NIH Public Access
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Addict Biol. Author manuscript; available in PMC 2012 January 30.

Published in final edited form as:
Addict Biol. 2010 April ; 15(2): 169–184. doi:10.1111/j.1369-1600.2009.00194.x.

Acute withdrawal, protracted abstinence and negative affect in alcoholism: Are they linked?

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Abstract

The role of withdrawal-related phenomena in development and maintenance of alcohol addiction remains under debate. A “self-medication” framework postulates that emotional changes are induced by a history of alcohol use, persist into abstinence, and are a major factor in maintaining alcoholism. This view initially focused on negative emotional states during early withdrawal: these are pronounced, occur in the vast majority of alcohol dependent patients, and are characterized by depressed mood and elevated anxiety. This concept lost popularity with the realization that, in most patients, these symptoms abate over 3 – 6 weeks of abstinence, while relapse risk persists long beyond this period. More recently, animal data have established that a prolonged history of alcohol dependence induces more subtle neuroadaptations. These confer altered emotional processing that persists long into protracted abstinence. The resulting behavioral phenotype is characterized by excessive voluntary alcohol intake and increased behavioral sensitivity to stress. Emerging human data support the clinical relevance of negative emotionality for protracted abstinence and relapse. These developments prompt a series of research questions: 1) Are processes observed during acute withdrawal, while transient in nature, mechanistically related to those that remain during protracted abstinence? 2) Is susceptibility to negative emotionality in acute withdrawal in part due to heritable factors, similar to what animal models have indicated for susceptibility to physical aspects of withdrawal? 3) To what extent is susceptibility to negative affect that persists into protracted abstinence heritable?

Keywords

alcoholism; withdrawal; neuroadaptation; stress

1. Introduction

Symptoms that emerge when prolonged and excessive alcohol consumption is discontinued are characteristic of the alcohol dependence syndrome, or alcoholism (Edwards & Gross 1976). Although neither necessary nor sufficient for a diagnosis, withdrawal symptoms belong to consensus diagnostic criteria for this disease (American Psychiatric Association et

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disclosures

Author HB has received consulting fees from Eli Lilly & Co.

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al. 1994). Despite this central role, understanding the role of withdrawal symptoms for excessive drinking or relapse remains challenging.

"Self-medication" views of addiction posit that a desire to avoid or relieve pre-existing or withdrawal-related aversive states is a key motivation behind excessive drug use and relapse (Markou et al. 1998). Pharmacologically based theories such as those of Wikler (Wikler 1948) and Dole (Dole et al. 1966; Dole 1965) focused on relief from drug withdrawal symptoms as the basis for continued drug use. This perspective contrasts with subsequent views emphasizing the positive reinforcing actions of drugs (Wise & Bozarth 1985; Koob *et al.* 1987; Di Chiara & Imperato 1988). The distinction has important therapeutic implications. For instance, the most successful treatment for an addictive disorder to date, methadone maintenance for heroin dependence, was developed based on the hypothesis that relieving withdrawal symptoms would diminish the desire to continue heroin use (Dole 1965). The main objective of the present paper is to examine the nature and relevance of alcohol withdrawal symptoms for maintaining alcoholism, from the specific perspective of evaluating how well we model them in animals and identifying their genetic and neurobiological underpinnings. While there are interesting data from many species, we confine our analysis to the rodent species used in the vast majority of studies.

Withdrawal is a diverse and temporally dynamic process. When its different aspects are assessed clinically, a summary rating of withdrawal severity is routinely derived (Sullivan et al. 1989), but different withdrawal symptoms follow different time courses. Traditionally, the focus is on physical manifestations. However, as will be discussed below, psychological changes, e.g. increased anxiety, low mood and attenuated ability to experience pleasure from natural rewards, are also key components of the withdrawal syndrome. It remains unclear which, if any, of these diverse withdrawal manifestations that are linked to motivational processes are involved in maintaining alcoholism. The objective of the present paper is to identify conceptual and methodological issues that need to be resolved to address this question more effectively.

2. Historical perspective

2.1 A central role for physical dependence

Although specific symptoms differ, alcohol shares a general pattern of pharmacodynamic tolerance (i.e., reduced sensitivity to alcohol's effects) and physical withdrawal with other addictive drugs. The presumption historically has been that postponement or avoidance of early, physical withdrawal symptoms such as tremors, autonomic nervous system hyperactivity and seizures, is key to sustaining heavy alcohol use. This thinking was influenced by research on opiate dependence. For instance, Dole (Dole 1965) largely focused on the physical symptoms of acute opiate withdrawal, and considered the desire to relieve the "sick" feeling of acute withdrawal to be a major motivation for drug seeking and use. Wikler and O'Brien (Wikler 1948; O'Brien et al. 1977) observed that long after acute physical withdrawal symptoms subsided in a treatment setting, detoxified heroin addicts began to experience physical withdrawal symptoms and craving when exposed to drug-associated stimuli. Groundbreaking operant drug self-administration studies were performed under the assumption that morphine self-administration would not be sustained in animals unless they were first made physically dependent (Spragg 1940; Headlee *et al.* 1955; Weeks 1962; Thompson & Schuster 1964).

2.2 Drugs as positive reinforcers

Over time, it became clear that physical dependence and withdrawal are not required for sustaining drug use. Clinical studies noted that while 70 – 80% of subjects with any addiction relapsed within the first year, the vast majority of relapses occurred long after

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acute physical withdrawal symptoms had resolved (Hunt et al. 1971). Also, while acute alcohol withdrawal became easily managed with benzodiazepines (Mayo-Smith 1997), relapse rates were not reduced by these treatments. Finally, with the spread of psychostimulant use, it became clear that an addictive process can share core clinical characteristics of excessive use and frequent relapse in the absence of physical dependence.

In laboratory studies, morphine self-administration was eventually observed in animals with no prior history of morphine exposure (Deneau et al. 1969). Drugs which do not produce evident signs of physical dependence, such as the psychomotor stimulants, were also readily self-administered by laboratory animals (Pickens & Thompson 1968; Balster & Schuster 1973). In addition, the relationship between physical withdrawal symptoms and ethanol self-administration was found to be complex, with some studies reporting diminished alcohol self-administration in the presence of severe acute physical withdrawal signs, while others observed increased drinking when withdrawal symptoms were less severe (see below).

In light of these observations, acute withdrawal and its dramatic physical symptoms were concluded to be of lesser relevance for understanding the addictive process. Instead, addiction was explained in terms of positive reinforcement principles. In this view, drug use occurs to the exclusion of other behaviors because drug reinforcers are more potent than alternative positive reinforcers. The contingency relationship between behavior and its consequences is viewed as more important than drug-receptor actions in defining this effect of drugs, as animals will work to reject or receive the same highly addictive drug, depending on the experimental conditions (Spealman 1979).

A highly productive research line emphasized drug actions upon neural substrates of reward and positive reinforcement, primarily focusing on mesolimbic dopamine circuitry (Wise & Bozarth 1985; Koob *et al.* 1987; Di Chiara & Imperato 1988). Over the course of three decades, the view of addiction shifted markedly. Opiates, with their distinct physiological withdrawal syndrome, were once viewed as the quintessential addictive drugs. Following the cocaine epidemic, psychomotor stimulants with dopaminergic action began to define the prototypical properties of an addictive substance. This view also emphasized similarities rather than differences between addictive drugs. There is now clear evidence for a role of the mesolimbic dopamine pathway in mediating the acute positive reinforcing properties of alcohol (Di Chiara *et al.* 1996; Ahlenius *et al.* 1973; Weiss *et al.* 1996; Weiss *et al.* 1993; Tanda & Di Chiara 1998; Spanagel & Weiss 1999), but it is noteworthy that consumption and self-administration of alcohol does not rely on the integrity of this system (Rassnick et al. 1993b; Kiianmaa et al. 1979). Indeed, a review of 9 mouse studies comparing null mutants for dopamine D1, D2, D3, and D4 receptors, the dopamine transporter DAT, or the vesicular monoamine transporter VMAT with their respective wild types revealed a wide range of effects (or lack thereof) on ethanol preference drinking (Crabbe et al. 2006)

Rather than directly mediating the rewarding effects of natural and drug reinforcers, more recent hypotheses focus on the role of mesolimbic dopamine as a motivational learning signal (Spanagel & Weiss 1999), a signal of pathological associative learning in addiction (Di Chiara 2002), a neural substrate of incentive salience (Robinson & Berridge 2003), or a signal informing about the predictability of reward related to cues associated with drug availability (Fiorillo et al. 2003). To what extent these phenomena contribute to clinical alcoholism is currently unknown.

2.3 Withdrawal revisited: focus on changes in affective processing

Most recently, there has been a return to emphasis on chronic alcohol use and the role of dependence in vulnerability to relapse and in sustaining substance use. Among the several factors which have led to this shift, three are of particular relevance for the present paper:

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a. Recognition that affective (psychological) components of withdrawal and protracted abstinence influence alcohol/drug use rather than simply avoidance of physiological symptoms of withdrawal.

b. Advances in research approaches that enable detecting changes in affective components of withdrawal, e.g. human functional brain imaging and laboratory procedures; and animal behavioral and neurochemical/molecular procedures (Koob 2009).

c. Refinement of animal models that better reflect the course of alcohol/drug use from initiation and sustained use to the development of dependence.

The renewed focus on processes related to chronic alcohol use, dependence and withdrawal takes into account the limitations of early views centered upon physical manifestations of acute withdrawal, as pointed out e.g. in (Robinson & Berridge 2003). Instead, a neuroadaptive view of alcoholism focuses on long-term plasticity that leads to a persistent negative affective state and altered function of key motivational systems as the proximal cause of relapse and excessive alcohol drinking. In this scenario, phenomena encountered during acute withdrawal and early abstinence are of interest primarily if they reflect events that are critical to the induction of long-term plasticity. Against this background, it becomes critical to define the different phases that follow discontinuation of alcohol use.

3. The withdrawal process

3.1 Time course of acute withdrawal, early abstinence and protracted abstinence

Clinically, alcohol withdrawal follows a characteristic temporal course (See Figure 1). In the absence of co-morbid conditions, other drug use or treatment, three relatively distinct phases are observed:

Acute withdrawal reflects generalized nervous system hyperexcitability, and is dominated by tremors, autonomic nervous system hyperactivity, risk for delirium tremens and seizures. Seizures typically occur within the first 48h following discontinued consumption, with a peak around 24h; tremor follows a similar time course; while delirium tremens typically peaks around 72h. After the first week, symptoms in the acute category are rarely encountered. During acute withdrawal, treatment focus is on controlled return from generalized hyperexcitability, and prevention of seizures and delirium tremens (Victor & Adams 1953; Mayo-Smith 1997).

Early abstinence—We use this term in reference to an intermediate period that follows, during which anxiety, low mood and disturbed sleep continue, but are now expressed in the absence of acute physical symptoms. The elevated anxiety resolves over 3 – 6 weeks after discontinued alcohol use (Schuckit & Hesselbrock 1994), somewhat more slowly in women than in men (Bokström et al. 1991).

Protracted abstinence—During this final phase, elevated anxiety and dysphoria are not necessarily detected by standard assessment methods, but patients continue to report what will here be called a shift in affective processing. During this phase, small, normally insignificant challenges provoke negative affect, craving and relapse (Sinha & Li 2007). An interesting corollary is an attenuation or absence of expected positive responses to normally pleasurable events. This shift can be captured by functional brain imaging, and is associated with craving and relapse risk (Heinz *et al.* 2007; George *et al.* 2008; Gilman & Hommer 2008). Whether these negative affective changes are a key component of protracted abstinence in any given individual may be related to heterogeneity of alcoholics. Such heterogeneity was critically captured by classical adoption studies (Cloninger 1987;

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Sigvardsson et al. 1996; Cloninger et al. 1981). This is highlighted by more recent human data, in which alcoholics without antisocial personality disorder (ASPD) show increased potentiation of the startle response by negative affective stimuli when compared to normal non-alcoholic controls. In contrast, alcoholics with co-morbid ASPD in fact have a lower degree of startle potentiation (Miranda, Jr. et al. 2003; Miranda, Jr. et al. 2002). The former group clearly represents an internalizing (Cloninger – Bohman type I) form of the disease, while the latter is at the extreme of an externalizing subtype (Cloninger – Bohman type II).

3.2 Acute withdrawal vs. protracted abstinence – relation to relapse

Renewed intake of alcohol for relief of acute withdrawal symptoms is one of the diagnostic criteria for alcoholism (American Psychiatric Association et al. 1994). It is, however, unlikely that acute withdrawal, dominated by physical symptoms, is a major motivational factor for inducing relapse by the time that patients seek treatment. One indication that this is not the case is provided by the observation that concurrent use of benzodiazepines, unless provided under the controlled conditions of a detox unit, will not only be ineffective in preventing return to heavy drinking, but in fact increase the risk for it [see e.g. (Malcolm 2003)].

In contrast, protracted abstinence and the affective shift that remains during this phase are emerging as major factors behind craving and relapse (Heinz *et al.* 2003; Breese *et al.* 2005a; Sinha & Li 2007; Heilig & Koob 2007). The accumulated evidence for prolonged pathological activation of brain systems mediating negative affective responses have been captured in an intuitively attractive term as “relief craving” (Heinz et al. 2003). In classical learning theory, this represents negative reinforcement, i.e., the elimination or avoidance of a negative situation.

While affective dysregulation in protracted abstinence is likely to be of immediate relevance for relapse to excessive alcohol use, the link between the early withdrawal phenomena and subsequent affective dysregulation remains unclear. If such a link exists, it would provide a strong rationale for revisiting the biology and genetics of acute withdrawal symptoms.

4. Modeling human withdrawal phenotypes in animals

4.1 Methods to Induce Dependence

A major limitation in modeling clinical withdrawal phenomena has for a long time been that most laboratory animals will not voluntarily consume sufficient amounts of alcohol to produce dependence. Although several lines of rats and mice have been developed through selective breeding to exhibit high avidity for alcohol [for reviews see (Ciccocioppo & Hyytia 2006; Ciccocioppo *et al.* 2006; Colombo *et al.* 2006; Sommer *et al.* 2006; Quintanilla *et al.* 2006; Murphy *et al.* 2002)], few studies have focused on whether voluntary oral consumption of alcohol in these models leads to dependence and, in particular, emergence of withdrawal upon termination of drinking. One exception involves a genetic model, in which a subgroup of P (Preferring) rats selectively bred for high alcohol preference were given unlimited access to alcohol for a period of time (15–20 weeks). This subgroup was chosen for further study because they ingested more than 5 g/kg ethanol/day and showed greater than 67% preference for the 10% ethanol solution vs water. These highest-drinking P rats were shown to exhibit withdrawal signs upon termination of drinking (Waller et al. 1982). In a more recent study, P rats drinking 10% ethanol by choice for 10 weeks and then withdrawn were shown to have 30% reductions in threshold sensitivity to bicucculine seizures (Kampov-Polevoy et al. 2000). It is also clear that both duration and pattern of voluntary ethanol intake contribute to whether signs of withdrawal will emerge (Holter et al. 2000).

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Most animal models of physical alcohol dependence involve experimenter-administered alcohol. Numerous procedures can be used to induce dependence, with three approaches being most common (Becker 2000). Repeated gastric intubations (Majchrowicz 1975) avoid problems of injecting large volumes or high alcohol concentrations intraperitoneally, and allow the dose and timing to be controlled. They also may avoid issues of taste aversion, which develops if oral consumption of unmasked alcohol is forced (Wise 1975). Alternatively, alcohol consumption can be forced by provision in a liquid diet offered as the sole source of fluid and calories. With this procedure, the investigator controls the duration of exposure, but the animal determines the amount and pattern of alcohol consumption. Finally, chronic inhalation of alcohol vapor offers the tightest control over dose and timing of exposure (Rogers *et al.* 1979; Goldstein & Pal 1971).

It is well established in both animal and clinical studies that the amount and duration of alcohol exposure play a significant role for the development of dependence and expression of withdrawal (Finn & Crabbe 1997). Additionally, the pattern of chronic alcohol exposure has been recognized as an important variable in defining the severity of the withdrawal reaction (Becker 1998). Greater severity of withdrawal symptoms has consistently been found when chronic alcohol exposure is delivered in an intermittent rather than continuous fashion (Becker 1999). As discussed below, a growing body of evidence suggests that "kindling" or sensitization of alcohol withdrawal severity may significantly contribute to the negative emotional state that endures into the protracted abstinence phase, as well as enhance relapse vulnerability (Becker 2008; Breese *et al.* 2005a; Heilig & Koob 2007).

4.2 Withdrawal-Related Phenotypes

Regardless of the methods used to induce dependence, animal models have effectively demonstrated numerous physiological and behavioral measures of withdrawal when exposure to alcohol is terminated or significantly reduced [for reviews see (Becker 2000; Deitrich *et al.* 1996; Finn & Crabbe 1997; Friedman 1980; Metten & Crabbe 1996)]. Moreover, these withdrawal responses to a great extent correspond to withdrawal signs and symptoms observed in humans. The following is an overview of alcohol withdrawal-related phenotypes identified in rodent models and the extent to which they correspond to clinical signs and symptoms of the human alcohol withdrawal syndrome. Special attention is given to withdrawal phenotypes that are purported to most strongly affect the vulnerability to relapse and perpetuation of excessive drinking that is characteristic of alcohol dependence.

4.2.1 Measures of Central Nervous System (CNS) Hyperexcitability—A hallmark feature of alcohol withdrawal is CNS hyperexcitability. Because it is relatively easy to measure, withdrawal-related seizures are well documented in animals and humans by electrophysiological as well as behavioral measures (Becker 2000; Deitrich *et al.* 1996; Porjesz & Begleiter 1996; Victor 1970). These include increased frequency of spontaneous as well as evoked perturbations in EEG activity that include spike and sharp wave epileptiform activity and more global synchronized high-voltage spindling activity. 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. While the time course for spontaneous and various experimentally induced convulsions may differ, the general time-dependent waxing and waning of seizure susceptibility is very similar in time course to that observed clinically (Finn & Crabbe 1997; Becker 2000). Further, both electrographic and behavioral measures of seizure activity in animals are highly sensitive to clinically effective anticonvulsants (Becker & Veatch 2002; Becker *et al.* 2006; Crabbe 1992; Veatch & Becker 2005; Watson *et al.* 1997). Thus, withdrawal seizure susceptibility is extensively characterized and clinically relevant. What is uncertain is whether it represents manifestations of those

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neuroadaptations that will affect motivational changes occurring later in withdrawal to engender high risk for relapse and harmful drinking.

Enhanced sensory reactivity is another measure thought to reflect heightened CNS excitability during withdrawal in human alcoholics [e.g., (Grillon et al. 1994; Krystal et al. 1997). A number of studies have been conducted in rats and mice examining the startle response to auditory or tactile (air puff) stimuli. An appealing aspect of this work is that methodology and outcome measures are similar for human and animal studies. However, only a few controlled studies have been conducted in humans, and results from animal studies are generally mixed (i.e., startle reactivity is reported to be increased, decreased, or unchanged during alcohol withdrawal) (Chester *et al.* 2005; Chester & Barrenha 2007; Macey *et al.* 1996; Ponomarev & Crabbe 1999; Rassnick *et al.* 1992; Vandergriff *et al.* 2000). Interestingly, modulation of the acoustic startle response has been shown to be altered in human alcoholics (Miranda, Jr. et al. 2003) as well as in those with a genetic predisposition for the disease (Miranda, Jr. et al. 2002), depending on the emotional valence of presented visual cues. This suggests that the acoustic startle response may be a useful tool for unveiling a shift in affective processing in which a negative emotional state is predominantly associated with alcohol dependence. This possibility has not been examined in animal models, and stress-induced modulation of the startle response during alcohol withdrawal may be a fruitful approach. Conversely, it has recently been shown in animals that neutral stimuli that have been associated with primary reinforcers suppress acoustic startle, presumably providing a measure of hedonic reactivity (Schneider & Spanagel 2008). This is an approach that presumably could be adapted for use with humans.

4.2.2 Measures of Autonomic Nervous System (ANS) Hyperactivity

Physiological symptoms commonly experienced during acute alcohol withdrawal include those that reflect heightened ANS activation and, in particular, increased sympathetic activity [e.g., (Hawley et al. 1994; King et al. 1994). These include tachycardia (increased heart rate), increased blood pressure, diaphoresis (heavy sweating), body temperature dysregulation, and gastrointestinal disturbances (nausea, vomiting). Animal models demonstrate many of these classic sympathomimetic withdrawal symptoms, including altered cardiovascular function, central and behavioral thermal dysregulation, diarrhea, and reduced food and water intake (Crawshaw et al. 1994; Friedman 1980; Rasmussen et al. 2006). However, given the complex and dynamic nature of variables that influence autonomic function, the reliability and practical utility of these measures is questionable (Bar et al. 2006). Further, most of these symptoms resolve within the acute to early phase of abstinence. Thus, the relevance of autonomic perturbations for triggering relapse and sustained heavy drinking is also questionable.

4.2.3 Motor Abnormalities—Tremor is a frequent symptom of alcohol withdrawal. It has all the characteristics of essential (postural) tremor and 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) as well as more quantitative measures (Macey et al. 1996; Meert et al. 1992) to demonstrate increased tremor during withdrawal. Most of this work has been conducted in rats and, to our knowledge, only one study has been performed using mice. Withdrawal Seizure-Prone mice, bred for severe convulsions following chronic ethanol vapor inhalation, were shown to have greater tremor during withdrawal than Withdrawal Seizure-Resistant mice, bred for low convulsion severity (Kosobud & Crabbe 1986).

The time course for withdrawal-related tremor appears to be similar in both animal and clinical studies, predominantly manifesting during acute abstinence, although in humans

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tremor can extend into the early abstinence phase. Interestingly, although anecdotal, alcoholics often report resumption of drinking linked to a desire to self-medicate the "shakes" (tremor). Given that tremor can be measured objectively in both humans and animals along with its potential relevance to relapse, this might be a withdrawal phenotype worthy of further investigation. However, none of the animal studies have examined time points longer than 12hr following withdrawal, so it is unknown how long tremors persist, or whether they can be exacerbated by the application of stress. A recent study reported that the motor performance of mice on a rotarod is compromised for up to 24 hr following withdrawal from chronic vapor inhalation, but is normalized by one week. These studies indicate a genetic contribution to the phenotype, since effects observed differed as a function of genetic background, and suggest that they are more likely due to compromised motor capacity than to compromised ability to acquire this task, which also involves motor learning (Philibin et al. 2008).

4.2.4 Anxiety and negative affect—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 particular relevance to this article, the psychological 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 (Becker 1999; Driessen et al. 2001; Koob 2003; Roelofs 1985). Indeed, both preclinical and clinical studies suggest a link between anxiety and propensity to self-administer alcohol (Henniger *et al.* 2002; Willinger *et al.* 2002; Ciccocioppo *et al.* 2006; Barrenha & Chester 2007; Spanagel *et al.* 1995; Holter *et al.* 1998), although this link is by no means simple either in human alcoholics or in animals (Schuckit & Hesselbrock 1994; Henniger *et al.* 2002).

Of note, while numerous studies reveal comorbid anxiety and depression in human alcoholics, other studies demonstrate a link between alcohol dependence and externalizing psychopathology, which is characterized by a pathological *absence* of anxiety. Not only do these studies illustrate the heterogeneity of alcoholism, but they also suggest that alcohol dependence can arise from susceptibilities anchored to either extreme of the anxiety spectrum. This has implications for animal studies seeking to examine the relationship between anxiety and alcohol drinking.

Several animal models have been used to demonstrate increased anxiety-like behavior during withdrawal from alcohol (Becker 2000; Kliethermes 2005). Many of these models involve procedures that exploit the natural tendency of rodents to avoid exposure to bright and/or open spaces during free exploration. For example, increased withdrawal anxiety-like behavior has been reported in rats using the elevated plus-maze procedure following chronic alcohol exposure in a liquid diet (Baldwin et al. 1991; Rassnick et al. 1993a) and following withdrawal from a single large alcohol dose (presumably reflecting "hangover anxiety") (Doremus et al. 2003; Gehlert et al. 2007; Prediger et al. 2006). Interestingly, both these phenotypes are reversed by blockade of CRH receptors, presumably of the CRH1 subtype within the amygdala (Rassnick et al. 1993a; Baldwin et al. 1991; Gehlert et al. 2007), while increased release of CRH within the central amygdala has been shown during alcohol withdrawal (Pich et al. 1995). These findings are in agreement with the observation that homozygous null-mutation for the CRH1 receptor gene blocks anxiety-like behavior caused by ethanol withdrawal (Timpl et al. 1998). Based on a principle similar to the plus-maze, mice have been shown to exhibit increased avoidance (reduced exploration) of a brightly illuminated portion of a two-compartment chamber when testing is conducted during alcohol withdrawal (Hascoet et al. 2001). Another test, used to assess anxiety-like behavior in rats after withdrawal from extended alcohol exposure (Overstreet et al. 2002) and in an acute

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("hangover anxiety") model (Varlinskaya & Spear 2004), involves detecting a reduction in social interaction behavior in a novel environment.

All of these models have some degree of pharmacological validation, i.e. the anxiety-like behavior during withdrawal is restored to normal by drugs that are effective anxiolytics in humans. They are relatively simple to conduct and, in some instances, allow automated monitoring of behavioral measures. However, while findings of withdrawal anxiety using these procedures have been generally consistent in rats (Heilig & Koob 2007), results in mice have been more variable (for review, see (Kliethermes 2005)). This may in part be related to the labile nature of the behavioral outcomes measured and their sensitivity to environmental testing conditions (Crabbe et al. 1999). A more challenging issue relates to the confound of non-specific reduction in activity during early alcohol withdrawal. Operant procedures have been employed to train animals to discriminate between subjective (interoceptive) cues associated with an anxiogenic state experienced during withdrawal (Gauvin et al. 1992). This approach circumvents confounds from general activity suppression, but it requires extensive training prior to testing, and the extent to which discriminative stimulus effects arising during withdrawal correspond to other behavioral manifestations of anxiety must be considered.

Given that anxiety is a complex construct that requires operational definition in animal studies, it may be advantageous to employ several tasks to draw firm conclusions about the anxiety component of alcohol withdrawal in rodent models. On the other hand, a recent study compared multiple inbred mouse strains on three common behavioral assays of anxiety-like behavior: the elevated zero maze, an open field, and a light/dark box. This study found little differentiation between behavioral indices of "anxiety" and those thought to assess "activity," either within a task or across tasks. This suggests that simply adding additional tasks may be insufficient to resolve the effects of withdrawal on anxiety from those on activity (Milner & Crabbe 2008). Also, as is the case for tremor and other ANS signs, the temporal course of anxiety-like behavior during withdrawal has not been extensively studied. Although some longer term effects have been reported (Valdez et al. 2002; Sommer et al. 2008), most studies examine only a few hours or at most a few days following withdrawal (Kliethermes 2005). A recent paper reported that depression-like behaviors (swim test immobility) and anxiety-like behaviors (in an elevated plus maze) emerged at distinct time points following abstinence from voluntary alcohol drinking in mice (Stevenson et al. 2008). Clearly, this is an area of research that would benefit from more study, especially in relating withdrawal anxiety to relapse.

4.2.5 Sleep Disturbances—Sleep disturbances are common during early withdrawal and often extend into protracted abstinence (Brower 2001; Landolt & Gillin 2001). Clinical studies have noted a 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). Clinical studies have recently begun to evaluate treatment strategies for addressing this aspect of the abstinence syndrome, especially in the context of relapse prevention ((Brower et al. 2008; Le Bon et al. 2003; Malcolm et al. 2007; Staner et al. 2006). Despite their potential clinical significance, there have been surprisingly few animal studies focused on studying alcohol withdrawal-related sleep disturbances. Analysis of EEG in freely moving rats (Slawecki et al. 2000) and mice (Veatch 2006) undergoing alcohol withdrawal has revealed significant and long-lasting alterations in sleep architecture. Use of animal models involving objective measures of abstinence-related sleep disturbances may prove beneficial for elucidating mechanisms underlying the problem, and its potential relation to relapse.

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4.2.6 Increased Sensitivity to Stress and Discomfort—Beyond the early stages of withdrawal, overt anxiety subsides both in patients and experimental animals. However, as recently reported in a variety of models, increased reactivity to stress (i.e., exaggerated anxiety responses to stressful stimuli/events) persists for a protracted period of time (Valdez et al. 2003; Valdez et al. 2002; Sommer et al. 2008; Breese et al. 2005a). Although complaints about irritability and increased sensitivity to every day stressors have long been recognized clinically in alcoholic patients, corresponding human data are just beginning to emerge. For instance, recent neuroimaging (fMRI) studies have revealed selectively exaggerated brain responses to negative affective stimuli (George *et al.* 2008; Gilman & Hommer 2008), and an influence of stress on craving and relapse is beginning to be recognized (Fox *et al.* 2007; Sinha & Li 2007; Sinha 2009).

Both clinical and experimental studies have documented profound disturbances in endocrine stress responses involving the hypothalamic-pituitary-adrenocortical (HPA) axis following chronic alcohol exposure and withdrawal (Rivier 2000; Wand 2000). For example, in humans and rodents, heightened HPA axis activation associated with alcohol withdrawal usually resolves within a few days, but blunted HPA axis responsiveness to stress challenges appears to persist for a protracted period of time (Adinoff et al. 1990; Adinoff et al. 1991; Costa et al. 1996; Lovallo et al. 2000). However, one animal study suggests that stress-induced relapse is independent of HPA-axis function (Le et al. 2000). Rather, HPA-axis changes may be a key signal for the neuroadaptive processes that drive increased sensitivity to stress and relapse vulnerability through extra-hypothalamic effects. In addition to HPA axis related effects, chronic alcohol alters CRH activity independent from the HPA axis (Heilig & Koob 2007; Koob & Le Moal 2001).

Animal studies have shown that increased CRH release in brain structures intimately tied to reward and stress pathways plays a key role in mediating withdrawal-related anxiety and dysphoria both in the acute phase (Rassnick et al. 1993a; Baldwin et al. 1991; Pich et al. 1995) and during their emergence in protracted abstinence (Breese et al. 2005b; Sommer et al. 2008; Valdez et al. 2002). CRH expression within the amygdala complex and the Bed Nucleus of Stria Terminalis (BNST) is under positive transcriptional control by glucocorticoids, in contrast to hypothalamic CRH (Makino et al. 2002). This offers a potential mechanistic link through which increased glucocorticoid release (HPA axis activation) during cycles of withdrawal drives activation of extra-hypothalamic stress circuitry that is at the core of motivational neuroadaptations in alcoholism. Thus, chronic alcohol exposure and withdrawal experience can be viewed as potent stressors that disrupt the functional integrity of the HPA axis along with recruiting extra-hypothalamic CRH systems, and this perturbation in brain/neuroendocrine stress axes may have significant implications regarding motivation for alcohol self-administration behavior.

CRH activity plays a key role in mediating relapse provoked by stressors, as well as excessive drinking in dependent animals (Funk *et al.* 2006; Funk *et al.* 2007; Gehlert *et al.* 2007; Liu & Weiss 2002; Valdez *et al.* 2002; Le *et al.* 2000). These actions of CRH are independent of HPA axis activity (Le et al. 2000; Gehlert et al. 2007). Furthermore, repeated cycles of chronic alcohol exposure and withdrawal lead to not only an exacerbation of physiological symptoms of withdrawal, but also enhanced susceptibility to relapse. For instance, such treatment was found to enhance sensitivity to various stressors, as measured by their ability to activate the HPA axis (Becker 1999), produce anxiety-like behavior (Breese et al. 2005b; Breese et al. 2005a; Sommer et al. 2008), and trigger relapse-like behavior (Ciccocioppo et al. 2003). In all these cases increased CRH transmission was a critical mediating factor, lending support to the idea that enhanced CRF activity represents a key neuroadaptive change that is fueled by repeated withdrawal experience, and this drives

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(at least in part) motivation to drink as well as amplifies responsiveness to stimuli/events that provoke relapse (Heilig & Koob 2007; Koob & Le Moal 2008).

Other neuropeptides that interact with the CRH circuitry have also been implicated in ethanol drinking. One of these is urocortin 1, a member of the CRH family (Ryabinin & Weitemier 2006). Another player is neuropeptide Y (NPY), an endogenous anti-stress mediator that counteracts the effects of CRH system activations (Heilig et al. 1994). Activation of NPY transmission selectively suppresses excessive alcohol drinking in the post-dependent state (Rimondini et al. 2005; Gilpin et al. 2008), although it remains unclear whether this reflects plasticity within the NPY circuitry itself.

While the CRH actions described above are mediated through extra-hypothalamic circuits and do not directly involve glucocorticoid effects, activation of the HPA axis associated with alcohol dependence has also been postulated to contribute directly to amplified motivation to drink. For example, animal studies have indicated that elevation of corticosteroid hormones may enhance propensity to drink through an interaction with the mesocorticolimbic reward circuitry (Fahlke *et al.* 1994b; Fahlke *et al.* 1994a; Piazza & Le 1997).

Taken together, there is a substantial body of evidence suggestig that phenomena associated with alcohol dependence, particularly the withdrawal experience, are stressful events that activate brain/neuroendocrine stress pathways. This may directly and/or through mediating withdrawal-related anxiety and stress/dysphoria responses influence motivation to engage in alcohol self-administration behavior. While it is generally acknowledged that stressful life events play a prominent role in influencing alcohol drinking and, in particular, triggering relapse ((Brady & Sonne 1999; Sillaber & Henniger 2004; Sinha 2001; Sinha & Li 2007; Weiss 2005), the circumstances and manner in which stress influences drinking behavior is complex and not well understood. Future research efforts are needed to further elucidate how dependence/withdrawal modulates stress responsiveness and how such an interaction affects the course of alcohol addiction.

4.2.7 Anhedonia/Dysphoria—Another common feature of the alcohol abstinence 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 aspect of the abstinence syndrome, recent clinical studies have used a number of assessment instruments to better quantify the subjective anhedonic/dysphoric state that endures throughout the protracted abstinence phase (Janiri et al. 2005; Martinotti et al. 2008; Pozzi et al. 2008). Animal studies examining this topic are quite limited. In one study, withdrawal-related anhedonia was demonstrated using an intracranial self-stimulation (ICSS) model. During withdrawal from chronic alcohol exposure, rats evidenced 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). To our knowledge, similar studies have not been conducted in mouse models of alcohol dependence and withdrawal. It has been suggested that a dopamine hypofunctional state may underlie the anhedonia/dysphoria associated with protracted withdrawal (Bailey et al. 2001; Diana et al. 1996; Heinz et al. 1995; Weiss et al. 1996), although other neuroadaptations may contribute [e.g., (Shippenberg et al. 2007)]. It is relatively difficult to study this aspect of withdrawal in animals and development of other models would be beneficial. For example, conditioning models (e.g., conditioned place learning, suppression of acoustic startle by conditioned reinforcers) may be useful to study the aversive/dysphoric aspect of alcohol withdrawal. Again, to the extent that individuals may resume drinking in an attempt to self-medicate the anhedonia/dysphoria associated with abstinence, further investigation into this

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may be valuable for elucidating the underlying mechanisms and time course, as well as for evaluating therapeutic agents that may be used for relapse prevention.

4.2.8 Dependence/Withdrawal vs Relapse and Excessive Alcohol Intake—The phenotypes most directly relevant for linking withdrawal processes with maintenance of alcoholic drinking are excessive voluntary alcohol intake/self-administration, and propensity for relapse. Over several decades, numerous rodent and primate models have been employed to study the relationship between alcohol dependence, experience with withdrawal, and subsequent self-administration behavior (Cappell & LeBlanc 1981; Grant 1995). Early studies generally yielded equivocal findings (Begleiter 1975; Deutsch & Koopmans 1973; Hunter *et al.* 1974; Myers *et al.* 1972; Numan 1981; Samson & Falk 1974; Schulteis *et al.* 1996; Winger 1988), but this was most likely due to procedures that did not sufficiently establish the reinforcing effects of alcohol prior to dependence induction. In these situations, subjects had minimal opportunities to associate alcohol drinking with its withdrawal-alleviating consequences (Meisch 1983; Meisch & Stewart 1994). Incorporating these procedural considerations, more recent studies in mice (Becker & Lopez 2004; Chu *et al.* 2007; Dhaher *et al.* 2008; Finn *et al.* 2007; Lopez & Becker 2005) and rats (O'Dell et al. 2004; Rimondini et al. 2002; Roberts et al. 2000; Sommer et al. 2008; Valdez et al. 2002) have demonstrated increased alcohol responding and/or drinking in dependent compared to non-dependent subjects. In some studies, the enhanced alcohol consumption during withdrawal in dependent animals was shown to produce blood and brain alcohol levels that nearly reached the levels attained during the forced chronic alcohol exposure that produced the dependent state (Griffin et al. 2009; Roberts et al. 2000). Also, just as demonstrated in clinical studies, animals with a history of alcohol dependence exhibit exaggerated sensitivity to the effect of alcohol-related cues and stressors to enhance alcohol-seeking behavior (Gehlert *et al.* 2007; Liu & Weiss 2002; Sommer *et al.* 2008). These effects have been observed up to several months after termination of the alcohol exposure (Lopez & Becker 2005; Valdez *et al.* 2002; Sommer *et al.* 2008), supporting the notion that during *protracted* abstinence there is a latent (subclinical) enhanced vulnerability to relapse that perpetuates the addiction. Recent findings suggest that an additional component of this vulnerability may be a long-lasting tolerance to alcohol following a history of dependence (Rimondini et al. 2008).

A convergent body of preclinical and clinical evidence has demonstrated that a history of multiple detoxification (withdrawal) experiences can result in "kindling" or sensitization of the alcohol withdrawal syndrome (Ballenger & Post 1978; Becker 1998; Becker & Littleton 1996; Breese *et al.* 2005a; Heilig & Koob 2007). As reviewed above, animal studies have shown that experience with repeated cycles of chronic alcohol exposure and withdrawal leads to not only an exacerbation of physical symptoms of withdrawal (e.g., seizures), but also enhanced severity of symptoms that constitute psychological components of the withdrawal syndrome. These models have suggested a link between induction of dependence with repeated withdrawal experiences, and elevated alcohol consumption or self-administration as a consequence, both in rats (Roberts et al. 2000; Rimondini et al. 2002; Rimondini et al. 2003; O'Dell et al. 2004; Sommer et al. 2008) and in mice (Becker & Lopez 2004; Dhaher *et al.* 2008; Finn *et al.* 2007; Lopez & Becker 2005; Chu *et al.* 2007; Lopez *et al.* 2008). Further support for such a link is provided by findings that increased self-administration or consumption in this type of model is selectively sensitive to CRH1 antagonists (Funk et al. 2007; Funk et al. 2006), just as is the increased behavioral responses to stress in the post-dependent state. Interestingly, the alpha-2 adrenoceptor antagonist yohimbine, which potently induced anxiety responses in alcoholics (Krystal et al. 1996), also reinstates alcohol seeking and induces excessive alcohol self-administration in a CRH1 dependent manner (Marinelli et al. 2007).

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5. Conclusions

A growing literature indicates that a history of physical dependence on alcohol that involves repeated cycles of withdrawal is accompanied by increased motivation to self-administer alcohol and propensity to relapse. Robust measures of alcohol withdrawal in humans and experimental animals have long been available, but have mainly focused on physical withdrawal phenomena, and the early stages of the withdrawal process. It remains unknown whether these commonly studied withdrawal phenomena reflect pathophysiological processes that give rise to the motivational aspects of the post-dependent state, or whether they are merely correlative. Human studies are to some extent further along in defining this relationship, through the demonstration that elevated stress-reactivity during early withdrawal from both cocaine and alcohol predicts relapse (Sinha 2008; Sinha et al. 2006). Our paper discusses several withdrawal-related phenotypes that could be studied in animals, and would potentially be more closely related to motivational adaptations relevant for maintaining alcoholism. These types of models would allow studies to determine whether shared or distinct pathophysiology underlies physical and motivational consequences of repeated alcohol withdrawal.

Acknowledgments

The authors wish to acknowledge support by the NIAAA intramural research program (MH), NIH grants AA10760, AA13519, and a grant from the US Department of Veterans Affairs (JC), and NIH grants AA010761, AA014095 and VA Medical Research (HB).

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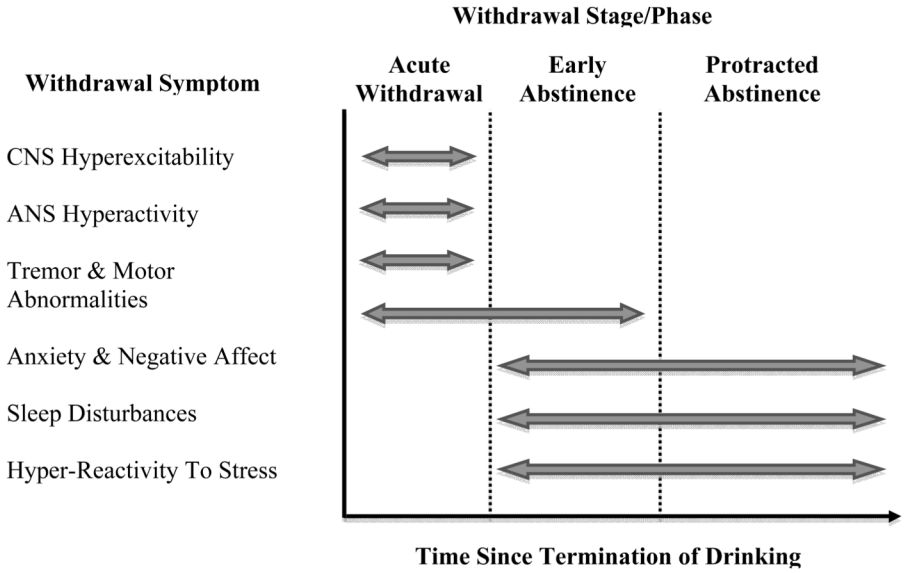

Figure 1. Alcohol Withdrawal Syndrome: Temporal Pattern of Withdrawal Symptoms
Acute Withdrawal Phase: Humans (48–72 hours); Animals (24–48 hours)
Early Abstinence Phase: Humans (3–6 weeks); Animals (1–2 weeks)
Protracted Abstinence Phase: Humans (>3 months); Animals (>1 month)