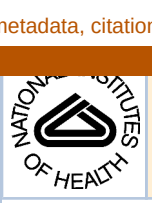

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Conceptual framework for the etiology of alcoholism: a "kindling"/stress hypothesis

George R. Breese, **David H. Overstreet**, and **Darin J. Knapp**
Bowles Center for Alcohol Studies, Departments of Psychiatry and Pharmacology, University of North Carolina School of Medicine, 3007 Thurston-Bowles Building CB-7178, Chapel Hill, NC, 27599-7178, USA, Tel.: +1-919-9663081, Fax: +1-919-9665679

George R. Breese: george_breese@med.unc.edu

Abstract

Rationale—The rationale for proposing the "kindling"/stress hypothesis is to provide a conceptual basis for the insidious development and maintenance of alcohol abuse.

Objective and results—An objective of the hypothesis is to emphasize how continued alcohol abuse is linked to progressive neural adaptation. Work has shown that repeated withdrawals from chronic low levels of alcohol sensitize ("kindle") anxiety-like behavior ("anxiety") in rats, a finding consistent with multiple withdrawal kindling of seizure activity. Additionally, stress substitutes for initial cycles of the multiple withdrawal protocol to sensitize withdrawal-induced anxiety, which is indicative that stress is capable of facilitating neuroadaptive processes related to withdrawal. The persistence of adaptation caused by stress and multiple withdrawals is revealed by the appearance of withdrawal-induced anxiety following a future re-exposure to a single 5-day period of alcohol. This persisting adaptation also permits stress to induce anxiety during a period of abstinence—a response not observed in animals without previous exposure to alcohol. Furthermore, stress interacts with repeated withdrawals to enhance voluntary alcohol drinking. Results of other preclinical and clinical studies reported in the literature are integrated with these investigations in support of the proposed hypothesis.

Conclusions—The "kindling"/stress hypothesis is based on the premise that repeated withdrawals from cycles of chronic alcohol exposure contribute to a progressive development of persisting adaptive change that sensitizes withdrawal-induced anxiety and allows stress to evoke symptoms associated with negative affect during abstinence. Thus, these consequences of repeated withdrawals account for the evolution of major characteristics of alcoholism, which include worsened acute withdrawal symptoms and increased stress-induced negative affect during abstinence, both of which enhance the likelihood of relapse—and with relapse an inability to limit an abusive pattern of alcohol intake. The "kindling"/stress hypothesis provides a clear strategy for future studies to explore the advancing neural adaptation proposed to contribute to the pathogenesis of alcoholism.

Keywords

Multiple withdrawals; Restraint stress; Anxiety; Alcohol drinking; Neural adaptation; Alcohol deprivation effect; Alcoholism; Kindling; Kindling/stress hypothesis

Correspondence to: George R. Breese, george_breese@med.unc.edu.

Introduction

Li (2000) has provided an excellent overview of definitions and characteristics of alcoholism. Although symptoms are not readily observable from initial social drinking, alcoholism is associated with an advancing increase in withdrawal symptoms and an evolving desire to drink during abstinence, which leads to loss of control to limit alcohol drinking and ultimately to an inability to function. These characteristics of the alcoholic are thought to result from an enduring adaptive change in central nervous system (CNS) function induced by excessive alcohol consumption (Heyne et al. 2000; Koob 2003a,b; Koob et al. 2004; Weiss et al. 2001). Although Koob (2003a) emphasized the potential importance of gradual neuroadaptation in alcohol abuse, the premise rested primarily on data from preclinical investigations of long-term continuous exposure to large amounts of alcohol. Few studies examined the neurobiological course of adaptation to intermittent alcohol exposure proposed to initiate and maintain the pathological state of alcoholism.

The present overview supports the concept that repeated withdrawals from chronic alcohol progressively worsen ("kindle") withdrawal-induced anxiety-like behavior and negative affect —a neuroadaptive process that supports continued abuse of alcohol. Evidence also indicates that stress enhances voluntary drinking, sensitizes withdrawal-induced anxiety-like behavior and induces anxiety-related behavior during abstinence from previous chronic alcohol exposure. These preclinical consequences of stress accommodate the stated role of stress in alcoholism (Sinha 2001). The "kindling"/stress hypothesis of alcoholism proposes that the adaptive changes that accompany an escalating abuse of alcohol interact with stress to maintain the pathology of alcoholism. Specific details from literature consistent with this view will be provided.

Concept of kindling seizure susceptibility with repeated withdrawals

The process by which the threshold for seizure activity is lowered with repeated stimulation of brain is defined as kindling (Goddard 1967; Goddard et al. 1969). Pinel et al. (1975) introduced the concept that multiple stimulations of brain can sensitize the alcohol withdrawal syndrome. Ballenger and Post (1978) noted that the number of repeated detoxifications increased the susceptibility of alcoholics for withdrawal-induced seizures and proposed a kindling process to account for this correlation. This theory of kindling seizure activity was subsequently supported by several clinical investigations (Booth and Blow 1993; Brown et al. 1988; Lechtenberg and Worner 1990, 1991, 1992; Worner 1996). Work in rats showing that repeated withdrawals from chronic alcohol facilitate inferior collicular kindling afforded critical support for the kindling hypothesis (McCown and Breese 1990), as did other animal studies that demonstrated enhanced seizure susceptibility following repeated withdrawals (Baker and Cannon 1979; Becker and Hale 1993; Becker et al. 1997, 1998; Clemmesen and Hemmingsen 1984; Kokka et al. 1993; Maier and Pohorecky 1989; Meert and Huysmans 1994; Ripley et al. 2002; Stephens et al. 2001; Ulrichsen et al. 1995, 1998). This concept of "kindling" of seizure activity following repeated detoxifications has been a major advance, as it provided an appreciation of the necessity of progressive adaptive change preceding withdrawal-induced seizure activity in alcoholics.

Sensitization of multiple withdrawal-induced anxiety-like behavior

The theoretical position that seizure activity is "kindled" by multiple detoxifications from alcohol abuse provided an important basis for suggesting that withdrawals from repeated episodes of alcohol ingestion result in adaptive processes within the CNS distinct from those responsible for seizure susceptibility (Adinoff et al. 1995). Ballenger and Post (1978) indeed implied that symptoms of alcoholics unrelated to seizure sensitivity increased with the duration of chronic excessive drinking. Anxiety, negative affective states and depression are known to

be prominent symptoms of acute withdrawal in the alcoholic (Duka et al. 2002; Liappas et al. 2002). Based on a "kindling-like" contribution, a progressive increase of such withdrawal symptoms would be expected during the developing course of alcohol abuse. Consistent with this view, long-term amygdala kindling alters emotional behavior (Kalynchuk et al. 1997). Consequently, "anxiety-like behavior" was assessed in animals to test whether repeated withdrawals from moderate amounts of alcohol would sensitize ("kindle") this behavior common to withdrawal in the alcoholic (Overstreet et al. 2002; Breese et al. 2004a).

Figure 1 shows that a three-cycle withdrawal protocol reduces social interaction when measured 5–6 h after the final withdrawal. Such anxiety-like behavior following repeated alcohol exposures is also apparent in the elevated-plus maze (Overstreet et al. 2002,2004b). Following a continuous alcohol diet for 15 days to provide an equal amount of alcohol as repeated cycling, no measurable change in social interaction is seen during withdrawal (Fig. 1;Overstreet et al. 2002). Thus, sensitization of anxiety-like behavior by repeated withdrawals is not due solely to the presence of alcohol. Selected drugs [i.e., a corticotropin-releasing factor type-1 (CRF-1) receptor antagonist, flumazenil and buspirone] administered during the initial two withdrawals, but not the final withdrawal of the repeated cycling, block the increase in anxiety-associated behavior (Breese et al. 2004a;Knapp et al. 2004b;Overstreet et al. 2003b, 2004a). This latter observation affords critical evidence that repeated withdrawals induce adaptation that accumulates from one cycle to the next to sensitize this withdrawal symptom. Since no change in locomotor activity is observed with withdrawal (Overstreet et al. 2002;Breese et al. 2004a), a change in this behavior could not account for the reduction in social interaction. Additionally, pharmacological studies have indicated that any change in locomotor activity induced by multiple withdrawals does not correlate with withdrawal-induced anxiety-like behavior (Overstreet et al. 2002,2003b,2004a;Breese et al. 2004a).

The adaptation associated with repeated withdrawals persists for a sufficient period to support anxiety-like behavior for up to 32 days after withdrawal from a single 5-day future re-exposure to chronic alcohol (Overstreet et al. 2002). Withdrawal from a single 5-day exposure to alcohol is without effect on social interaction behavior (Overstreet et al. 2002). This protocol of re-introducing chronic alcohol to uncover functional change is reminiscent of previous work in which priming injections of drugs of abuse altered responding for the drug that would not otherwise be apparent (de Wit and Stewart 1981), an approach suggested to be related to drug relapse (see reviews by Shaham et al. 2003; Katz and Higgins 2003; Epstein and Preston 2003).

In another investigation consistent with adaptive change, an extended chronic alcohol vapor exposure followed by repeated bouts of alcohol self-administration produced persistent anxiety-like behavior in the elevated-plus maze in the absence of withdrawal from re-exposure to an additional alcohol challenge (Valdez et al. 2002). Likewise, Rasmussen et al. (2001) provided evidence of anxiety-related behavior in the elevated-plus maze 4 weeks after cessation of a 4-week exposure to an alcohol diet. An uncertainty requiring future examination is whether a continuous high level of alcohol exposure results in the same adaptation(s) responsible for the "kindling-like" sensitization of anxiety-like behavior that follows repeated withdrawals from short exposures to a lesser amount of alcohol. Another future investigation would be to determine how low the concentration of alcohol could be reduced for multiple withdrawals to sensitize withdrawal-induced anxiety-like behavior. This knowledge can provide an understanding of the threshold for the amount of alcohol and the duration of alcohol exposure endured before causing adaptive changes that result in enhanced symptoms of withdrawal (Coper et al. 1990). Finally, it has yet to be determined whether repeated withdrawals from 4.5% alcohol diet make these animals more seizure prone during the final withdrawal. This repeated withdrawal experiment would test whether the "kindling process" responsible for

enhanced anxiety-associated behavior is distinct from neural adaptation that facilitates seizure susceptibility.

Repeated stress sensitizes withdrawal-induced anxiety

The view that stress affects the process of drug abuse has been revived (Sinha 2001). Based on multiple cases of withdrawal-induced sensitization of anxiety-like behavior (Overstreet et al. 2002), restraint stress was applied twice at weekly intervals (i.e., to substitute for repeated withdrawals), followed by withdrawal from a single 5-day exposure to an alcohol-containing diet, to determine whether social interaction would be reduced. While the single 5-day exposure to the alcohol diet alone did not affect anxiety-related behavior, the prior repeated restraint stress experience reduced social interaction during withdrawal (Breese et al. 2004a). Stress in the absence of subsequent alcohol exposure did not induce an anxiety-related response. Although stress is well known to increase peripheral corticosterone in rats, two weekly administrations of corticosterone instead of stress did not decrease social interaction after withdrawal from the 5-day exposure to chronic alcohol (Breese et al. 2004a). Thus, peripheral release of corticosterone is not responsible for stress sensitization of withdrawal-induced "anxiety." Consistent with a persistence of adaptive change with repeated withdrawals (Overstreet et al. 2002), re-exposure of rats to 5 days of an alcohol diet 16 days after being subjected to the stress/withdrawal protocol significantly enhanced withdrawal-induced anxiety (Breese et al. 2004a). A future determination will define whether stresses differing from restraint sensitize withdrawal-induced "anxiety."

Stress-induced anxiety after previous chronic alcohol exposure

Given that stress substitutes for repeated withdrawal sensitization of anxiety-like behavior, the possibility existed that adaptation to previous alcohol exposures would allow a subsequent stress to induce an anxiety-related response. As shown in Fig. 2, restraint stress applied 3 days after a final withdrawal from the repeated withdrawals reduced social interaction (Breese et al. 2004b). Animals exposed to the multiple withdrawal protocol, but not stressed, exhibited no anxiety-associated behavior when tested 3 days after the final withdrawal. Social interaction after stress in the rats exposed to the control-liquid diet was comparable to that seen in non-stressed rats on a control diet. Valdez et al. (2003) previously demonstrated anxiety-related behavior following stress during alcohol abstinence but, as noted here, only in animals with a previous history of extended chronic alcohol exposure. Collectively, these data emphasize that the adaptation related to previous alcohol exposure(s) is a necessity for stress to produce an anxiety-like response. Such data strengthen the view that stress can emulate the adaptive change associated with repeated withdrawals (Breese et al. 2004a). Therefore, "stress" in an abstinent alcoholic may be perceived as a "withdrawal-like syndrome" capable of producing anxiety-associated symptoms.

Repeated alcohol withdrawals and the alcohol-deprivation effect: relationship to self-administration and alcohol seeking

The alcohol deprivation effect, first described by Sinclair and Senter (1967, 1968), is defined as an increase in voluntary alcohol consumption after a period of abstinence from drinking. This procedure models craving and loss of control on relapse to drinking (Heyser et al. 1997; Rodd-Henricks et al. 2000a,b; Sinclair and Li 1989; Spanagel and Hölter 2000). The characteristics of this important property of chronic alcohol pharmacology have been examined in numerous investigations (Heyser et al. 1998, 2003; Hölter et al. 2000; Koros et al. 1999a; Lê and Shaham 2002; McBride et al. 2002; McKinzie et al. 1998; Rimondini et al. 2002; Rodd et al. 2003; Samson and Chappell 2001; Serra et al. 2002; Sinclair and Li 1989; Spanagel and Hölter 1999, 2000; Spanagel et al. 1996; Vengeliene et al. 2003). Because the consequence of

alcohol deprivation remains after prolonged periods of abstinence (Sinclair 1972; Sinclair and Li 1989; Wolffgramm and Heyne 1995), a persistent adaptive change must accompany this exposure to chronic alcohol. With respect to whether repeated deprivations affected this alcohol-drinking phenomenon, Hölter et al. (1998) reported that such multiple deprivation episodes increased voluntary drinking of a higher concentration of an alcohol solution. Rodd-Henricks et al. (2000a,b, 2001) also found that repeated deprivations from extended alcohol exposure increased the initial degree of voluntary drinking as well as the duration of elevated alcohol intake in ethanol-preferring P-rats. Likewise, Rimondini et al. (2002) reported a long-lasting increase in voluntary alcohol intake following repeated cycles of withdrawal (i.e., deprivations). Subsequently, Breese et al. (2004a) found that exposure of ethanol-preferring P-rats to multiple withdrawals from voluntary alcohol drinking facilitated alcohol consumption during the final 5-day re-exposure to alcohol—an observation consistent with the alcohol deprivation effect being activated.

Utilization of the sucrose-fading procedure to obtain reliable bar pressing for ingestion of alcohol is a popular apvproach to investigate alcohol drinking (Brown et al. 1998; Ciccocioppo et al. 2004; Lê et al. 1999, 2003; Rogowski et al. 2003; Roberts et al. 1996; Samson 1986; Valdez et al. 2002; Weiss et al. 1993). However, while extended absence from bar pressing increased intake when alcohol was restored in some investigations (i.e., similar to alcohol deprivation; Heyser et al. 1997; Hölter et al. 1997; McKinzie et al. 1998), Samson and Chappell (2001) found no effect of deprivation on intake using a limited access operant procedure. However, with ethanol-preferring P-rats, repeated alcohol deprivations increase the magnitude and duration of their response for an alcohol lever (Rodd et al. 2003). Animals previously physically dependent on alcohol exhibit elevated operant responding for alcohol during withdrawal (Roberts et al. 2000) and for an extended period post-withdrawal (Roberts et al. 2000; Valdez et al. 2002).

Testing motivation for alcohol involves a post-extinction return to pressing a bar previously associated with alcohol responding, but in the absence of alcohol available to drink (Backstrom et al. 2004; Bienkowski et al. 2000; Chiamulera et al. 1995; Ciccocioppo et al. 2002, [2003], [2004]; Koros et al. 1999b; Lê et al. 1998, 2003; Lê and Shaham 2002; Liu and Weiss 2002a,b). Animals trained to lever press for access to alcohol in the presence of auditory or visual cues will not necessarily reinstate lever pressing to these cues after extended extinction (Katner et al. 1999; see also Bienkowski et al. 2000). However, non-contingent “priming” with alcohol reinstates responding on the “alcohol bar” (Chiamulera et al. 1995; see review by Lê and Shaham 2002). Likewise, when exposed to a combination of an olfactory cue for alcohol and a previously presented auditory or visual cue (Katner et al. 1999; Bienkowski et al. 2000), alcohol-seeking behavior is reinstated. An alternative approach to facilitate motivation for alcohol after extinction is to induce alcohol dependence prior to testing (Ciccocioppo et al. 2003; Liu and Weiss 2002a,b). It is noteworthy that multiple withdrawals did not enhance cue-induced reinstatement of alcohol seeking (Ciccocioppo et al. 2003).

While data are consistent with repeated withdrawals (deprivations) increasing voluntary alcohol ingestion (Breese et al. 2004a; Rodd-Henricks et al. 2000a,b, 2001) or bar pressing for alcohol (Rodd et al. 2003), inconsistencies appear to exist between these latter findings and those obtained with models of alcohol motivation. Therefore, it would seem wise to undertake future investigations to resolve these apparent differences associated with voluntary alcohol drinking, self-administration of alcohol with bar pressing and models of alcohol-seeking behavior, particularly with respect to previous repeated deprivations from chronic alcohol exposure. Resolution of these possible inconsistencies could point to alternative views concerning the pathology of alcohol seeking and ingestion.

Stress during withdrawal from multiple alcohol exposures increases alcohol drinking: relationship to stress effects on self-administration and alcohol seeking

Based on the tension-reduction hypothesis, investigators have assumed that increased alcohol intake relates to reducing stress-induced “tension” (Cooper et al. 1992; Kalodner et al. 1989; Kushner et al. 1994; Young et al. 1990; Brown et al. 1990, 1995). However, this concept continues to be a matter of debate as stressors have had mixed effects on alcohol drinking in preclinical studies (Pohorecky 1990; Lê and Shaham 2002; Chester et al. 2004; Breese et al. 2004a). With regard to anxiety as a reflection of “tension,” Henniger et al. (2002) were unable to relate alcohol ingestion to anxiety in rats selectively bred for anxiety-like behavior.

Because stress facilitated withdrawal-induced anxiety-like behavior (Breese et al. 2004a) and repeated deprivations enhanced voluntary alcohol intake in ethanol-preferring P-rats (Breese et al. 2004a; Rodd-Henricks et al. 2000a,b), stress was applied during the initial two withdrawals of the repeated-cycling (deprivation) protocol to determine whether voluntary alcohol ingestion would be affected. Following this stress exposure protocol, significantly greater voluntary alcohol drinking occurred in ethanol-preferring P-rats during the final 5 days of alcohol exposure than in those drinking in groups not exposed to stress or in rats that experienced only repeated deprivations or continuous alcohol availability (Breese et al. 2004a; Overstreet et al. 2003a). Thus, stress not only stimulates adaptive changes responsible for enhancing withdrawal symptoms, but also influences the magnitude of voluntary alcohol drinking in this alcohol-preferring rat strain undergoing repeated deprivations (Breese et al. 2004a). Following restraint stress application for ten consecutive days, Chester et al. (2004) reported an initial decrease in alcohol intake in alcohol-preferring rats during stress that was not apparent in NP and low alcohol drinking (LAD) rats. Following the first few days after stress was terminated, voluntary alcohol intake increased in ethanol-preferring P-rats, but not in high alcohol drinking (HAD) rats. Collectively, these findings are consistent with stress enhancing voluntary drinking; however, timing between stress application and assessment of drinking as well as genetic background influence this action of stress.

It is noteworthy that voluntary drinking in ethanol-preferring P-rats driven by repeated stresses during each deprivation has a different drinking pattern than that seen in rats exposed only to multiple deprivations. In the absence of previous stresses, the magnitude of the increased consumption of alcohol observed on day 1 of the third reintroduction to alcohol rapidly returns to baseline (Breese et al. 2004a). However, voluntary intake in ethanol-preferring P-rats exposed to stress persists at this initial elevated level for the remaining 4 days after reinstatement to the alcohol solution (Breese et al. 2004a). Thus, this extended ethanol intake after stress application during repeated withdrawals results in a significant increase in the total consumed over the final extended 5-day period when compared with the group that underwent multiple deprivations without stress.

Just as stress accentuates drinking related to repeated alcohol deprivations in ethanol-preferring P-rats (Breese et al. 2004a), stress can enhance alcohol drinking in mice (Sillaber et al. 2002). Likewise, stress can increase alcohol-seeking behavior (Lê et al. 1998, 1999, 2000; Lê and Shaham 2002; Liu and Weiss 2002b, 2003; Martin-Fardon et al. 2000; Weiss et al. 2001). In fact, stress is a more powerful stimulus for alcohol seeking than “priming” doses of alcohol (Lê et al. 1998). Liu and Weiss (2003) found that conditioned stress increased alcohol-seeking behavior in post-dependent rats, with conditioned stress and alcohol cues interacting to further facilitate alcohol seeking. However, despite these data, Koros et al. (1999b) found that restraint stress did not affect the alcohol dose–response curve for alcohol discrimination.

The “kindling”/stress hypothesis: conceptual framework for the etiology of alcoholism

Alcoholism is a disorder that progresses from “social drinking” to a state of uncontrolled abuse (Wolffgramm et al. 2000). The multiple withdrawal sensitization of anxiety-like behavior documents that a series of withdrawals allows adaptation to accumulate (“kindling-like process”; Breese et al. 2004a; Overstreet et al. 2002). This accumulative adaptive process following repeated withdrawals is proposed to emulate the advancing pathogenesis associated with the development of alcoholism (Fig. 3, phase I). That adaptation follows excessive chronic alcohol intake and contributes to maintaining alcohol abuse is not a unique concept (Adinoff et al. 1995; Koob and LeMoal 1997; Koob 2003a; Koob et al. 2004; Robinson and Berridge 2000; Weiss et al. 2001). Koob and LeMoal (1997) presented the “hedonic homeostatic dysregulation” hypothesis to explain the adaptation associated with alcoholism. Later, the process of developing alcohol abuse was stated as the “allostasis model of alcoholism” (Koob and LeMoal 2001; Koob 2003a; Roberts et al. 2000). This view of “allostasis” arose in part from a previous conceptual framework espoused by Sterling and Eyer (1988) and McEwen (1998, 2000). While allostasis was initially viewed as an adjustment to environmental change through the establishment of new physiological set-points (Sterling and Eyer 1988), the concept of allostatic load was introduced as a pathophysiological state related to excessive allostasis (McEwen 1998, 2000). With regard to repeated alcohol exposures, an increase in allostatic load to continuing exposures allows biological stability (Koob 2003a; Roberts et al. 2000). With entrenchment of the allostatic load, removal of alcohol results in an abrupt pathological response (e.g., withdrawal symptoms). Likewise, because the allostatic load persists, it can support a persistent vulnerability to future challenges (e.g., alcohol cues, alcohol itself, stress). Thus, the progressive increases in allostatic load (adaptation) that accompany repeated withdrawals provide a physiological basis for the gradual worsening of symptoms (“kindling process”) that ultimately contributes to the alcoholic state.

Although Duka et al. (2002) did not observe increased anxiety associated with multiple detoxifications in an alcoholic population, other clinical findings support the view that symptoms and selected functions associated with withdrawal (but unrelated to seizure sensitivity) are adversely affected with the increasing duration of excessive drinking or previous detoxifications (Duka et al. 2003; Krystal et al. 1997; Malcolm et al. 2000b; Townshend and Duka 2003; see also Duka et al. 2004). Further, Pelc et al. (2002) reported that the number of detoxifications was inversely related to therapeutic outcome, a finding presumably related to symptoms. Thus, the evolution of increased withdrawal symptoms with the development of alcoholism is presumed to contribute to continued alcohol abuse (Fig. 3, phases I and II; Adinoff et al. 1995; Koob 2003a; Li 2000).

Following removal from chronic alcohol exposure, the acute withdrawal syndrome in alcoholic individuals is associated with symptoms that can include anxiety, depression, a negative affective state and confusion (Fig. 3, phase IIIa; Duka et al. 2002;Liappas et al. 2002)—the nature of the withdrawal symptoms being dependent on the amount of alcohol previously ingested and the duration of alcohol abuse (Ballenger and Post 1978). When alcohol drinking occurs during an acute withdrawal state, alcoholics indicate they “feel better.” Drinking to alleviate the “distress” induced by the negative affective state during withdrawal requires previous knowledge that alcohol intake diminishes acute withdrawal symptoms—a conclusion consistent with views of Heyne et al. (2000) and Wolffgramm et al. (2000). In accord with a report by Cooney et al. (1997),Koob et al. (2004) recently reviewed the concept that a negative motivational state drives addiction. Consequently, one basis for continued alcohol abuse is related to an avoidance of “distress” from worsening acute withdrawal symptoms induced by a “kindling” process that advances the course of alcoholism.

A sign of acute withdrawal "distress" in an alcohol-abusing individual is "craving" (Fig. 3, phase IV; Heinz et al. 2003a,b;Isbell 1955;Stockwell et al. 1984). "Craving" for alcohol can be defined as the desire to drink to avoid a negative state (Koob 2000; see also Franken 2003). Craving is presumed to be a significant component of alcohol use when adaptation to previous excessive alcohol intake reaches a "point of no return" with respect to diminished capability to control drinking—a view expressed by Coper et al. (1990). The importance of craving in diagnosed alcoholics is exemplified by the high degree of desire to drink after non-treated alcoholics view alcohol cues, whereas "social drinkers" do not exhibit this response (George et al. 2001;Myrick et al. 2004). These findings provide evidence that craving can be a significant symptom in the alcoholic irrespective of the state of withdrawal. Consistent with repeated withdrawals contributing to worsening symptoms, Malcolm et al. (2000a) reported elevated craving during withdrawal in patients who had undergone more than two previous detoxifications. Without treatment to minimize the worsening "psychological" and emotional symptoms of acute withdrawal (Li 2000;Malcolm et al. 2000a,b), the craving expressed by an alcoholic during withdrawal will be a driving force for relapse and resumption to abusive drinking (Fig. 3, phases IV and V).

In addition to "craving" during withdrawal, evidence indicates that craving is present following recovery from the acute withdrawal phase (Fig. 3, phases IIIb and IV; Isbell 1955;Roelofs 1985). In this respect, emotions that include anxiety, depression, and negative affect have been observed during abstinence (Kushner et al. 2001;Liappas et al. 2002;Roelofs 1985;Willinger et al. 2002)—symptoms similar to those observed with acute withdrawal. In accord with the concept that symptoms during abstinence resemble those induced by withdrawal, Begleiter and Porjesz (1979) reported a persistent "subacute withdrawal syndrome" in abstinent alcoholics. Likewise, Roelofs (1985) described a subacute withdrawal syndrome associated with craving during abstinence that involved hyperventilation and anxiety, symptoms that correlated with the duration of chronic alcohol abuse. What could be the neurobiological basis for the appearance of a "withdrawal-like syndrome" that results in craving during abstinence in the alcoholic?

Adaptive processes seen with repeated withdrawals from chronic alcohol exposures do not return rapidly to normal (Breese et al. 2004a; Overstreet et al. 2002). Therefore, a likely explanation for craving during abstinence is that stress on a background of persistent adaptive change induced by previous alcohol abuse contributes to this syndrome. In support of this view, repeated stresses sensitize withdrawal-induced anxiety-like behavior (Breese et al. 2004a), a finding consistent with stress having a similar neurobiological basis of adaptation as withdrawal. Additionally, adaptation induced by repeated withdrawals or extended alcohol exposure allows stress to cause anxiety-like behavior in the absence of alcohol (Fig. 2; Breese et al. 2004b; Valdez et al. 2003). Thus, stressful events during abstinence on a background of adaptation induced by previous chronic alcohol abuse are presumably perceived in part as "withdrawal" (Begleiter and Porjesz 1979). Such symptoms in the alcoholic contribute to maintenance of negative symptomatology in the absence of alcohol (Adinoff et al. 1995; Begleiter and Porjesz 1979; De Soto et al. 1985; Roelofs 1985; Sinha and O'Malley 1999; Sinha 2001; Willinger et al. 2002), just as suggested for other psychopathologies (Schulkin et al. 1994). What promotes stress in the alcoholic during abstinence?

Cues related to alcohol ingestion result in craving in abstinent alcoholics (Cooney et al. 1997; Heinz et al. 2003a,b; Childress et al. 1993; De Soto et al. 1985; Glautier and Drummond 1994; Monti et al. 2000; Sinha 2001; Sinha and O'Malley 1999), just as occurs with cues in non-abstinent alcoholics (George et al. 2001; Myrick et al. 2004). Additionally, Townshend and Duka (2001) found an attentional bias to alcohol-related stimuli in heavy drinkers. In the alcoholic attempting to be temperate, cues related to alcohol can be considered "stressful." The basis of craving following exposure to stressful environmental cues during abstinence is

presumably dependent on persistent adaptation induced by multiple previous exposures to chronic alcohol (Fig. 3). The ability of stress to increase alcohol seeking (Lê et al. 1998, 1999, 2000; Lê and Shaham 2002; Liu and Weiss 2002a, 2003; Martin-Fardon et al. 2000) is consistent with stress enhancing the probability of relapse and furthering alcohol abuse. Further, the risk of relapse in alcoholics is reportedly increased by stress (Brown et al. 1990, 1995; Pohorecky 1991; Sinha 2001), with anxiety during abstinence being a predictor of end-state drinking (Kushner et al. 1994, 2000, 2001; Sloan et al. 2003; Willinger et al. 2002). However, it is emphasized that not all alcoholics describe an occurrence of anxiety during abstinence (Li 2000; contact with psychiatrists); rather, other symptoms observed that facilitate craving during alcohol-free periods include depression and negative affect (Duka et al. 2002; Liappas et al. 2002).

Another characteristic of the alcoholic is the inability to control the degree of drinking with relapse (Fig. 3, phase V). The alcohol deprivation phenomenon is proposed to reflect the distinct neural adaptation responsible for loss of control in alcoholics (Koob 2000;McBride et al. 2002;Sinclair and Senter 1968;Sinclair and Li 1989;Wolffgramm and Heyne 1995). As noted earlier, preclinical observations indicate that repeated withdrawals (deprivations) from extended exposure to alcohol increase the alcohol deprivation effect in both initiation and duration of excessive drinking (Rodd-Henricks et al. 2000a,b,2001). Stresses combined with repeated withdrawals also facilitate duration of drinking initiated by alcohol deprivation (Breese et al. 2004a). Thus, repeated withdrawals from previous drinking and exposure to stressful events facilitate adaptation that strengthens the probability of “craving” and reduces the likelihood that an alcoholic will drink only moderate amounts of alcohol with relapse (Fig. 3). Further withdrawals in the dependent alcoholic continue the progression of “kindling” that ultimately results in an increased susceptibility of seizure activity during withdrawal (Ballenger and Post 1978).

In addition to the adaptation that accompanies alcohol abuse, genetic background can unquestionably contribute to the susceptibility of an individual for alcoholism (Cloninger et al. 1981; Cloninger 1987; Dick et al. 2002; Heath et al. 1997; Merikangas 1990; Merikangas et al. 1998; Reich et al. 1998). To account for this susceptibility, it is presumed that the adaptive consequences of repeated chronic alcohol exposures and stresses are facilitated in individuals with a genetic vulnerability for alcohol abuse. Thus, less time may be required in genetically susceptible individuals for repeated alcohol exposures to induce adaptive processes that progress to a pathological state. In preclinical support of this view of genetic susceptibility, ethanol-preferring P-rats exhibit withdrawal-induced anxiety after a single 5-day exposure to a 7% alcohol diet, whereas Sprague-Dawley rats do not (unpublished data). Further testing in various genetic models having differing response characteristics to alcohol (Vengeliene et al. 2003) would allow critical testing that appropriate genetic background can facilitate adaptive processes that enhance vulnerability.

Another contributing factor for alcohol abuse can arise from the pre-existence of anxiety or depressive symptoms (Kushner et al. 2000, 2001; Stewart et al. 1997). However, while preexisting genetic susceptibility (Cloninger et al. 1981; Dick et al. 2002; Merikangas et al. 1998) or disease (Kushner et al. 2000, 2001; Stewart et al. 1997) can enhance the probability for alcoholism, environmental factors can also contribute (Johnson et al. 1996a,b; Slutske et al. 1999; True et al. 1996). Nonetheless, irrespective of predisposing factors, if individuals are exposed to excessive amounts of alcohol, the basic adaptive processes of alcohol abuse will result in a progressive path to those characteristics defining alcoholism.

In summary, excessive use of alcohol over time leads to persistent adaptive changes, which enhance the probability of alcohol abuse being maintained (Fig. 3). Because a “kindling-like” process sensitizes functional changes associated with withdrawal from chronic alcohol

exposures, a desire to drink (craving) during withdrawal is evoked—an occurrence enhancing the probability of relapse (Isbell 1955). Likewise, withdrawal-like symptoms during abstinence in the alcoholic are precipitated by cues in the environment that result in negative affect and anxiety (Begleiter and Porjesz 1979;Roelofs 1985)—another circumstance that results in craving and the likelihood of continued alcohol abuse (Cooney et al. 1997;Sinha 2001;Sinha and O'Malley 1999;Sloan et al. 2003;Willinger et al. 2002). Collectively, the advancing adaptive changes from excessive alcohol drinking interacting with stress result in increased severity of withdrawal symptoms, a desire to drink to reduce negative affect (i.e., craving) during acute withdrawal and abstinence and, ultimately, to a loss of control to limit alcohol consumed with relapse. To account for the progressive development of pathogenesis associated with these characteristics of the alcoholic, the “kindling”/stress hypothesis of alcoholism is proposed (Fig. 3). This theoretical position provides a clear strategy for future preclinical and clinical studies.

Future directions

Whereas an antagonist for the CRF_2 receptor was unable to block repeated withdrawal-induced “anxiety,” data implicated CRF_1 receptors in the repeated withdrawal and the stress/withdrawal protocols (Breese et al. 2004a; Knapp et al. 2001, 2003, 2004b; Overstreet et al. 2003b, 2004a). However, removal of the gene for the CRF_2 receptor resulted in anxiety (Bale et al. 2000; Kishimoto et al. 2000). Risbrough et al. (2004) suggested that CRF_1 and CRF_2 receptors have opposing influences on startle behavior, and Bale and Vale (2004) reported that both CRF receptor subtypes contribute to coordinating responses to stress. Therefore, pharmacological investigations to characterize the possible interactive role of CRF_1 and CRF_2 receptors in controlling withdrawal-induced and stress-induced anxiety are desirable.

Reports indicate that multiple withdrawals from alcohol impair learning of a conditioned emotional response (CER; Stephens et al. 2001; Ripley et al. 2003, 2004), a result consistent with a persistent adaptive change. Based on these findings, Stephens et al. (2001) argued that altered affective state is not likely to drive relapse. This conclusion is seemingly contrary on the hypothesis being proposed (Fig. 3). A major consideration for interpretation is the absence of anxiety-like behavior 2 weeks following the repeated withdrawals (Overstreet et al. 2002), the time period at which the CER is measured (Stephens et al. 2001). In order to elicit anxiety-like behavior at this later period after repeated withdrawals, animals have to be provoked by re-introduction to withdrawal from a subsequent ethanol challenge or to stress (Overstreet et al. 2002; Fig. 2). Therefore, the conditioned fear inferred from the CER study may not share overlapping sensitization with brain circuits/regions supporting anxiety (McHugh et al. 2004; Walker et al. 2003). Comparing the effects of pharmacological challenges on CER and anxiety-like behavior (Overstreet et al. 2003b, 2004a; Knapp et al. 2004b) should assist in resolving differences in interpretation of these persistent consequences associated with repeated withdrawals.

The amygdala and “extended amygdala” (Alheid et al. 1995) are brain regions presumed to play a key role in supporting withdrawal-induced anxiety-like behavior (Koob 2003b; Merlo Pich et al. 1995; Rassnick et al. 1993). In preliminary data, Knapp et al. (2004a) reported that flumazenil acts in the amygdala to antagonize sensitization of multiple withdrawal-induced anxiety-associated behaviors. Thus, future work should assess whether this brain site supports CRF and serotonin involvement (Overstreet et al. 2003b, 2004a) in adaptive change responsible for sustaining the anxiety-associated behavior that follows the repeated withdrawal and stress/withdrawal protocols (Breese et al. 2004a; Overstreet et al. 2003b, 2004a). Based on the interaction of CRF with serotonergic mechanisms in the medial raphe on alcohol seeking (Lê et al. 2002), the possible involvement of this brain site in the serotonin and CRF contribution to repeated withdrawal and stress-induced sensitization of “anxiety” should be assessed (Breese

et al. 2004a; Overstreet et al. 2003b, 2004a). To explore the hypothesis that repeated withdrawals "kindle" differing symptoms of withdrawal (e.g., locomotor activity, seizures, anxiety, etc.) by affecting distinct regions of brain, testing the possible influence of the inferior colliculus on withdrawal-induced anxiety would seem worthwhile. Likewise, defining the mechanism by which repeated withdrawals facilitate inferior collicular seizures, while reducing kindling of the amygdala (McCown et al. 1987) and hippocampus (Veatch and Gonzalez 1999, 2000), should receive attention. Additionally, it would be of interest to test opiate antagonists on multiple withdrawal-induced anxiety at sites where they reduce alcohol self-administration and alcohol deprivation (Heyser et al. 1999). Finally, another worthy goal would be to examine whether anxiety-like behavior relates to brain sites implicated in other actions of alcohol (Besheer et al. 2003; Hodge and Cox 1998; Hodge et al. 1996; June et al. 2003; Rodd-Henricks et al. 2000c, 2003).

The success of drug treatment on alcoholism generally focuses on alcoholics remaining sober during abstinence and limiting the degree of drinking upon relapse. Opiate antagonists (Heinälä et al. 2001; Litten and Allen 1998; O'Malley et al. 1992; Monti et al. 2001; Rubio et al. 2001; Volpicelli et al. 1992), acamprosate (Ansoms et al. 2000; Besson et al. 1998; Chick et al. 2000; Lesch et al. 2001; Rubio et al. 2001; Sass et al. 1996; Tempesta et al. 2000; Litten and Allen 1998; see overview by Mason 2001) or a combination of these drugs (Kranzler and Van Kirk 2001) are currently prescribed to reduce alcohol consumption in alcoholics. In preclinical studies, opiate antagonists are capable of minimizing acute drinking of alcohol (Altshuler et al. 1980; Badia-Elder et al. 1999; Froehlich et al. 1990; Heyser et al. 2003; Hölter and Spanagel 1999; Hyytia and Sinclair 1993; Overstreet et al. 1999; Samson and Doyle 1985), as well as reducing alcohol seeking by an alcohol conditioned stimulus (Liu and Weiss 2002a; Koob et al. 2003). However, naltrexone's maintenance of abstinence in alcohol-dependent patients was not remarkable in one study (Guardia et al. 2002) and was absent in another (Krystal et al. 2001). Chick et al. (2000) provided disappointing effectiveness of acamprosate in their investigation. It is important to note that continuous use of opiate antagonists induces a rebound increase in central opiate receptors (Cowen et al. 1999; Overstreet et al. 1999; Parkes and Sinclair 2000). These latter preclinical data are consistent with the view that testing of naltrexone prior to each drinking episode in the alcoholic is a superior approach for decreasing loss of control (Sinclair 2001; Heinälä et al. 2001) than continuous treatment (Guardia et al. 2002; Krystal et al. 2001; O'Malley et al. 1992; Rubio et al. 2001). Therefore, future basic and clinical investigations should identify the best strategy for opiate antagonist treatment of alcoholism. Finally, a priority should be given to translation of preclinical to clinical research to identify means to minimize the persistent adaptive changes induced by sustained alcohol abuse (Heinz et al. 2003a,b; Longo et al. 2002; Malcolm et al. 2001, 2002).

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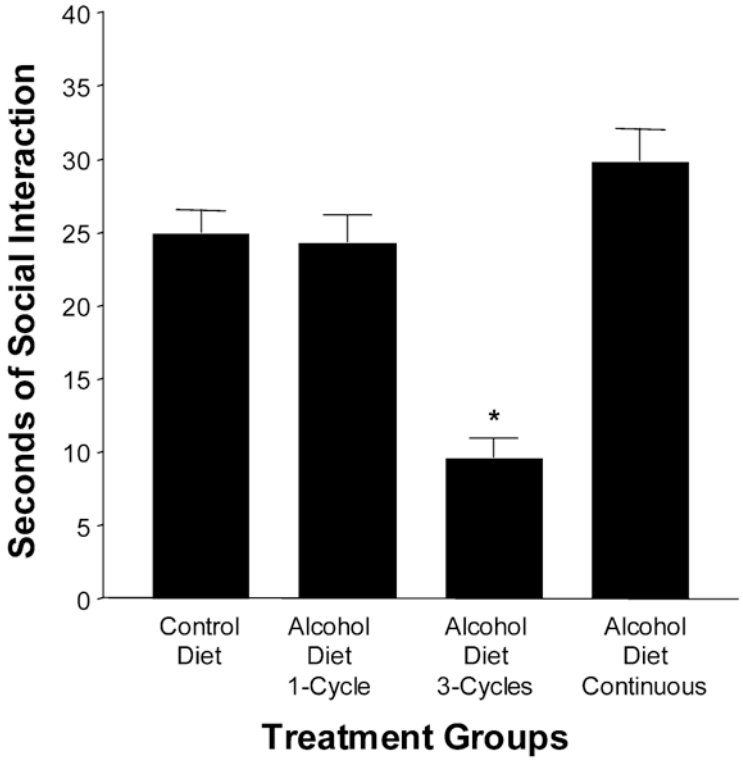

Fig. 1.

Repeated alcohol sensitization of withdrawal-induced anxiety-like behavior. Male Sprague-Dawley rats (8–10 per group) were exposed to either control diet, one cycle of 5 days of 4.5% alcohol diet (alcohol diet, 1-cycle), three cycles of 5 days of 4.5% alcohol diet with 2 days interruption after withdrawal from the first two cycles of alcohol exposure (alcohol diet, 3-cycles), or 15 consecutive days of 4.5% alcohol diet (alcohol diet, continuous). Social interaction was measured 5–6 h after the final withdrawal from alcohol diet. No change in locomotor activity was observed in these groups. Social interaction was the primary approach used to assess anxiety-like behavior because this test is well validated (File 1980; File and Hyde 1978; File and Seth 2003; Sams-Dodd 1995). Data modified from Overstreet et al. (2002) by permission of publisher. *P<0.01 compared with the other groups

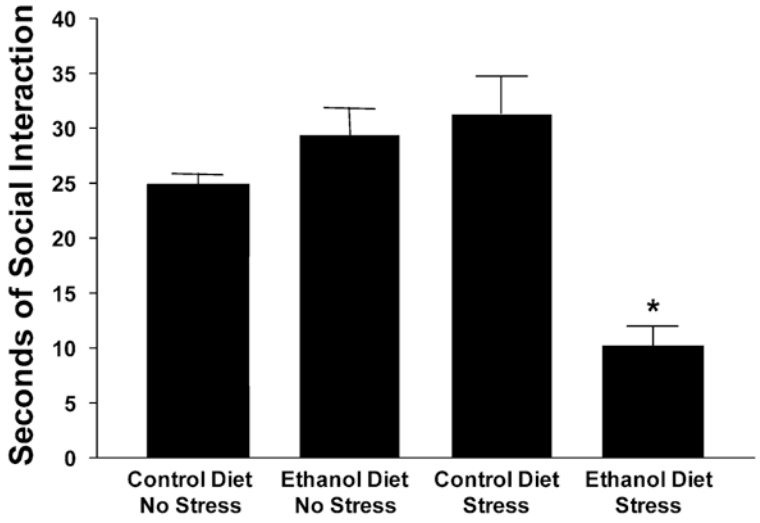

Fig. 2.

Stress induces anxiety-like behavior in animals with previous experience of chronic alcohol (ethanol) diet. Rats (8–10 per group) were exposed to restraint stress for 45 min 3 days after receiving control diet (control diet stress) or multiple withdrawals from 4.5% ethanol diet (ethanol diet stress). Included were groups that received control diet without stress (control diet, no stress) or multiple withdrawals with no stress (ethanol diet, no stress). To assess anxiety-like behavior, social interaction was measured 30 min after receiving restraint stress. *P<0.02 when alcohol diet stress is compared with the other groups

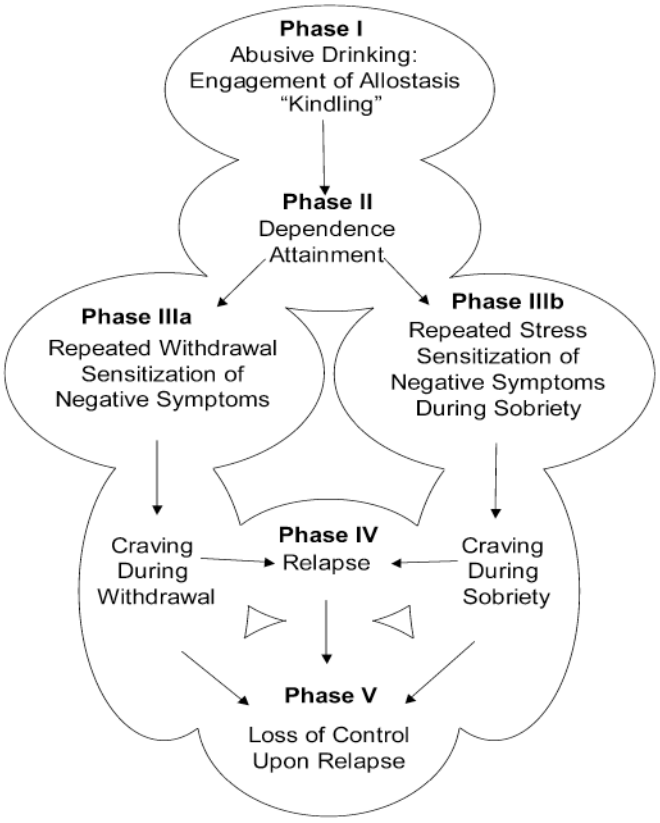

Fig. 3.

Schematic representation of the "kindling"/stress contribution to the etiology of alcoholism. The initial engagement of "kindling" in alcoholism (phase I) is proposed to follow withdrawals from repeated cycles of alcohol abuse. This "kindling" results in an insidious neural adaptation that persists (i.e., an increasing allostatic load), a change that accounts for the progression of alcohol use from social drinking to alcohol dependence (phase II). The adaptation to repeated alcohol exposures reflects the "kindling" component of the "kindling"/stress hypothesis. The accumulated adaptive change caused by repeated withdrawals facilitates negative affect during acute withdrawal (phase IIIa) and results in craving and an increased probability of relapse (phase IV). Following recovery from acute withdrawal, the persistent adaptation induced by alcohol abuse interacts with stress to promote negative affect during abstinence (phase IIIb), a circumstance that also induces a desire to drink (craving) and an increased probability of relapse (phase IV). This negative affect and craving initiated by stress during abstinence forms the "stress" component of the "kindling"/stress hypothesis. The persistent adaptation related to alcohol abuse presumably contributes to the inability of an alcoholic to control intake upon relapse (phase V). The renewed alcohol abuse with relapse and subsequent repeated withdrawals will continue over years to "kindle" adaptation until an increased sensitivity for withdrawal seizure susceptibility evolves (Ballenger and Post 1978)