdrawal-related CNS perturbations may be important, as early intervention may be significant in

quelling a kindling-like process and providing preventive care for alcoholics (Malcolm et al., 2000, 2002; Veatch and Becker, 2005).

Enhanced sensory reactivity is also thought to reflect heightened CNS excitability during alcohol withdrawal. In humans, this is typically measured by assessing a startle response (eye blink) to an auditory stimulus. In contrast to the dampening effect of alcohol on acoustic startle amplitude in healthy controls (Grillon et al., 1994), exaggerated startle responses have been reported in detoxified alcohol-dependent subjects (Krystal et al., 1997; Schellekens et al., 2012). In several animal studies the startle response has been measured in response to auditory or tactile (air puff) stimuli following withdrawal from chronic alcohol exposure, but these studies have generally yielded mixed results, i.e., startle reactivity has been reported to be increased, decreased, or unchanged during alcohol withdrawal (Rassnick et al., 1992; Macey et al., 1996; Ponomarev and Crabbe, 1999; Vandergriff et al., 2000; Chester et al., 2005; Chester and Barrenha, 2007; Reilly et al., 2009). Deficits in prepulse inhibition of the startle response have been suggested to be related to increased risk for alcoholism (Grillon et al., 2000), and a study in rats indicated that this phenotype may be predictive of more severe withdrawal symptoms following subsequent chronic alcohol exposure (Kayir et al., 2010).

Autonomic Nervous System Hyperactivity

An array of physiologic symptoms commonly experienced during withdrawal reflect manifestations of heightened autonomic nervous system activity, more specifically, increased sympathetic activity (e.g., Hawley et al., 1994; King et al., 1994; Patkar et al., 2003; Kahkonen, 2004; Rasmussen et al., 2006). These include tachycardia, increased blood pressure, diaphoresis (heavy sweating), body temperature dysregulation, and gastrointestinal disturbances (nausea, vomiting). Animal models have demonstrated many of these classic sympathomimetic withdrawal symptoms, including altered cardiovascular function (Kashkin et al., 2008; Shirafuji et al., 2010), central and behavioral thermal dysregulation (Crawshaw et al., 1994), and gastrointestinal-related symptoms, such as diarrhea and reduced food and water intake (Friedman, 1980; Kliethermes, 2005). Most of these symptoms resolve within the acute phase of withdrawal. Given evidence indicating elevated sympathetic activity associated with alcohol withdrawal, it is not surprising that drugs that reduce noradrenergic tone, such as adrenergic beta-blockers and alpha-2 agonists, have been shown to be useful as adjuncts for treatment of alcohol withdrawal symptoms related to sympathetic overdrive (Mayo-Smith, 1997; Riihioja et al., 1997; Muzyk et al., 2011).

Tremor is another frequent symptom of alcohol withdrawal, and it is thought to emerge as a manifestation of sympathetic hyperactivity (Koller et al., 1985; Charles et al., 1999). Animal studies have used subjective rating scores (Frye et al., 1983; Bone et al., 1989) as well as more quantitative measures (Macey et al., 1996) to demonstrate increased tremor during withdrawal. Interestingly, while mostly anecdotal, human alcoholics often report resumption of drinking linked to a desire to self-medicate the “shakes” (tremor) during early abstinence. In this vein, it is interesting that alcohol withdrawal has been reported to potentiate the tremorogenic effects of nicotine (Gothoni and Ikola, 1985). Thus, the high prevalence/

comorbidity of alcohol and nicotine dependence may relate, at least in part, to alcohol's ability to moderate tremor resulting from alcohol withdrawal as well as nicotine use.

Sleep Disturbances

A common complaint among alcoholics is disruption in sleep, which typically emerges during early periods of abstinence and often extends to the more protracted phase of abstinence (Brower et al., 2001; Landolt and Gillin, 2001; Cohn et al., 2003; Colrain et al., 2009; Brower and Perron, 2010). Insomnia during abstinence is characterized by fragmentation of sleep architecture that manifests as increased sleep latency, reduced total sleep, compromised sleep efficiency, and a transient increase (rebound) in rapid-eye movement sleep. Animal studies employing techniques to measure EEG in freely moving rats (Ehlers and Slawecki, 2000; Kubota et al., 2002) and mice (Veatch, 2006; Wiggins et al., 2013) undergoing alcohol withdrawal have demonstrated significant and long-lasting alterations in sleep architecture that are similar to those observed in human alcoholics during abstinence. Chronic alcohol exposure and withdrawal also have been shown to alter circadian clock function (which is critical for regulation of the wake–sleep cycle) in rats (Rosenwasser et al., 2005; Sharma et al., 2010) and mice (Seggio et al., 2009; Brager et al., 2010; Logan et al., 2012). Likewise, disruptions in circadian clock function have been noted in human alcoholics during abstinence (Brower et al., 2001; Rosenwasser, 2001), and there is recent evidence for decreased expression of several circadian clock genes (Huang et al., 2010a) as well as a polymorphism in one of the genes (*Per3*) that is associated with insomnia severity in alcohol-dependent subjects (Brower et al., 2012). Clinical studies have noted the self-reported link between disrupted sleep during abstinence and increased risk of relapse (Clark et al., 1998; Drummond et al., 1998; Feige et al., 2007; Malcolm et al., 2007; Steinig et al., 2011; Smith et al., 2013). It is noteworthy that a number of clinical studies have recently begun to evaluate treatment strategies for addressing this aspect of the abstinence syndrome, especially in the context of relapse prevention (Le Bon et al., 2003; Staner et al., 2006; Malcolm et al., 2007; Brower et al., 2008).

Measures of Psychologic Discomfort and Negative Affect

Anxiety—Increased anxiety represents a significant component of the alcohol withdrawal syndrome. In humans, anxiety emerges during the early abstinence phase and in many cases lingers for an extended period of time. Of significance, the psychologic discomfort associated with anxiety experienced during abstinence, even after most acute physical symptoms have subsided, has been suggested to play a prominent role in increasing risk for relapse as well as perpetuating continued use/abuse of alcohol (Roelofs, 1985; Becker, 1999; Koob and Le Moal, 2001; Schneider et al., 2001). Indeed, both preclinical and clinical studies suggest a link between anxiety and propensity to self-administer alcohol (Spanagel et al., 1995; Willinger et al., 2002; Barrenha and Chester, 2007), although this relationship is by no means simple in animals or human alcoholics (Schuckit and Hesselbrock, 1994; Henniger et al., 2002; Correia et al., 2009; Heilig et al., 2010).

A number of experimental procedures have been used to demonstrate increased behavioral anxiety in animal models of alcohol dependence and withdrawal (Becker, 2000; Kliethermes, 2005). Many of these models involve procedures that exploit the natural

tendency for rodents to avoid environments that may be considered dangerous or threatening and, thereby, elicit an internal state of “fear” or “anxiety” (e.g., bright open spaces). For example, behavioral measures of elevated anxiety during withdrawal have been demonstrated in animals, as indexed by reduced activity in the central portions of an open field arena or in open quadrants of a maze (e.g., elevated plus/zero mazes), reduced entries (increased avoidance) of a brightly illuminated portion of a two-compartment chamber (light–dark box test), and reduced social interaction behavior in a novel environment (Becker, 2000; Kliethermes, 2005). While these models have been effectively used to document alcohol withdrawal-related behavioral measures of anxiety, results have sometimes been variable (especially in studies using mice) due to a number of confounds, most notably, non-specific reductions in general activity (Kliethermes, 2005). Nevertheless, anxiety and other symptoms reflective of a state of psychologic discomfort (e.g., irritability, agitation) are firmly established as clinically significant components of the alcohol withdrawal syndrome. In fact, many treatments commonly used for managing detoxification (e.g., benzodiazepines) not only serve to reduce life-threatening aspects of the syndrome (e.g., grand mal seizures), but also target symptoms such as anxiety that contribute to negative affect and increased relapse vulnerability.

Heightened Stress Responsiveness—Increased stress reactivity is another feature of alcohol withdrawal that has been studied in humans and animal models. In many instances, heightened stress responsiveness persists long after physical signs and even many overt psychologic symptoms of withdrawal have dissipated. Although complaints about irritability and increased sensitivity to everyday stressors have long been recognized clinically in alcoholic patients, corresponding human data are just beginning to emerge. For example, an increased stress response (elevated heart rate and cortisol levels) was reported in abstinent alcoholics following exposure to a social stressor (Trier Social Stress test), with the effect modified by the degree of drinking history and duration of abstinence prior to testing (Starcke et al., 2013). Recent neuroimaging (functional magnetic resonance imaging) studies have demonstrated exaggerated brain responses to visual stimuli that evoked negative emotions, with results suggesting altered functional neural connectivity indicative of aberrant cortical modulation of emotional processing (George et al., 2008; Gilman and Hommer, 2008; O’Daly et al., 2012). There is also evidence indicating that alcohol-dependent patients abstinent for 4–8 months exhibit altered brain activation in response to stress- or alcohol-relevant cues (as opposed to neutral cues), and this altered cortical activation was predictive of greater relapse susceptibility and severity (Seo et al., 2013). Collectively, these results add to a growing body of literature that indicates abstinent alcohol-dependent individuals display stress-induced emotional and physiologic dysregulation along with dysfunctional brain activity, which all contribute to increased alcohol craving and relapse vulnerability (Sinha, 2013).

Similarly, increased behavioral reactivity to stress following chronic alcohol exposure and withdrawal has also been demonstrated in animals. For example, enhanced response to stress- induced anxiety has been reported in alcohol-dependent rats using a number of testing protocols, with the effects often persisting over a long period of time (months) following withdrawal (Valdez et al., 2003; Breese et al., 2005; Rylkova et al., 2009; Huang

et al., 2010b; Gillett et al., 2013). Of clinical significance, a history of chronic alcohol exposure and withdrawal has been shown to enhance the ability of stress to trigger relapse-like behavior in animal models (Le et al., 2000; Liu and Weiss, 2002a; Gehlert et al., 2007; Marinelli et al., 2007; Sommer et al., 2008). Clinical and experimental evidence indicates that increased sensitivity to stress during abstinence reflects, in large part, adaptations in neuroendocrine and brain stress systems induced by chronic alcohol exposure (see below). Taken together, enhanced stress reactivity in dependent subjects has both physiologic implications as well as cognitive/behavioral potential for influencing relapse vulnerability.

Anhedonia/dysphoria—Another common feature of the alcohol withdrawal syndrome relates to anhedonia, i.e., a reduced ability to derive pleasure from events/stimuli typically perceived as rewarding. Although anecdotal reports have long noted the significance of this dysphoric aspect of alcohol withdrawal, recent clinical studies have used a number of assessment instruments to better quantify the subjective anhedonic/dysphoric state that has been shown, in many cases, to endure for a protracted period of time during abstinence (Janiri et al., 2005; Martinotti et al., 2008; Pozzi et al., 2008; Hatzigiakoumis et al., 2011). Withdrawal-related anhedonia has typically been modeled in animal studies using an intracranial self-stimulation (ICSS) procedure. For example, during withdrawal from chronic alcohol exposure, rats have been shown to exhibit significant increases in ICSS threshold (i.e., the minimal amount of electrical stimulation delivered to reward pathways in the brain that is perceived as rewarding) (Schulteis et al., 1995; Chester et al., 2006; Rylkova et al., 2009). It has been suggested that a dopamine hypofunctional state may underlie anhedonia/dysphoria associated with protracted withdrawal (Heinz et al., 1995; Diana et al., 1996; Weiss et al., 1996; Bailey et al., 2001; Martinez et al., 2005), although other neuroadaptive changes (e.g., corticotropin-releasing factor (CRF), dynorphin/kappa opiate receptors) undoubtedly play a contributory role as well (Heilig and Koob, 2007; Shippenberg et al., 2007). Recently, some clinical studies have targeted withdrawal-related anhedonia in efforts to treat alcohol-dependent subjects (Martinotti et al., 2010, 2011).

NEUROCHEMICAL ADAPTATIONS PRODUCED BY CHRONIC ALCOHOL AND WITHDRAWAL

Prolonged excessive alcohol consumption sets in motion a host of neuroadaptive changes initially triggered to compensate for, and mitigate effects of, continued presence of alcohol in the brain. With continued drinking, adaptations in other systems not initially affected by alcohol emerge that contribute to a state of CNS disequilibrium and dysfunction. When abstinence is attempted and alcohol is eliminated from the CNS, manifestations of these adaptations are unveiled, as evidenced by the expression of myriad signs and symptoms that constitute the alcohol withdrawal syndrome (Fig. 9.1). As previously noted, many of these adaptations also have significant motivational implications with regard to increased relapse vulnerability and excessive drinking, both characteristic of dependence. This section will provide an overview of adaptations in a wide array of neurochemical and neuromodulatory systems associated with alcohol dependence, with particular emphasis on their relationship to various signs and symptoms of the alcohol withdrawal syndrome, as well as their

postulated role in underlying enhanced relapse susceptibility and perpetuation of excessive, unhealthy alcohol consumption.

Adaptations In Amino Acid Neurotransmitter Systems

The amino acids glutamate and γ-aminobutyric acid (GABA) are the major excitatory and inhibitory neurotransmitters, respectively, in the CNS. While alcohol initially facilitates the inhibitory actions of GABA and inhibits excitatory effects mediated by glutamate transmission, chronic alcohol exposure results in compensatory changes in these amino acid transmitter systems that are opposite in nature and revealed upon withdrawal. Manifestations of this resultant imbalance in GABA-mediated inhibition and glutamate-mediated excitation in the CNS are known to underlie expression of various withdrawal symptoms, most notably CNS hyperexcitability (Becker, 1998; Littleton, 1998; Hillbom et al., 2003). Indeed, it is well established that neuroadaptations in glutamatergic and GABAergic signaling systems following chronic alcohol exposure play a prominent role in mediating a variety of dependence and withdrawal-related sequlae (Fadda and Rossetti, 1998; Lovinger and Roberto, 2013).

Glutamate—The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) subtypes of glutamate receptors are among the most widely distributed and abundant receptors in the brain. AMPA receptors are heterotetramers comprising GluR1–4 subunits and mediate most fast synaptic neurotransmission. NMDA receptors are also heterotetramers and are composed of an obligatory GluN1 subunit co-assembled with a least one type of regulatory GluN2A–D subunit. The majority of NMDA receptors in the adult brain are composed of GluN2A and GluN2B subunits. NMDA receptors mediate the slow component of excitatory postsynaptic potentials. Glutamate also operates at two metabotropic receptor subtypes: mGluR1-like (mGlur1 and mGluR5) and mGluR2-like (mGluR2, mGluR3, and mGluR4). Both ionotropic (AMPA and NMDA) and metabotropic (mGluRs) receptors have been implicated in a wide array of alcohol-associated phenotypes, including those related to dependence and withdrawal.

Compensatory changes produced by chronic alcohol exposure produce a hyperglutamatergic state in the brain that underlies increased susceptibility to chronic alcohol exposure/withdrawal-induced neurotoxicity (Stepanyan et al., 2008; Prendergast and Mulholland, 2012) and altered synaptic plasticity (Chandler et al., 2006; McCool et al., 2010; Holmes et al., 2012; Zorumski et al., 2014). Also resulting is behavioral expression of several withdrawal symptoms, particularly those associated with CNS hyperexcitability (e.g., seizures) (Hillbom et al., 2003; Gass and Olive, 2008).

Studies using a variety of preparations have demonstrated that increased NMDA receptor-mediated excitatory transmission following chronic alcohol exposure are highly complex, involving changes in trafficking and phosphorylation of NMDA receptor subunits. For example, *in vitro* and *in vivo* studies have shown that chronic alcohol exposure results in compensatory trafficking of NMDA receptors containing GluN1 and GluN2B subunits to synaptic sites without alterations in expression of NMDA receptors in extrasynaptic domains (Mulholland and Chandler, 2007; Kroener et al., 2012). Further, evidence suggests that

increased expression of GluN1 subunits leading to activity-dependent enhanced targeting of NMDA receptors to the synapse involves alternative splicing of the carboxyl-terminal (C2' cassette) of GluN1 subunits (Mu et al., 2003; Clapp et al., 2010). At the same time, there is evidence for internalization of GluN2A subunits via clathrin-dependent endocytosis (Suvarna et al., 2005), with the result being an increased proportion of NMDA receptors reflecting a GluN1/GluN2B conformation.

Chronic alcohol exposure also results in phosphorylation of the GluN2B subunits by the Src family tyrosine kinase Fyn (via dissociation from the scaffolding protein RACK1), resulting in increased NMDA receptor channel activity (Miyakawa et al., 1997; Yaka et al., 2003). Interestingly, downregulation of protein tyrosine phosphatase in the dorsomedial striatum prevented phosphorylation of GluN2B, reduced withdrawal-associated NMDA receptor activity, and excessive alcohol drinking in mice (Ben Hamida et al., 2013). These adaptive changes in NMDA expression and function are suggested to contribute to withdrawal-related CNS hyperexcitability and escalation of drinking and cognitive impairments associated with dependence (Wang et al., 2010; Kroener et al., 2012; Ben Hamida et al., 2013).

Similarly, chronic alcohol-induced enhancement of AMPA receptor expression and function has been reported in cortex (Haugbol et al., 2005), hippocampus (Bruckner et al., 1997), basolateral amygdala (Lack et al., 2007), and dorsomedial striatum (Wang et al., 2012). Selective pharmacologic blockade of AMPA receptors in the basolateral amygdala attenuated withdrawal-related anxiety-like behaviors in rats, suggesting a role for adaptations in AMPA receptors in expression of withdrawal symptoms (Lack et al., 2007).

Recent clinical studies have employed imaging technology involving magnetic resonance spectroscopy procedures to measure glutamate levels in brain. Some studies have reported reduced cortical glutamate levels associated with dependence and acute withdrawal (Mon et al., 2012; Ende et al., 2013), while other studies have shown elevated glutamate activity in anterior cingulate and striatum in alcohol-dependent subjects (Hermann et al., 2012; Bauer et al., 2013). Congruent with these latter findings, studies in rats utilizing a dependence model that involves chronic exposure to alcohol vapor have shown increased glutamate levels in prefrontal cortex (Hermann et al., 2012) and basal ganglia (Zahr et al., 2009; Gu et al., 2013). Likewise, mouse and rat studies employing microdialysis procedures have demonstrated chronic alcohol and acute withdrawal-induced elevation in extracellular glutamate levels in several brain regions, including hippocampus and dorsal and ventral subregions of the striatum (Rossetti and Carboni, 1995; Dahchour et al., 2000; Dahchour and De Witte, 2003; Kapasova and Szumlinski, 2008). Repeated cycles of chronic intermittent exposure to alcohol vapor were shown to increase basal levels of glutamate in the nucleus accumbens (NAc) at time points beyond acute withdrawal. Pharmacologic studies demonstrated that increased glutamate tone in this brain region plays an important role in promoting excessive drinking associated with dependence (Griffin et al., 2014).

Finally, a history of alcohol dependence in rats also has been shown to alter functional activity and sensitivity of mGluR2/3 and mGluR5 receptors to drugs that modulate alcohol-seeking behavior and reinstatement of alcohol responding following presentation of cues previously associated with alcohol reinforcement (Sidhpura et al., 2010; Kufahl et al., 2011;

Meinhardt et al., 2013). These results have clinical implications because a number of drugs known to alter central glutamate activity have been investigated as potential treatments for reducing alcohol craving and consumption in human alcoholics. Unfortunately, mixed results have been generated from some of these studies with acamprosate (Umhau et al., 2010; Mann et al., 2012; Mason and Lehert, 2012; Berger et al., 2013b; Yahn et al., 2013) and anticonvulsants such as topiramate, gabapentin, pregabalin, and levetiracetam (De Sousa, 2010; Johnson and Ait-Daoud, 2010; Guglielmo et al., 2012; Mason et al., 2014). Clearly, this is an area that warrants more exploration and examination.

GABA—GABA operates at two types of receptors: ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors. $GABA_A$ receptors are composed of at least 19 subunit variants (α1–6, β1–3, γ1–3, δ, ε, π, θ, and ρ1–3), and the assembly of these different subunits confers unique pharmacologic sensitivity and receptor function. In comparison, there are two subtypes of $GABA_B$ receptors that form functional heterodimers in brain. Chronic exposure to alcohol is well documented to induce neuroadaptive changes in pre- and postsynaptic GABAergic transmission and expression of receptor subunit transcript/peptide levels that are temporally, subunit, and brain region-dependent (Kumar et al., 2009; Lovinger and Roberto, 2013). For example, studies in hippocampal and cortical pyramidal neurons have shown that chronic alcohol exposure reduces the frequency, amplitude, and decay time of mini inhibitory postsynaptic currents, effects that all contribute to increased neural excitability during withdrawal (Fleming et al., 2009). Chronic alcohol also reduces α1 subunits and increases α4 subunits of synaptic $GABA_A$ receptors, and this bidirectional effect on α1 and α4 subunit expression and trafficking can be modulated by protein kinase C phosphorylation (Kumar et al., 2002). Evidence also suggests that the enhanced internalization of the $GABA_A$ α1 subunit by chronic alcohol exposure is regulated by adaptor complex-2 and clathrin-mediated endocytosis. Additionally, chronic alcohol exposure decreases extrasynaptic $GABA_A$-mediated tonic current recorded from neurons in the hippocampus and cortex (Liang et al., 2004; Fleming et al., 2011), and this corresponds with a decrease in extrasynaptic $GABA_A$ receptors containing the δ subunit in hippocampus (Cagetti et al., 2003). Collectively, these $GABA_A$ receptor adaptations play a prominent role in mediating expression of various withdrawal signs and symptoms, including general CNS hyperexcitability and affective components, including anxiety.

Positive allosteric modulators of $GABA_A$ receptors (i.e., benzodiazepines) have been the gold standard for treatment of alcohol detoxification in the United States, owing to their anticonvulsant and anxiolytic pharmacologic profile. However, concerns about their abuse and dependence liability, amnestic effects, and potential for untoward ethanol interactions have spurred attention and greater investigation of other anticonvulsant agents (e.g., gabapentin, topiramate) as alternatives (Johnson and Ait-Daoud, 2000; Litten et al., 2005; Malcolm et al., 2007; Myrick et al., 2009; Addolorato et al., 2012; Cooper and Vernon, 2013).

Although the effects of chronic alcohol exposure on $GABA_B$ receptors have not been extensively studied, alcohol dependence also appears to regulate presynaptic $GABA_B$ receptor function. For example, alcohol-dependent rats showed decreased sensitivity to $GABA_B$ receptor agonists and antagonists on evoked inhibitory postsynaptic currents

recorded from central amygdala neurons (Roberto et al., 2008). Studies in animals and humans have suggested that direct $GABA_B$ receptor agonists, such as baclofen, are effective in reducing alcohol self-administration (Colombo et al., 2000; Addolorato et al., 2006, 2012). In one study, rats with a history of dependence exhibited a leftward shift in the dose–effect curve for baclofen to reduce alcohol consumption (greater sensitivity) compared to non-dependent rats (Walker and Koob, 2007).

Adaptations in Monoamine Systems

Dopamine—The role of dopamine in various facets of alcohol (and other drug) addiction has been extensively studied over several decades. Dopamine transmission is mediated via two groups of G-protein-linked receptors: D1-like (D1 and D5 receptors) and D2-like (D2, D3, and D4 receptors) that are classified on the basis of opposing transduction mechanisms that involve stimulating versus inhibiting adenylate cyclase activity, respectively. Dopamine, through its actions via mesolimbic and mesocortical pathways, has long been viewed as playing a central role in mediating alcohol reward (Gonzales et al., 2004; Spanagel, 2009). Chronic alcohol exposure has been reported to produce persistent neuroadaptive changes in dopamine transmission within the meso-accumbens reward circuitry, including increased firing rate in ventral tegmental area (VTA) dopamine neurons (Brodie, 2002), increased basal extracellular levels of dopamine in the NAc (Smith and Weiss, 1999; Sahr et al., 2004; Thielen et al., 2004), and alterations in dopamine receptor function (Liu and Weiss, 2002b; Engleman et al., 2003). By contrast, withdrawal from chronic alcohol exposure has been reported to result in decreased VTA dopamine neuronal activity (Diana et al., 1996; Bailey et al., 2001), and reduced basal levels of dopamine in ventral and dorsal subregions of the striatum, possibly due to enhanced dopamine uptake (Weiss et al., 1996; Budygin et al., 2007; Barak et al., 2011).

Many of these effects have been shown to persist beyond acute withdrawal, and this dopamine hypofunctional state has been suggested to underlie, in part, the negative affect and dysphoria associated with protracted abstinence, as well as the motivation to re-engage in alcohol-drinking behavior (Diana, 2011; Charlet et al., 2013). While there is some evidence that dopamine antagonists reduce alcohol craving and consumption, concern about their side-effects has hampered their general use in treating alcohol dependence (Swift, 2010). The D2 dopamine receptor partial agonist aripiprazole has shown some efficacy in treating alcohol dependence (Anton et al., 2008a; Kranzler et al., 2008; Martinotti et al., 2009). The mixed agonist/antagonist mechanism of this drug may enable restoration of dopamine function during acute withdrawal and then blunt dopamine stimulation produced by drinking (relapse) (Myrick et al., 2010).

Altered cortical dopamine activity has been suggested to contribute to severe alcohol withdrawal symptoms that typically constitute delirium tremens (e.g., extreme agitation, hallucinations, psychosis). Antipychotics (both typical and atypical) have been used to manage such severe withdrawal, but they are typically used as an adjunct treatment (often administered in combination with benzodiazepines or anticonvulsants) because alone, they offer no protection against seizures. There are also concerns about severe sedation and potential respiratory depression (Mayo-Smith, 1997; Mainerova et al., 2013).

Norepinephrine—Norepinephrine is widely distributed throughout the brain, arising principally from neurons within the locus coeruleus, and noradrenergic activity has been shown to play a key role in regulating behaviors related to attention, arousal, and stress. The norepinephrine system also has been implicated in alcohol dependence, and alcohol withdrawal in particular. Chronic alcohol exposure results in increased peripheral and central noradrenergic activity, which underlies both somatic and affective manifestations of alcohol withdrawal. For example, drugs that temper noradrenergic activity either by stimulating presynaptic autoreceptors (alpha-2 adrenergic agonists: e.g., clonidine, dexmedetomidine) or blocking postsynaptic receptors (beta-adrenergic antagonists: e.g., propranolol) have been shown in preclinical and clinical studies to ameliorate various withdrawal symptoms related to heightened autonomic (sympathetic) nervous activity. Accordingly, this pharmacologic approach has proven to be useful as an adjunct in the management of alcohol detoxification (Muzyk et al., 2011).

Additionally, there is evidence that alcohol dependence-related adaptations in brain norepinephrine activity might play a role in influencing motivation to drink. For example, blocking postsynaptic alpha-1 adrenergic receptors with the antagonist prazosin reduced alcohol consumption in both dependent rats (Walker et al., 2008) and alcohol-dependent humans (Simpson et al., 2009). Likewise, treatment with beta-adrenoceptor antagonists (e.g., propranolol) also reduced drinking in dependent rats (Gilpin and Koob, 2010).

Serotonin—Serotonin predominantly arises from neurons within the raphe nuclei of the hindbrain, which send broad projections that innervate all levels of the brain. Serotonin exerts its known role in modulating various regulatory behaviors (e.g., feeding, sleep/arousal, aggression), mood, and emotional aspects of motivational behavior via several metabotropic (5-HT1 and 5-HT2 subtypes) and ionotropic (5-HT3) receptor systems throughout the brain. While changes in serotonin activity are not thought to play a significant role in mediating somatic signs of alcohol withdrawal, its general role in regulating mood and affect suggests serotonin may contribute to withdrawal-related dysphoria, as well as motivational effects of alcohol. Indeed, chronic alcohol exposure reduces serotonin levels in several brain regions, and there is a large body of evidence indicating a negative relationship between serotonin levels in brain and propensity to self-administer alcohol (Murphy et al., 2002; Casu et al., 2004; Petrakis, 2006). As is the case with dopamine, alcohol self-administration following withdrawal restored reduced extracellular levels of serotonin in the NAc produced by chronic alcohol exposure in rats (Weiss et al., 1996).

Given the role of serotonin in affective illness, it is not surprising that selective serotonin reuptake inhibitors (SSRIs) have been the focus of treatment for alcohol dependence and comorbid depression (Pettinati et al., 2010), anxiety (Book et al., 2008), and posttraumatic stress disorder (Petrakis et al., 2012). While there is some evidence indicating that SSRIs reduce drinking in animal studies (Maurel et al., 1999; Naranjo and Knoke, 2001), results are more mixed in clinical studies, possibly related to a unique polymorphism in the serotonin transporter (Kranzler et al., 2012), the presence and nature of comorbid illness (Johnson and Ait-Daoud, 2000), and other alcoholism-related endophenotypes (Pettinati et al., 2000). Interestingly, a drug that selectively inhibits serotonin reuptake (fluoxetine) and

one that blocks both serotonin and norepinephrine reuptake (milnacipran) were both found to be effective in reducing alcohol self-administration in dependent rats (Simon O'Brien et al., 2011), while a novel triple monoamine uptake inhibitor was reported to reduce alcohol intake in rats with a genetic predisposition for high alcohol preference (Yang et al., 2012). Finally, the 5-HT3 receptor antagonist ondansetron has been shown to reduce alcohol consumption in animals (Hodge et al., 2004) and human alcohol-dependent subjects (Johnson et al., 2000; Kranzler et al., 2003; Johnson, 2004), with recent evidence suggesting that polymorphisms in the 5-HT3 receptor and serotonin transporter moderate treatment efficacy (Johnson et al., 2013).

Adaptations in Neuropeptide Systems

Corticotropin-Releasing Factor—Chronic alcohol exposure engages a number of neuropeptide systems in the brain, with CRF most extensively studied in animal models of dependence (Heilig and Koob, 2007; Koob and Zorrilla, 2010; Lowery and Thiele, 2010). CRF is a 41-amino-acid neuropeptide that is widely distributed throughout the brain and, along with related peptides (urocortin; Ucn1, Ucn2, Ucn3), interacts with two G-protein-coupled receptor subtypes (CRF1 and CRF2) to produce its physiologic and behavioral effects (Bale and Vale, 2004). While there is some evidence indicating a role for urocortin peptides (especially Ucn2 and Ucn3) and CRF2 receptors in alcohol dependence and withdrawal (e.g., Valdez et al., 2004; Funk and Koob, 2007; Ryabinin et al., 2012), most attention has focused on adaptations in CRF–CRF1 receptor activity within brain and neuroendocrine systems in relation to chronic alcohol exposure and withdrawal-related consequences.

CRF emanating from the hypothalamus plays a key role in regulating the neuroendocrine function of the hypothalamic–pituitary–adrenocortical (HPA) axis. Specifically, CRF neurons residing in the paraventricular nucleus of the hypothalamus regulate HPA axis activity via control of glucocorticoid production and release, which is critical for orchestrating behavioral and physiologic responses to stress. A large preclinical and clinical literature has demonstrated profound disturbances in HPA axis function following chronic alcohol exposure (Rivier, 2000; Wand, 2000; Stephens and Wand, 2012). Elevated glucocorticoid levels resulting from dependence-related HPA axis activation not only underlie altered stress responsiveness in dependent subjects, but it also may contribute to amplified motivation to drink as well as other ramifications of the dependence state. Studies in mice and rats also have shown that withdrawal following chronic alcohol consumption produced elevated corticosterone levels in the prefrontal cortex and hippocampus that persisted long after plasma corticosterone levels returned to baseline levels (Little et al., 2008). There are also significant changes in expression of receptors in brain that bind glucocorticoids (glucocorticoid but not mineralocorticoid receptors) during abstinence, and there is recent evidence that activity at these receptors may play a role in relapse and perpetuation of excessive alcohol consumption (Vendruscolo et al., 2012). These results are congruent with findings showing that elevated corticosteroids enhance the propensity to consume alcohol through an interaction with mesolimbic and mesocortical reward pathways (Fahlke et al., 1995, 1996; Piazza and Le Moal, 1997; Koenig and Olive, 2004; Uhart and Wand, 2009). Further, elevations in brain glucocorticoid concentrations following chronic

alcohol exposure and withdrawal may contribute to the cognitive deficits and neurotoxic damage that are commonly associated with alcohol dependence (Rose et al., 2010).

Beyond alterations in neuroendocrine (HPA axis) function, chronic alcohol exposure has been shown to alter CRF activity independently of the HPA axis (Heilig and Koob, 2007; Heilig et al., 2010; Koob and Zorrilla, 2010). Increased CRF activity in several brain structures following chronic alcohol exposure is thought to play a key role in the emergence of negative affective withdrawal symptoms (e.g., anxiety, dysphoria) that may be especially relevant in enhancing susceptibility to relapse and promoting return to excessive levels of drinking (Koob and Kreek, 2007; Heilig et al., 2010; Lowery and Thiele, 2010; Becker, 2012). For example, studies in rats involving pharmacologic manipulation of CRF activity has implicated a role of CRF1 receptors in mediating increased anxiety associated with withdrawal from chronic alcohol exposure delivered in a liquid diet (Baldwin et al., 1991; Rassnick et al., 1993; Valdez et al., 2003; Breese et al., 2005; Huang et al., 2010b), by intragastric administration (Gehlert et al., 2007), and via vaporized alcohol in inhalation chambers (Sommer et al., 2008), although a role for CRF2 receptors cannot be ruled out (Valdez et al., 2004). Additionally, increased CRF activity in brain structures integral to reward and stress pathways has been shown to play an important role in mediating the ability of stress to trigger relapse-like behavior (Le et al., 2000; Liu and Weiss, 2002a; Gehlert et al., 2007; Marinelli et al., 2007; Sommer et al., 2008). A number of studies have shown that pharmacologic blockade or genetic deletion of CRF1 receptors impedes escalation of alcohol consumption in dependent animals (Chu et al., 2007; Funk et al., 2007; Gehlert et al., 2007; Gilpin et al., 2008b; Sommer et al., 2008; Roberto et al., 2010; Molander et al., 2012). Finally, studies in humans (Chen et al., 2010; Schmid et al., 2010; Blomeyer et al., 2011), non-human primates (Barr et al., 2008, 2009), and rats (Hansson et al., 2006; Ayanwuyi et al., 2013) have indicated a strong genetic influence on the role of CRF in mediating stress responsiveness as well as alcohol drinking and risk for dependence. Taken together, there is a large body of evidence that indicates that dependence-related alterations in brain CRF activity both within and outside the HPA axis play a significant role in mediating various symptoms of alcohol withdrawal as well as excessive drinking associated with dependence.

Neuropeptide Y—Neuropeptide Y (NPY) is a 36-amino acid peptide that is widely distributed in the CNS and operates at five distinct receptors (Y1–5). NPY is commonly viewed as an “antistress,” anxiolytic signaling molecule (Heilig et al., 1994; Valdez and Koob, 2004), and it has been implicated in various facets of alcohol dependence and withdrawal (Thorsell, 2007; Gilpin, 2012). For example, reduced NPY mRNA and protein levels in the central and medial (but not basolateral) subregions of the amygdala were shown to be associated with withdrawal-related anxiety behavior following chronic alcohol treatment in rats (Roy and Pandey, 2002; Zhang and Pandey, 2003; Zhang et al., 2010). Intraventricular administration of NPY following chronic exposure to alcohol vapor reduced alcohol self-administration (Thorsell et al., 2005a, b). Additionally, central administration of NPY during repeated withdrawal cycles from chronic alcohol vapor exposure blocked the progressive increase in alcohol consumption in rats (Gilpin et al., 2011). Similar results were obtained in another study with direct infusion of NPY into the central nucleus of the

amygdala following chronic alcohol treatment in a liquid diet (Gilpin et al., 2008a). While studies have demonstrated a role for Y1 (Sparrow et al., 2012), Y2 (Thorsell et al., 2002), and Y5 (Schroeder et al., 2005) receptors in modulating alcohol consumption, few studies have dissected the relative role of these NPY receptor subtypes in mediating alcohol withdrawal anxiety and drinking. Nevertheless, evidence to date suggests that adaptive changes in NPY function in dependence contributes to withdrawal-related anxiety and increased propensity to self-administer alcohol.

Opioid Polypeptides—Alcohol interactions with endogenous opioid systems in the brain are well established in the animal and human literature. The endogenous opioid polypeptides endorphin, enkephalin, and dynorphin are distributed throughout the brain and principally operate at mu (MOR), delta (DOR), and kappa (KOR) opiate receptors, respectively, to produce their behavioral and physiologic actions (Bodnar, 2012). Activity at mu and delta receptors mediates classic opioid effects (e.g., analgesia, euphoria, sedation) while drugs that mimic the endogenous ligand for kappa receptors exert an opposite pharmacologic profile (e.g., increased pain sensitivity, dysphoria). Given the role of endogenous opioids in reward processes and motivational behaviors, most attention has focused on pharmacologic agents that alter endogenous opioid activity as treatments for alcohol dependence. A host of studies have shown that opiate antagonists (primarily targeting mu receptors) reduce alcohol craving and consumption, ultimately leading to naltrexone being Food and Drug Administration-approved as a medication for treatment of alcoholism (O'Malley et al., 1992; Volpicelli et al., 1992). Recent studies have shown that a polymorphism in mu opiate receptors confers differential sensitivity to the treatment efficacy of naltrexone (Ray and Hutchison, 2007; Anton et al., 2008b). Also, there is some evidence that antagonists with greater selectivity for delta receptors (e.g., nalmefene) may have promise as effective treatments (Mason et al., 1999; Mann et al., 2013). While there is ample preclinical evidence indicating that antagonism of both MOR and DOR is effective in reducing alcohol consumption (e.g., Ciccocioppo et al., 2002), some studies have shown that sensitivity to DOR antagonism is greater in dependent compared to non-dependent animals (Walker and Koob, 2008; Nealey et al., 2011).

There is growing interest in chronic alcohol-induced changes in the dynorphin/KOR system, particularly as such changes bear on somatic as well as the emergence of dysphoria/anxiety components of alcohol withdrawal (Walker et al., 2012). For example, there is some evidence to indicate that dynorphin (prodynorphin mRNA) expression in brain relates to genetic propensity for withdrawal seizures following chronic alcohol treatment (Beadles-Bohling et al., 2000). Additionally, KOR antagonists were shown to attenuate acute alcohol withdrawal ("hangover") anxiety (Schank et al., 2012; Valdez and Harshberger, 2012); KOR activity has been implicated in negative affect/emotional states produced by chronic exposure to alcohol via a liquid diet (Gillett et al., 2013) or vapor inhalation (Berger et al., 2013a; Kissler et al., 2013). Also, KOR antagonism has been demonstrated to reduce escalated alcohol consumption in dependent rats without altering responding/intake in non-dependent rats (Walker and Koob, 2008; Nealey et al., 2011; Walker et al., 2012). Interestingly, a polymorphism in the gene encoding KOR (*OPRK1*) was shown to be associated with human alcohol dependence (Edenberg et al., 2008). Collectively, these

studies indicate that increased dynorphin/KOR activity resulting from chronic alcohol exposure significantly contributes to dysphoric and negative emotional aspects of withdrawal, and blockade of KOR effectively suppresses alcohol self-administration that would otherwise be elevated as a function of dependence.

Nociceptin—Nociceptin (orphanin FQ) is a 17-amino-acid peptide that is structurally similar to dynorphin, but it possesses unique pharmacologic actions through binding with high affinity to opioid receptor-like 1 (ORL-1), also known as NOP (Reinscheid et al., 1995; Lambert, 2008). Devoid of mu, delta, and kappa receptor activity, nociceptin exerts antianxiety and antistress effects at NOP receptors. Recent studies have suggested that this peptide may be involved in the expression of various alcohol withdrawal symptoms, as well as alcohol self-administration behavior. For example, the gene that encodes the NOP receptor (*Oprl1*) was shown to be robustly upregulated in prefrontal cortex following chronic alcohol exposure in a mouse model of dependence (Melendez et al., 2012). Further, central administration of nociceptin reduced expression of somatic signs of withdrawal as well as increased anxiety following chronic alcohol treatment (Economidou et al., 2011; Aujla et al., 2013). While several studies have shown that nociceptin (and NOP agonists) decreases alcohol consumption, particularly in rats with a genetic predisposition for high alcohol intake (Ciccocioppo et al., 2004; Economidou et al., 2008), dependent rats have been shown to exhibit greater sensitivity to this effect in comparison with non-dependent animals (Martin-Fardon et al., 2010). The potential for drugs that target NOP receptors for treatment of alcohol dependence awaits further investigation.

Other Neuropeptides—Other neuropeptides recently implicated in alcohol dependence include orexin/hypocretin (Bayerlein et al., 2011; von der Goltz et al., 2011; Kim et al., 2012), substance P/neurokinin1 receptors (George et al., 2008; Thorsell et al., 2010; Schank et al., 2011), and neuropeptide S (Ruggeri et al., 2010; Enquist et al., 2012). While all these neuropeptide system have been implicated in motivational effects of alcohol, their role in mediating withdrawal symptoms as well as excessive alcohol consumption associated with dependence remains to be determined.

Adaptations in Ion Channels

CNS neurons express a wide range of calcium- or voltage-gated potassium (K^+) and calcium (Ca^{2+}) ion channels. These ion channels play a critical role in modulating many aspects of neuronal physiology (i.e., intrinsic excitability, dendritic integration, tonic firing frequency, spike frequency adaptation, and action potential repolarization). The distribution and density of K^+ and Ca^{2+} ion channels can vary by cell type and subcellular localization within the dendritic field. For example, some channels are enriched in dendritic spines of pyramidal neurons in the hippocampus and cortex, while others are highly expressed on interneurons or distal apical dendrites of CA1 pyramidal neurons. Findings from recent studies have demonstrated that chronic alcohol exposure can produce adaptive changes in the expression and function of these dendritic ion channels. Below, we describe evidence that neuroadaptations in voltage-gated Ca^{2+} channels (VGCCs), small-conductance (SK) and large-conductance (BK) K^+ channels, and voltage-gated K^+ (Kv) channels critically regulate

hyperexcitability, local inhibitory neurocircuitry, and seizure activity associated with withdrawal from chronic alcohol exposure.

Voltage-gated Ca^{2+} channels—Activation of VGCCs at depolarized membrane potentials allows Ca^{2+} entry into neurons through the channel pore where it can then influence Ca^{2+}-activated K^+ channels, gene expression, neuronal excitability and firing patterns, and neurotransmitter release. VGCCs can be classified as low- or high-threshold voltage-activated or by their sensitivity to selective toxins. Chronic alcohol exposure has been shown to increase high-voltage activated L-type VGCCs in brain (Littleton, 1998; Walter and Messing, 1999; Katsura et al., 2005). Blocking L-type channels significantly reduces the severity of seizure activity during withdrawal and prevented c-Fos induction in the cortex, hippocampus, and striatum (Bouchenafa and Littleton, 1998). Prolonged alcohol exposure also increases high-voltage activated N- and P-type VGCCs in the frontal cortex, hippocampus, and inferior colliculus (McMahon et al., 2000). More recently, chronic intermittent alcohol exposure or prolonged consumption of an alcohol liquid diet produced increases in low-threshold, transient T-type VGCCs in thalamic neurons (Nordskog et al., 2006; Graef et al., 2011). Like the hippocampus, the thalamus contributes to the generation of brain rhythms (e.g., theta oscillations, sleep spindles) (Buzsaki, 2002; Steriade, 2006). Thalamic neurons in the midline reuniens nucleus have strong recurrent connections with the frontal cortex and hippocampus and drive corticothalamic-hippocampal network activity (Bertram et al., 2008). Increased T-type channel function during alcohol withdrawal is associated with enhanced burst firing of thalamic neurons and disruptions in EEG theta power (Graef et al., 2011). Further, alcohol withdrawal-related disruption in theta power was prevented in mice by treatment with ethosuximide, a T-type channel blocker (Graef et al., 2011). Collectively, these data suggest that the neuroadaptations in VGCCs produced by alcohol dependence contribute to CNS hyperexcitability during withdrawal.

Small-Conductance Ca^{2+}-Activated K^+ Channels—SK channels regulate membrane excitability by shaping excitatory postsynaptic potentials (EPSP) and controlling intrinsic activity, dendritic integration, and pacemaker firing (Bond et al., 2005; Fakler and Adelman, 2008). SK channels are solely activated by transient elevations of intracellular Ca^{2+} and form functional heteromeric complexes with calmodulin, that acts as a high-affinity Ca^{2+} sensor (Lee et al., 2003; Maylie et al., 2004; Allen et al., 2007). In pyramidal neurons of the hippocampus, amygdala and prefrontal cortex, SK2 channels are enriched in the postsynaptic density of dendritic spines, where they form a Ca^{2+}-mediated negative-feedback loop with synaptic NMDA receptors (Faber et al., 2005; Ngo-Anh et al., 2005; Bloodgood and Sabatini, 2007; Lin et al., 2008; Faber, 2010; Mulholland et al., 2011). Activation of this feedback loop is thought to act as a postsynaptic shunt to decrease spine Ca^{2+} transients and synaptic depolarization. Consistent with this idea are studies showing that blocking SK channels in pyramidal neurons increases EPSP amplitude and facilitates NMDA receptor-dependent synaptic plasticity (Faber et al., 2005, 2008; Lin et al., 2008; Faber, 2010). SK channels also can modulate the ability of NMDA receptors to induce burst firing in midbrain dopamine neurons (Johnson and Seutin, 1997; Seutin et al., 1993).

Recent evidence has demonstrated that chronic alcohol exposure reduced SK-mediated currents recorded from cultured CA1 pyramidal neurons (Mulholland et al., 2011). Chronic alcohol exposure also decreased expression of SK2 channels while at the same time increasing expression of NMDA receptor GluN1 and GluN2B subunits in hippocampus. This bidirectional regulation of SK2 channels and NMDA receptors leads to a disruption of the Ca^{2+}-mediated negative-feedback loop and enhanced hyperexcitability during acute alcohol withdrawal (Mulholland et al., 2011). Positive modulation of SK channels attenuated acute withdrawal-related epileptiform burst firing and behavioral signs of seizure activity (Mulholland et al., 2011; Mulholland, 2012). Thus, these data demonstrate that downregulation of SK2 channels contributes to alcohol-associated plasticity of hippocampal glutamatergic synapses, and that reduced expression of SK2 channels in dendritic spines plays a role in the alcohol withdrawal syndrome.

In addition to alcohol-induced adaptations in hippocampal SK channels, recent studies have shown that acute and chronic alcohol exposure alters firing properties of VTA dopamine and NAc core medium spiny neurons through adaptations in SK channel function and expression (Brodie et al., 1999; Hopf et al., 2007, 2010). For example, SK-mediated currents were significantly reduced in rats 7 days following withdrawal from a chronic ethanol treatment regimen (Hopf et al., 2007). In another study, rats self-administering alcohol over a 5-week period exhibited increased intrinsic excitability of neurons in the NAc core (Hopf et al., 2010). Taken together, these data suggest that withdrawal from chronic alcohol exposure is associated with reduced SK channel function in the VTA and NAc core, and these adaptations are important for regulating intrinsic excitability and NMDA receptor-dependent burst firing during alcohol withdrawal.

Large-Conductance Voltage- and Ca^{2+}-Activated K^+ Channels—A number of studies have implicated an important role for somatodendritic BK channels in ethanol tolerance, adaptive plasticity, and withdrawal-associated seizures. BK channels are a product of the *KCNMA1* (*Slo1*) gene and its orthologs (e.g., d*Slo* in *Drosophila*), and are ubiquitously expressed in the CNS. BK channels are comprised of α and β auxiliary subunits in a 1:1 stoichiometry, and these channels can be activated by increases in intracellular Ca^{2+} or transmembrane positive voltage shifts (Latorre and Brauchi, 2006). BK channels serve to shape dendritic Ca^{2+} spikes and modulate the release of growth hormones, neuropeptides (vasopressin and oxytocin), and various neurotransmitters (Storm, 1990; Dopico et al., 1996; Jakab et al., 1997). Of relevance to alcohol, BK channels are known to influence neurotransmitter release, nociception, intrinsic excitability of NAc medium spiny neurons, motor incoordination, and alcohol withdrawal-induced seizures (Brodie et al., 2007; Treistman and Martin, 2009; Ghezzi et al., 2012).

Unlike other members of the voltage-gated, TM6 family of K^+ channels, BK channels are very sensitive to low (10–50 mM) alcohol concentrations in a number of structures (Treistman and Martin, 2009). Alcohol activation of BK channels has been reported in a wide variety of neuronal and non-neuronal preparations and model systems (i.e., oocytes, HEK 293 cells, *Caenorhabditis elegans*, *Drosophila*). Exposure of neuronal terminals to alcohol for 24 hours declusters and internalizes surface BK channels and renders them less sensitive to the potentiating effects of alcohol on channel function (Pietrzykowski et al.,

2004). While the β_4 subunit has been shown to play a critical role in mediating tolerance to alcohol-induced modulation of BK channel function (Martin et al., 2008), CaMKII phosphorylation of Thr107 of the alpha subunit of BK channels increased channel activity and mediated the switch from alcohol-induced activation of the channel-to-channel inhibition (Treistman and Martin, 2009). In *Drosophila*, alcohol exposure reduced seizure threshold at 1 and 7 days into withdrawal, but not in flies where *slo* expression was genetically eliminated (Ghezzi et al., 2012). Further, heat shock induction of *slo* mimicked the lowering effect of alcohol on seizure threshold, suggesting a role for *slo* induction in the susceptibility to withdrawal seizures. Thus, altered function of Ca^{2+}-activated K^+ channels represents a developing area that is of particular importance in understanding alcohol-associated molecular and behavioral tolerance, adaptive plasticity, and withdrawal severity.

A-Type K^+ Channels—Voltage-dependent potassium (Kv) channels composed of Kv1 and Kv4 subunits underlie the transient A-type K^+ current (I_A) in hippocampal, cortical, and NAc medium spiny neurons, where they influence a wide range of functions, including the shaping and propagation characteristics of action potentials, and complex cognitive processes (Hoffman et al., 1997; Chen et al., 2006; Lockridge and Yuan, 2011). Emerging evidence also suggests a role for Kv4 channels in ethanol dependence and withdrawal. For example, chronic intermittent alcohol exposure significantly increased I_A in NAc medium spiny neurons (Marty and Spigelman, 2012) and decreased I_A in hippocampal CA1 interneurons (Li et al., 2013). Chronic alcohol exposure and withdrawal also significantly reduce surface expression and function of Kv4.2 channels in CA1 pyramidal neurons (Mulholland et al., 2010). The chronic intermittent alcohol exposure-associated bidirectional changes between I_A in NAc medium spiny neuronss and hippocampus suggests divergent cell-specific regulation of Kv4 channel subunits or posttranslational modifications (Tkatch et al., 2000). Together, these data indicate divergent cell-specific regulation of Kv4 channel subunits, and suggest that neuroadaptations in Kv4 channels may be an important factor underlying altered synaptic plasticity, poor cognitive performance, and aberrant excitability associated with prolonged alcohol exposure and withdrawal.

CONCLUSIONS

Alcoholism is a chronic relapsing disease and, thus, it is not uncommon for many dependent individuals to attempt abstinence on numerous occasions, only to find themselves progressing to unhealthy excessive drinking once a “slip” (relapse) occurs. When dependent individuals completely stop or significantly reduce their alcohol drinking, a characteristic withdrawal syndrome ensues. The alcohol withdrawal syndrome includes signs of CNS hyperexcitability (i.e., seizure activity, sometimes culminating in behavioral convulsions and sensory hyperreactivity), physiologic manifestations of heightened autonomic nervous system activity (e.g., tachycardia, hypertension, diaphoresis, body temperature dysregulation, and gastrointestinal disturbances), motor problems (e.g., tremor) and, in its most severe form, hallucinosis and delirium tremens. In addition to these physiologic signs of withdrawal, a constellation of symptoms contributing to psychologic discomfort and negative affect constitutes a prominent component of the withdrawal syndrome. Withdrawal symptoms that fall within the domain of psychologic discomfort and negative affect (mood)

include sleep disturbances, anxiety and irritability, increased stress reactivity, and a general state of anhedonia/dysphoria. While most physiologic symptoms of withdrawal typically abate within a few days, many of the psychologic symptoms of withdrawal linger for protracted periods of time, and these latter symptoms are thought to play an important role in underlying increased susceptibility to relapse.

The development of alcohol dependence is a complex and dynamic process that involves profound perturbations in neuroendocrine systems (i.e., HPA axis activity) as well as neuroadaptations in a host of neurochemical systems, including classic neurotransmitter systems (e.g., glutamate, GABA, monoamines), neuropeptides (e.g., CRF, NPY, endogenous opioids), and numerous ion channels (e.g., VGCCs, SK channels, BK channels). The maladaptive nature of these changes induced by chronic alcohol exposure is revealed when alcohol is eliminated from the brain during withdrawal. Manifestations of these neuroadaptations are seen in the expression of various symptoms related to physiologic and psychologic components of the alcohol withdrawal syndrome. Further, many of these adaptive changes set in motion as a result of chronic alcohol exposure and withdrawal experience occur within brain reward and stress systems. The progressive dysregulation of brain reward and stress systems beyond normal homeostatic limits is thought to fuel a state of allostasis that not only underlies expression of withdrawal symptoms, but also drives enhanced relapse vulnerability perpetuation of excessive harmful levels of drinking. The challenge ahead is to better understand the pathophysiologic mechanisms of alcohol dependence so that more effective and targeted therapeutics can be developed that not only effectively treat symptoms of withdrawal, but also reduce risk of relapse and temper motivation to engage in unhealthy drinking.

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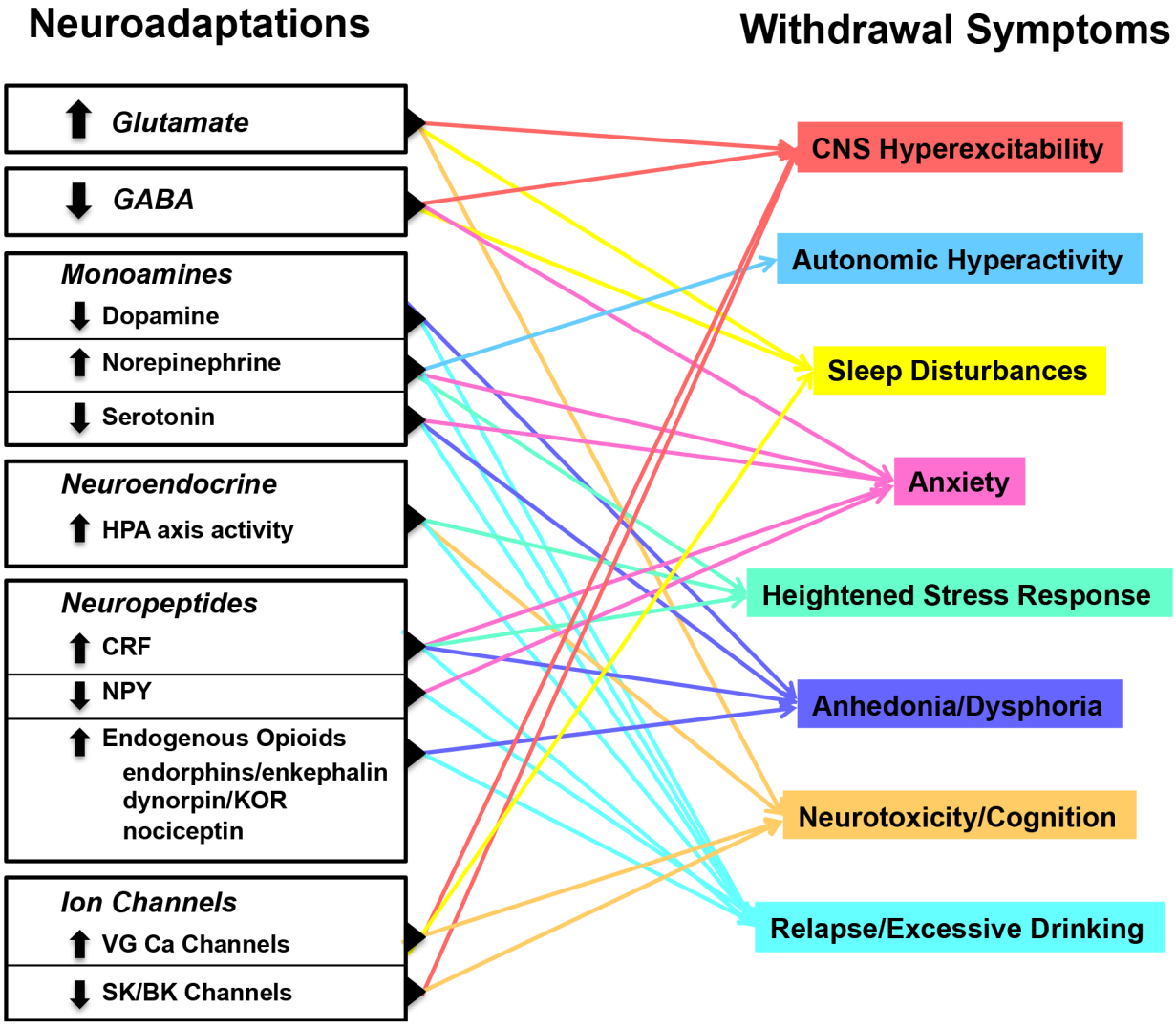

Fig. 9.1.

GABA, γ-aminobutyric acid; HPA, hypothalamic–pituitary–adrenocortical; CRF, corticotropin-releasing factor; NPY, neuropeptide Y; CNS, central nervous system; KOR, kappa opiate receptor; VG, voltage-gated; Ca, calcium; SK, small conductance; BK, large conductance.