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Theoretical Frameworks and Mechanistic Aspects of Alcohol Addiction: Alcohol Addiction as a Reward Deficit Disorder

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Abstract

Alcoholism can be defined by a compulsion to seek and take drug, loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug is prevented. Alcoholism impacts multiple motivational mechanisms and can be conceptualized as a disorder that includes a progression from impulsivity (positive reinforcement) to compulsivity (negative reinforcement). The compulsive drug seeking associated with alcoholism can be derived from multiple neuroadaptations, but the thesis argued here is that a key component involves the construct of negative reinforcement. Negative reinforcement is defined as drug taking that alleviates a negative emotional state. The negative emotional state that drives such negative reinforcement is hypothesized to derive from dysregulation of specific neurochemical elements involved in reward and stress within the basal forebrain structures involving the ventral striatum and extended amygdala, respectively. Specific neurochemical elements in these structures include not only decreases in reward neurotransmission, such as decreased dopamine and γ-aminobutyric acid function in the ventral striatum, but also recruitment of brain stress systems, such as corticotropin-releasing factor (CRF), in the extended amygdala. Acute withdrawal from chronic alcohol, sufficient to produce dependence, increases reward thresholds, increases anxiety-like responses, decreases dopamine system function, and increases extracellular levels of CRF in the central nucleus of the amygdala. CRF receptor antagonists also block excessive drug intake produced by dependence. A brain stress response system is hypothesized to be activated by acute excessive drug intake, to be sensitized during repeated withdrawal, to persist into protracted abstinence, and to contribute to the compulsivity of alcoholism. Other components of brain stress systems in the extended amygdala that interact with CRF and that may contribute to the negative motivational state of withdrawal include norepinephrine, dynorphin, and neuropeptide Y. The combination of loss of reward function and recruitment of brain stress systems provides a powerful neurochemical basis for a negative emotional state that is responsible for the negative reinforcement driving, at least partially, the compulsivity of alcoholism.

Keywords

Addiction; Opponent process; Stress; Extended amygdala; Corticotropin-releasing factor

1 Definitions and Conceptual Framework for Reward Deficit in Alcoholism

Alcoholism has many definitions that vary from social frameworks to a psychiatric framework embedded in the diagnosis of Substance Dependence on Alcohol defined in the

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Diagnostic and Statistical Manual of the American Psychiatric Association, 4th edition (DSM-IV; American Psychiatric Association 1994). Alcoholism, and more generically drug addiction, can be defined as a chronically relapsing disorder characterized by (i) compulsion to seek and take the drug (alcohol), (ii) loss of control in limiting (alcohol) intake, and (iii) emergence of a negative emotional state (e.g., dysphoria, anxiety and irritability) reflecting a motivational withdrawal syndrome when access to the drug (alcohol) is prevented (defined here as dependence: Koob and Le Moal 1997). Clinically and in animal models, the occasional but limited use of alcohol with the *potential* for abuse or dependence is distinct from escalated alcohol intake and the emergence of a chronic alcohol-dependent state. The thesis argued in the present synthesis is that alcoholism, similar to drug addiction, is a reward deficit disorder, and the "emergence of a negative emotional state" plays an important role in defining and perpetuating alcoholism. Alcoholism also involves substantial neuroadaptations that persist beyond acute withdrawal and trigger relapse and deficits in cognitive function that can also fuel compulsive drinking. However, the argument here is that the core deficit that sets up vulnerability to relapse in alcoholism, and possibly even deficits in cognitive function, is in fact decreased reward function.

To support this hypothesis, a holistic view of alcoholism will be presented with the following arguments. A negative emotional state is a common presentation in most alcoholics during withdrawal and protracted abstinence. Compulsivity observed in alcoholism has an important negative reinforcement component that perpetuates alcoholism. Such negative emotional states become sensitized over time and set up an allostatic state that perpetuates dependence. Negative emotional states set up a powerful motivational state for relapse. Finally, the neurobiological substrates underlying the motivation to seek alcohol will be reviewed, and an argument will be presented that it is loss of reward function and gain of brain stress function that mediate the negative emotional state outlined as key to alcoholism.

Drug addiction has generally been conceptualized as a disorder that involves elements of both impulsivity and compulsivity, in which *impulsivity* can be defined behaviorally as "a predisposition toward rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to themselves or others" (Moeller et al. 2001). Impulsivity is measured in two domains: the choice of a smaller, immediate reward over a larger, delayed reward (Rachlin and Green 1972) or the inability to inhibit behavior by changing the course of action or to stop a response once it is initiated (Logan et al. 1997). Impulsivity is a core deficit in substance abuse disorders (Allen et al. 1998) and neuropsychiatric disorders such as attention deficit hyperactivity disorder. Operationally, delay-to-gratification tasks (delayed discounting tasks; impulsive choice) and the stop-signal or go/no-go task (behavioral impulsivity) have been used as measures of impulsivity (Fillmore and Rush 2002; Green et al. 1994). *Compulsivity* can be defined as elements of behavior that result in perseveration of responding in the face of adverse consequences or perseveration in the face of incorrect responses in choice situations (e.g., operationally, responding for a drug or alcohol in the face of adverse consequences (Wolffgramm and Heyne 1995) or responding for a drug or alcohol on a progressive-ratio schedule of reinforcement (Walker et al. 2008)). Compulsivity is analogous to the symptoms of Substance Dependence outlined by the American Psychiatric Association: continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem and a great deal of time spent in activities necessary to obtain the substance (American Psychiatric Association 2000).

Collapsing the cycles of impulsivity and compulsivity yields a composite addiction cycle comprising three stages—*preoccupation/anticipation, binge/intoxication,* and *withdrawal/ negative affect*—in which impulsivity often dominates at the early stages and compulsivity

dominates at terminal stages (Fig. 1). As an individual moves from impulsivity to compulsivity, a shift occurs from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior (Koob 2004). Negative reinforcement can be defined as the process by which removal of an aversive stimulus (e.g., negative emotional state of drug withdrawal) increases the probability of a response (e.g., dependence-induced drug intake to relieve the negative emotional state). Note that negative reinforcement is not punishment, although both involve an aversive stimulus. In punishment, the aversive stimulus suppresses behavior, including drug taking (e.g., disulfiram [Antabuse]). Negative reinforcement can be perhaps described in lay terms as reward via relief (i.e., relief reward), such as removal of pain or in the case of alcoholism removal of the negative emotional state of acute withdrawal or protracted abstinence. The three stages are conceptualized as interacting with each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob and Le Moal 1997) (Fig. 1).

In alcohol addiction, or alcoholism, a pattern of oral drug taking evolves that is often characterized by binges of alcohol intake that can be daily episodes or prolonged days of heavy drinking and is characterized by a severe emotional and somatic withdrawal syndrome. Many alcoholics continue with such a binge/withdrawal pattern for extended periods of time, but some individuals can evolve into an opioid-like situation in which they must have alcohol available at all times to avoid the negative consequences of abstinence. Here, intense preoccupation with obtaining alcohol (craving) develops that is linked not only to stimuli associated with obtaining the drug but also to stimuli associated with withdrawal and the aversive motivational state. A pattern develops in which the drug must be obtained to avoid the severe dysphoria and discomfort of abstinence.

The pattern of alcohol addiction, related to reward dysfunction, can be amply illustrated by excerpts from two case histories from Knapp (1996) and Goodwin (1981). In the first representative case history, an individual progresses from the state where they stated, “I drank when I was happy and I drank when I was anxious and I drank when I was bored and I drank when I was depressed, which was often,” to, “I loved the way drink made me feel, and I loved its special power of deflection, its ability to shift my focus away from my own awareness of self and onto something else, something less painful than my own feelings,” and, “There’s a sense of deep need, and the response is a grabbiness, a compulsion to latch on to something outside yourself in order to assuage some deep discomfort” (Knapp 1996). Similarly, in a second representative case history, “Alcohol seemed to satisfy some specific need I had, which I can’t describe,” and, “There were always reasons to drink. I was low, tense, tired, mad, happy,” and, “The goal, always, was to maintain a glow, not enough, I hoped, that people would notice, but a glow,” and, “By now I was hooked and knew it, but desperately did not want others to know it. I had been sneaking drinks for years—slipping out to the kitchen during parties and such—but now I began hiding alcohol, in my desk, bedroom, car glove compartment, so it would never be far away, ever. I grew panicky even thinking I might not have alcohol when I needed it, which was just about always, “ and, “ I loathed myself. I was waking early and thinking what a mess I was, how I had hurt so many others and myself. The words ‘guilty’ and ‘depression’ sound superficial in trying to describe how I felt. The loathing was almost physical—a dead weight that could be lifted in only one way, and that was by having a drink” (Goodwin 1981; see Koob and Le Moal 2006, Appendix, for full quotations).

These case histories illustrate numerous key points regarding the present treatise, but the main point to be further discussed below is the transition from drinking to feel good to drinking to avoid feeling bad. To some extent, this transition is facilitated by personality differences, presumably shaped not only by genetics but also by developmental and even social factors. As Khantzian (1997) cogently argued, addiction can be considered a type of

chronic emotional distress syndrome that varies with the individual from physical and emotional pain to chronic dysphoria to stress and anxiety to interpersonal difficulties for which drugs can be argued to be sources of self-medication for such negative emotional states. Additionally, he argued that self-medication may be drug-specific—patients may have a preferential use of drugs that fits with the nature of the painful feeling states that they are self-medicating (e.g., opiates to counter intense anger and rage, stimulants as augmenting agents for high-energy individuals, energizing agents for low-energy individuals, and depressants [e.g., alcohol] for individuals who are tense and anxious). The common element argued by Khantzian is that each class of drugs serves as antidotes or correctives to dysphoric states and acts as a "replacement for a defect in the psychological structure" (Kohut 1971, p. 46) of such individuals (Khantzian 2003).

1.1 Theoretical Framework: Motivation, Withdrawal, and Opponent Process

Motivation is a state that can be defined as a "tendency of the whole animal to produce organized activity" (Hebb 1972), and such motivational states are not constant but rather vary over time. Early work by Wikler stressed the role of changes in drive states associated with dependence. Subjects described changes in withdrawal as a "hunger" or primary need and the effects of morphine on such a state as "satiation" or gratification of the primary need (Wikler 1952). Although Wikler argued that positive reinforcement was retained even in heavily dependent subjects (thrill of the intravenous opioid injection), dependence produced a new source of gratification, that of negative reinforcement (see above).

The concept of motivation in addiction was inextricably linked with hedonic, affective, or emotional states in the context of temporal dynamics by Solomon's opponent process theory of motivation. Solomon and Corbit (1974) postulated that hedonic, affective, or emotional states, once initiated by drugs, are automatically modulated by the central nervous system with mechanisms that reduce the intensity of hedonic feelings. The *a-process* includes affective or hedonic habituation (or tolerance), and the *b-process* includes affective or hedonic withdrawal (abstinence). The *a-process* in drug use consists of positive hedonic responses, occurs shortly after presentation of a stimulus, correlates closely with the intensity, quality, and duration of the reinforcer, and shows tolerance. In contrast, the *b-process* in drug use appears after the *a-process* has terminated, consists of negative hedonic responses, and is sluggish in onset, slow to build up to an asymptote, slow to decay, and gets larger with repeated exposure. The thesis here is that opponent processes begin early in drug taking, reflect changes in the brain reward and stress systems, and later form one of the major motivations for compulsivity in drug taking.

Thus, dependence or manifestation of a withdrawal syndrome after removal of chronic drug administration is defined in terms of *motivational* aspects of dependence, such as emergence of a negative emotional state (e.g., dysphoria, anxiety and irritability) when access to the drug is prevented (Koob and Le Moal 2001), rather than on the *physical*, signs of dependence. Indeed, some have argued that the development of such a negative affective state can define dependence as it relates to addiction:

> The notion of dependence on a drug, object, role, activity or any other stimulus-source requires the crucial feature of negative affect experienced in its absence. The degree of dependence can be equated with the amount of this negative affect, which may range from mild discomfort to extreme distress, or it may be equated with the amount of difficulty or effort required to do without the drug, object, etc (Russell 1976).

Alcoholics show dramatic evidence of dysphoric states during acute withdrawal that persist into protracted abstinence. Alcohol withdrawal in humans produces well documented physical (somatic) symptoms, such as tremor, autonomic hyperactivity, nausea, vomiting,

and seizures, but more importantly produces significant affective symptoms of anxiety, dysphoria, and depression-like symptoms. Acute withdrawal (i.e., the first week post-alcohol) is characterized by Beck Depression Inventory scores of approximately 20, which is categorized within the range of moderate depression (Potokar et al. 21997; 15–30), and Hamilton Depression Scores of 18, which is close to 20 (the cutoff for antidepressant medication in affective disorder; Brown and Schuckit 1988). Depression scores decline during subsequent weeks of treatment but remain at close to 10 for Hamilton Depression Scores for up to 4 weeks of an inpatient treatment program (Brown and Schuckit 1988). In another study of inpatient alcoholics during withdrawal, the Beck Depression Inventory score was at 15 at withdrawal and remained at 12.8 two days into withdrawal and at 9.4 two weeks post-withdrawal (de Timary et al. 2008). Similar results were obtained for anxiety measures (Potokar et al. 1997; de Timary et al. 2008). In another study with a long-term follow-up of 6 months after a 4-week inpatient detoxification. Beck Depression Inventory scores remained at approximately 6, and trait anxiety scores (STAI-X2) remained above 33 even in subjects without comorbid anxiety or depression (Driessen et al. 2001). Independent of comorbidity status, individuals who relapsed had higher trait anxiety scores than those who abstained (Driessen et al. 2001). Thus, although alcoholics show significant decreases in measures of depression and anxiety during withdrawal, there is a measurable level of depression-like symptoms that persist long after acute withdrawal into protracted abstinence that may be clinically (treatment) relevant.

More compelling for the present thesis, during a 2-week inpatient withdrawal study, alexithymia (defined as a state of deficiency in understanding, processing, or describing emotions: from the Greek *a* for “lack.” *lexis* for “word,” and *thymos* for “emotion”; Sifneos 1973; Taylor and Bagby 2000), which results in poor emotional regulation and stress management abilities, remained high and stable during the 2-week period (de Timary et al. 2008). Alexithymia scores did not decline between the 0 and 2 day time-points but remained high at a score of 57 and declined only to 53 at the 3-week time-point (de Timary et al. 2008). The authors argued that alexithymia is a stable personality trait in alcoholics rather than a state-dependent phenomenon, providing support for the self-medication hypothesis outlined above.

Animal models can also be used to test the hypothesis that there are opponent process-like motivational changes associated with the development of alcohol dependence. Electrical brain stimulation reward or intracranial self-stimulation has a long history as a measure of activity of the brain reward system and of the acute reinforcing effects of drugs of abuse. All drugs of abuse, when administered acutely, decrease brain stimulation reward thresholds (Kornetsky and Esposito 1979) and when administered chronically increase reward thresholds during withdrawal (see above). Brain stimulation reward involves widespread neurocircuitry in the brain, but the most sensitive sites defined by the lowest thresholds involve the trajectory of the medial forebrain bundle that connects the ventral tegmental area with the basal forebrain (Olds and Milner 1954; Koob et al. 1977). Although much emphasis was focussed initially on the role of the ascending monoamine systems in the medial forebrain bundle in brain stimulation reward, other nondopaminergic systems in the medial forebrain bundle clearly play a key role (Hernandez et al. 2006).

Rats made dependent using chronic ethanol vapor exposure at blood alcohol levels sufficient to drive excessive drinking showed an increase in brain reward thresholds during withdrawal that lasted up to 3 days post-withdrawal (Schulteis et al. 1995). However, data suggest that, similar to other drugs of abuse, such opponent-like processes can begin with a single dosing (Fig. 2).

An acute elevation in brain reward thresholds was observed during repeated acute withdrawal from ethanol, bearing a striking resemblance to human subjective reports (Schulteis and Liu 2006) (Fig. 2). These results demonstrate that the elevation in brain reward thresholds following prolonged access to alcohol may fail to return to baseline levels between repeated and prolonged exposure to alcohol self-administration (i.e., a residual reward deficit), thus creating the greater elevation in reward thresholds observed during withdrawal from chronic ethanol. Rapid acute tolerance and opponent process-like effects in response to the hedonic effects of alcohol have been reported in human studies using the alcohol clamp procedure (Morzorati et al. 2002). These data provide compelling evidence for brain reward dysfunction with chronic alcohol, which provides strong support for a hedonic allostasis model of alcoholism (Koob 2003).

The dysregulation of brain reward function associated with withdrawal from chronic administration of drugs of abuse is a common element of all drugs of abuse. Withdrawal from chronic cocaine (Markou and Koob 1991), amphetamine (Paterson et al. 2000), opioids (Schulteis et al. 1994), cannabinoids (Gardner and Vorel 1998), nicotine (Epping-Jordan et al. 1998), and ethanol (Schulteis et al. 1995) leads to increases in reward thresholds during acute abstinence, and some of these elevations in threshold can last for up to 1 week. These observations lend credence to the hypothesis that opponent processes can set the stage for one aspect of compulsivity in which negative reinforcement mechanisms are engaged.

More recently, the opponent process theory has been expanded into the domains of the neurobiology of drug addiction from a neurocircuitry perspective. An allostatic model of the brain motivational systems has been proposed to explain the persistent changes in motivation that are associated with dependence in addiction (Koob and Le Moal 2001, 2008). In this formulation, addiction is conceptualized as a cycle of increasing dysregulation of brain reward/anti-reward mechanisms that results in a negative emotional state contributing to the compulsive use of drugs. Counteradaptive processes that are part of the normal homeostatic limitation of reward function fail to return within the normal homeostatic range. These counteradaptive processes are hypothesized to be mediated by two mechanisms: within-system neuroadaptations and between-system neuroadaptations (Koob and Bloom 1988).

In a within-system neuroadaptation. “the primary cellular response element to the drug would itself adapt to neutralize the drug’s effects: persistence of the opposing effects after the drug disappears would produce the withdrawal response” (Koob and Bloom 1988). Thus, a within-system neuroadaptation is a molecular or cellular change within a given reward circuit to accommodate overactivity of hedonic processing associated with addiction resulting in a decrease in reward function.

The emotional dysregulation associated with the *withdrawal/negative affect* stage may also involve between-system neuroadaptations in which neurochemical systems other than those involved in the positive rewarding effects of drugs of abuse are recruited or dysregulated by chronic activation of the reward system. “In the between-systems opposing process, a different cellular system and separable molecular apparatus would be triggered by the changes in the primary drug response neurons and would produce the adaptation and tolerance” (Koob and Bloom 1988). Thus, a between-system neuroadaptation is a circuitry change in which another different circuit (anti-reward circuit) is activated by the reward circuit and has opposing actions, again limiting reward function. The remainder of this review explores the neuroadaptational changes that occur in the brain emotional systems to account for the neurocircuitry changes that produce opponent processes and are hypothesized to play a key role in the compulsivity of addiction.

2 Animal Models for Compulsive Alcohol Seeking

Methods of inducing binge-like drinking with alcohol range from having animals drink alcohol solutions that are made more palatable with the addition of a sweetener (Ji et al. 2008) to restricting intake to specific periods of the dark cycle (drinking in the dark; Rhodes et al. 2005) to models involving alcohol dependence in animals such as alcohol vapor inhalation, intragastric alcohol infusion, and alcohol-liquid diet. The compulsive use of alcohol derives from multiple sources of reinforcement, and animal models have been developed not only for the acute positive reinforcing effects of ethanol, but also for the negative reinforcing effects associated with removal of the aversive effects of ethanol withdrawal or an existing aversive state (i.e., self-medication of the aversive effects of abstinence from chronic ethanol or self-medication of a pre-existing negative affective state; Koob and Le Moal 1997). A major early breakthrough was the development of a training procedure involving access to a sweetened solution and a subsequent fading in of ethanol to avoid the aversiveness of the ethanol taste (for review, see Samson 1987). Subsequent work extended these procedures to measures of self-administration in dependent rats and post-dependent rats (Roberts et al. 1996; O'Dell et al. 2004).

High doses of alcohol solution will be self-administered intragastrically after animals are made dependent via passive intragastric infusion, and rats will self-infuse 4–7 g/kg per day of ethanol (Fidler et al. 2006). Here, blood alcohol levels average 0.12 g%, measured 30 min after the start of a bout in which rats infuse 1.5 g/kg per 30 min.

In an alcohol-liquid diet procedure, the diet is typically the sole source of calories available to rats (for example, see Moy et al. 1997), thereby forcing rats to consume the alcohol. Typically, rats are provided a palatable liquid diet containing 5–8.7% v/v ethanol as their sole source of calories sufficient to produce dependence and maintain blood alcohol levels of 100–130 mg% during the dark (active drinking) cycle (Schulteis et al. 1996; Brown et al. 1998; Valdez et al. 2004). High responders during withdrawal from liquid diet will reach blood alcohol levels of approximately 80–100 mg% (Schulteis et al. 1996; Gilpin et al. 2009).

Reliable self-administration of ethanol in dependent animals using ethanol vapor exposure has been extensively characterized in rats, in which animals obtain blood alcohol levels in the 100–150 mg% range (Roberts et al. 1999, 2000). Similarly, rats with a history of alcohol dependence show increased self-administration of ethanol, even weeks after acute withdrawal (Roberts et al. 2000). In a variant of alcohol vapor exposure with more face validity, intermittent exposure to chronic ethanol using alcohol vapor chambers (14 h on/10 h off) produces more rapid escalation to increased ethanol intake and higher amounts of intake (O'Dell et al. 2004; Rimondini et al. 2002), and blood alcohol levels are reliably above 140 mg% after a 30 min session of self-administration in dependent animals (Richardson et al. 2008). In both the liquid diet and ethanol vapor procedures, alcohol intake is directly related to the blood alcohol range and the pattern of intermittent high-dose alcohol exposure (Gilpin et al. 2009). Although the alcohol vapor model may have limited face validity, considering that alcohol is passively administered to animals, numerous studies demonstrated that it also has robust predictive validity for alcohol addiction (Heilig and Koob 2007; Koob et al. 2009).

A similar procedure has been developed for mice and produces reliable increases in ethanol self-administration during withdrawal. Now termed chronic intermittent exposure (CIE), C57BL/6 mice are exposed to intermittent durations of ethanol vapor (three cycles of 16 h of vapor and 8 h of air) and then tested in a 2 h limited access ethanol preference drinking test during the circadian dark period (Becker and Lopez 2004; Lopez and Becker 2005; Finn et

al. 2007). Intermittent ethanol vapor exposure significantly increased 15% (v/v) ethanol intake by 30–50% in the post-vapor period, usually after multiple cycles and usually after 24 h of withdrawal (Finn et al. 2007). Similar results have been reported using an operant response in mice in 60 min test sessions for 10% (w/v) ethanol with intermittent vapor exposure of 14 h on/10 h off (Chu et al. 2007).

3 Neural Substrates for the Negative Emotional State Associated with Alcoholism

3.1 Within-System Neuroadaptations that Contribute to the Compulsivity Associated with the Dark Side of Alcoholism

Within-system neuroadaptations to chronic drug exposure include decreases in function of the same neurotransmitter systems in the same neurocircuits implicated in the acute reinforcing effects of drugs of abuse. One prominent hypothesis is that dopamine systems are compromised in crucial phases of the addiction cycle, such as withdrawal and protracted abstinence. This decrease in dopamine function is hypothesized to lead to decreased motivation for non-drug-related stimuli and increased sensitivity to the abused drug (Melis et al. 2005). Activation of the mesolimbic dopamine system has long been known to be critical for the acute rewarding properties of psychostimulant drugs and to be associated with the acute reinforcing effects of alcohol (Koob 1992; McBride and Li 1998; Nestler 2005). However, the magnitude of the increase in dopaminergic activity produced by alcohol pales in comparison to that of psychostimulant "intoxication." For example, intravenous cocaine self-administration produces a 200% increase in extracellular dopamine (Weiss et al. 1992b) compared with ethanol which produces a 20% increase in extracellular dopamine in the nucleus accumbens (Doyon et al. 2003) and heroin (which does not increase extracellular dopamine in the nucleus accumbens) (Table 1). Such a relationship changes with the development of dependence and may change with genetic background (see Ramachandani et al. 2010, who demonstrated a nearly 200% increase with alcohol in animals that carried the OPRM1 118G variant).

More compelling in the mesolimbic dopamine domain are the decreases in activity of the mesolimbic dopamine system and decreases in serotonergic neurotransmission in the nucleus accumbens that occur during alcohol withdrawal in animal studies (Rossetti et al. 1992; Weiss et al. 1992a, 1996). In dependent male Wistar rats trained to self-administer ethanol during withdrawal, the release of dopamine and serotonin was monitored by microdialysis in the nucleus accumbens at the end of a 3–5 week ethanol (8.7% w/v) liquid diet regimen, during 8 h of withdrawal, and during renewed availability of ethanol involving the opportunity to operantly self-administer ethanol (10% w/v) for 60 min, followed by unlimited access to the ethanol liquid diet. In nondependent rats, operant ethanol self-administration increased both dopamine and serotonin release in the nucleus accumbens. Withdrawal from the chronic ethanol diet produced a progressive suppression in the release of these transmitters over the 8 h withdrawal period. Self-administration of ethanol reinstated and maintained dopamine release at pre-withdrawal levels but failed to completely restore serotonin efflux. These findings suggested that deficits in nucleus accumbens monoamine release may contribute to the negative affective consequences of ethanol withdrawal and thereby motivate ethanol-seeking behavior in dependent subjects (Weiss et al. 1996). Similar dramatic decreases in extracellular dopamine in the nucleus accumbens, measured by microdialysis, were found in a study in which animals were tested for 8 h into ethanol withdrawal produced by chronic repeated ethanol injections of up to 5 g/kg every 6 h for six consecutive days using the Majchrowicz procedure (Majchrowicz 1975; Rossetti et al. 1999). Thus, as a result, ethanol-dependent animals may show a much greater percentage increase in dopamine release in the nucleus accumbens during ethanol self-administration

during withdrawal because baseline levels of dopamine are so low during withdrawal (Weiss et al. 1996).

Imaging studies in drug-addicted humans have consistently shown long-lasting decreases in the numbers of dopamine D_2 receptors in alcoholics compared with controls (Volkow et al. 2002). Additionally, alcohol-dependent subjects had dramatically reduced dopamine release in the striatum response to a pharmacological challenge with the stimulant drug methylphenidate (Volkow et al. 2007). Decreases in the number of dopamine D_2 receptors, coupled with the decrease in dopaminergic activity, in cocaine, nicotine, and alcohol abusers are hypothesized to produce a decreased sensitivity of reward circuits to stimulation by natural rein-forcers (Martin-Solch et al. 2001; Volkow and Fowler 2000). These findings suggest an overall reduction in the sensitivity of the dopamine component of reward circuitry to natural reinforcers and other drugs in drug-addicted individuals (Table 2).

Other within-system neuroadaptations under this conceptual framework could include increased sensitivity of receptor transduction mechanisms in the nucleus accumbens. Drugs of abuse have acute receptor actions that are linked to intracellular signaling pathways that may undergo adaptations with chronic treatment. In the context of chronic alcohol administration, multiple molecular mechanisms have been hypothesized to counteract the acute effects of ethanol that could be considered within-system neuroadaptations. For example, chronic ethanol decreases γ-aminobutyric acid (GABA) receptor function, possibly through downregulation of the $\alpha 1$ subunit (Mhatre et al. 1993; Devaud et al. 1997). Chronic ethanol also decreases the acute inhibition of adenosine reuptake (i.e., tolerance develops to the inhibition of adenosine by ethanol; Sapru et al. 1994). Perhaps more relevant to the present treatise, whereas acute ethanol activates adenylate cyclase, withdrawal from chronic ethanol decreases CREB phosphorylation in the amygdala and is linked to decrease in function of neuropeptide Y (NPY) and to the anxiety-like responses observed during acute ethanol withdrawal (Chance et al. 2000; Pandey 2004).

3.2 Between-System Neuroadaptations that Contribute to Compulsivity Associated with the Dark Side of Alcoholism

Brain neurochemical systems involved in arousal-stress modulation may also be engaged within the neurocircuitry of the brain stress systems in an attempt to overcome the chronic presence of the perturbing drug (alcohol) and to restore normal function despite the presence of drug. The neuroanatomical entity termed the extended amygdala (Heimer and Alheid 1991) may represent a common anatomical substrate integrating brain arousal-stress systems with hedonic processing systems to produce some of the between-system opponent process elaborated above. The extended amygdala is composed of the central nucleus of the amygdala, bed nucleus of the stria terminalis, and a transition zone in the medial (shell) subregion of the nucleus accumbens. Each of these regions has cytoarchitectural and circuitry similarities (Heimer and Alheid 1991). The extended amygdala receives numerous afferents from limbic structures, such as the basolateral amygdala and hippocampus, and sends efferents to the medial part of the ventral pallidum and a large projection to the lateral hypothalamus, thus further defining the specific brain areas that interface classical limbic (emotional) structures with the extrapyramidal motor system (Alheid et al. 1995). The extended amygdala has long been hypothesized to play a key role not only in fear conditioning (Le Doux 2000) but also in the emotional component of pain processing (Neugebauer et al. 2004).

The brain stress system mediated by corticotropin-releasing factor (CRF) systems in both the extended amygdala and hypothalamic–pituitary–adrenal axis are dysregulated by chronic administration of all major drugs with dependence or abuse potential, with a common response of elevated adrenocorticotropic hormone, corticosterone, and extended amygdala

CRF during acute withdrawal from chronic drug administration (Rivier et al. 1984; Merlo-Pich et al. 1995; Koob et al 1994; Rasmussen et al. 2000; Olive et al. 2002; Delfs et al. 2000; Koob 2008a).

More specifically, alcohol withdrawal reliably produces anxiety-like responses in animal models that can be reversed by CRF receptor antagonists (Koob 2008a). Ethanol withdrawal produces anxiety-like behavior that is reversed by intracerebroventricular administration of CRF_1/CRF_2 peptidergic antagonists (Baldwin et al. 1991), small-molecule CRF_1 antagonists (Knapp et al. 2004; Overstreet et al. 2004; Funk et al. 2007), and intracerebral administration of a peptidergic CRF_1/CRF_2 antagonist into the amygdala (Rassnick et al. 1993). CRF antagonists injected intracerebroventricularly or systemically also block the potentiated anxiety-like responses to stressors observed during protracted abstinence from chronic ethanol (Breese et al. 2005; Valdez et al. 2003; Sommer et al. 2008).

Perhaps more relevant to the present thesis are studies showing that intermittent alcohol exposure sensitizes withdrawal of anxiety-like responses and that administration of drug treatments during withdrawal from the first and second alcohol cycles blocked this sensitization of withdrawal (Knapp et al. 2004). Diazepam, flumazenil (a $GABA_A$ receptor partial agonist), and baclofen (a $GABA_B$ receptor agonist) blocked the sensitization of withdrawal, consistent with a within-system neuroadaptation (Knapp et al. 2004, 2005, 2007; see above). However, a CRF_1, antagonist also prevented the sensitization of withdrawal-induced anxiety (Overstreet et al. 2004a. 2005). These results are consistent with a prolonged history of alcohol exposure producing persistent upregulation of both CRF and CRF_1, receptors in the brain (Roberto et al. 2010; Sommer et al. 2008; Zorrilla et al. 2001).

The ability of CRF antagonists to block the anxiogenic-like and aversive-like motivational effects of drug withdrawal would predict motivational effects of CRF antagonists in animal models of extended access to drugs. A particularly dramatic example of the motivational effects of CRF in dependence can be observed in animal models of ethanol self-administration in dependent animals. During ethanol withdrawal, extrahypothalamic CRF systems become hyperactive, with an increase in extracellular CRF within the central nucleus of the amygdala and bed nucleus of the stria terminalis in dependent rats (Funk et al. 2006; Merlo-Pich et al. 1995; Olive et al. 2002). The dysregulation of brain CRF systems is hypothesized to underlie not only the enhanced anxiety-like behaviors but also the enhanced ethanol self-administration associated with ethanol withdrawal. Supporting this hypothesis, the subtype nonselective CRF receptor antagonists α-helical $CRF_{9–41}$ and D-Phe $CRF_{12–41}$ (intracerebroventricular administration) reduced ethanol self-administration in dependent animals during acute withdrawal and during protracted abstinence (Valdez et al. 2002). When administered directly into the central nucleus of the amygdala, a CRF_1/CRF_2 antagonist blocked ethanol self-administration in ethanol-dependent rats (Funk et al. 2006). Systemic injections of small-molecule CRF_1, antagonists also blocked the increased ethanol intake associated with acute withdrawal and protracted abstinence (Gehlert et al. 2007; Funk et al. 2007). These data suggest an important role for CRF, primarily within the central nucleus of the amygdala, in mediating the increased self-administration associated with dependence. Consistent with the sensitization of the withdrawal response associated with repeated alcohol exposure, a CRF antagonist administered during repeated withdrawal also blocked the development of excessive drinking during withdrawal (Roberto et al. 2010).

Although less well developed, evidence supports a role of norepinephrine systems in the extended amygdala in the negative motivational state and increased self-administration associated with dependence. Substantial evidence has accumulated suggesting that in animals and humans, central noradrenergic systems are activated during acute withdrawal from ethanol. Alcohol withdrawal in humans is associated with activation of noradrenergic

function, and the signs and symptoms of alcohol withdrawal in humans are blocked by postsynaptic β-adrenergic blockade (Romach and Sellers 1991). Alcohol withdrawal signs are also blocked in animals by administration of α_1 antagonists and β-adrenergic antagonists and selective blockade of norepinephrine synthesis (Trzaskowska and Kostowski 1983). In dependent rats, the α_1, antagonist prazosin selectively blocked the increased drinking associated with acute withdrawal (Walker et al. 2008). Thus, converging data suggest that noradrenergic neurotransmission is enhanced during ethanol withdrawal and that noradrenergic functional antagonists can block aspects of ethanol withdrawal.

Dynorphin, an opioid peptide that binds to κ opioid receptors, has long been known to show activation with chronic administration of psychostimulants and opioids (Nestler 2004; Koob 2008a), and κ opioid receptor agonists produce aversive effects in animals and humans (Mucha and Herz 1985; Pfeiffer et al. 1986). Although κ agonists suppress nondependent drinking, possibly via aversive stimulus effects (Wee and Koob 2010), κ opioid antagonists block the excessive drinking associated with ethanol withdrawal and dependence (Holter et al. 2000; Walker and Koob 2008). Recently, some have argued that the effects of CRF in producing negative emotional states are mediated by activation of κ opioid systems (Land et al. 2008). However, κ receptor activation can activate CRF systems in the spinal cord (Song and Takemori 1992), and there is pharmacological evidence that dynorphin systems can also activate the CRF system. A CRF_1, antagonist blocked κ agonist-induced reinstatement of cocaine seeking in squirrel monkeys (Valdez et al. 2007).

The dynamic nature of the brain stress system response to challenge is illustrated by the pronounced interaction of central nervous system CRF systems and central nervous system norepinephrine systems. Conceptualized as a feed-forward system at multiple levels of the pons and basal forebrain. CRF activates norepinephrine, and norepinephrine in turn activates CRF (Koob 1999). Much pharmacologic, physiologic, and anatomic evidence supports an important role for a CRF-norepinephrine interaction in the region of the locus coeruleus in response to stressors (Valentino et al. 1991, 1993; Van Bockstaele et al. 1998). However, norepinephrine also stimulates CRF release in the paraventricular nucleus of the hypothalamus (Alonso et al. 1986), bed nucleus of the stria terminalis, and central nucleus of the amygdala. Such feed-forward systems were further hypothesized to have powerful functional significance for mobilizing an organism's response to environmental challenge, but such a mechanism may be particularly vulnerable to pathology (Koob 1999).

Neuropeptide Y is a neuropeptide with dramatic anxiolytic-like properties localized to the amygdala and has been hypothesized to have effects opposite to CRF in the negative motivational state of withdrawal from drugs of abuse (Heilig and Koob 2007). Significant evidence suggests that activation of NPY in the central nucleus of the amygdala can block the motivational aspects of dependence associated with chronic ethanol administration. Neuropeptide Y administered intracerebroventricularly blocked the increased drug intake associated with ethanol dependence (Thorsell et al. 2005a, b). Injection of NPY directly into the central nucleus of the amygdala (Gilpin et al. 2008) and viral vector-enhanced expression of NPY in the central nucleus of the amygdala also blocked the increased drug intake associated with ethanol dependence (Thorsell et al. 2007).

Thus, acute withdrawal from drugs increases CRF in the central nucleus of the amygdala, which has motivational significance for the anxiety-like effects of acute withdrawal from alcohol and the increased drug intake associated with dependence. Acute withdrawal may also increase the release of norepinephrine in the bed nucleus of the stria terminalis and dynorphin in the nucleus accumbens, both of which may contribute to the negative emotional state associated with dependence. Decreased activity of NPY in the central nucleus of the amygdala may contribute to the anxiety-like state associated with ethanol

dependence. Activation of brain stress systems (CRF, norepinephrine and dynorphin) combined with inactivation of brain anti-stress systems (NPY) elicits powerful emotional dysregulation in the extended amygdala. Such dysregulation of emotional processing may be a significant contribution to the between-system opponent processes that help maintain dependence and also set the stage for more prolonged state changes in emotionality such as in protracted abstinence.

4 Compulsivity in Alcoholism: an Allostatic View

Compulsivity in alcoholism can derive from multiple sources, including enhanced incentive salience, engagement of habit function, and impairment in executive function. However, underlying each of these sources is a negative emotional state that may strongly impact on compulsivity. The development of the negative emotional state that drives the negative reinforcement of addiction has been defined as the "dark side" of addiction (Koob and Le Moal 2005, 2008) and is hypothesized to be the *b-process* of the hedonic dynamic known as opponent process when the *a-process* is euphoria. The negative emotional state that comprises the *withdrawal/negative affect* stage consists of key motivational elements, such as chronic irritability, emotional pain, malaise, dysphoria, alexithymia, and loss of motivation for natural rewards, and is characterized in animals by increase in reward thresholds during withdrawal from all major drugs of abuse. Two processes are hypothesized to form the neurobiological basis for the *b-process:* loss of function in the reward systems (within-system neuroadaplation) and recruitment of the brain stress or anti-reward systems (between-system neuroadaptation; Koob and Bloom 1988; Koob and Le Moal 1997). Anti-reward is a construct based on the hypothesis that brain systems are in place to limit reward (Koob and Le Moal 2008). As dependence and withdrawal develop, brain stress systems, such as CRF, norepinephrine, and dynorphin, are recruited, producing aversive or stress-like states (Koob 2003; Nestler 2001; Aston-Jones et al. 1999). At the same time, within the motivational circuits of the ventral striatum-extended amygdala, reward function decreases. The combination of decreases in reward neurotransmitter function and recruitment of anti-reward systems provides a powerful source of negative reinforcement that contributes to compulsive drug-seeking behavior and addiction (Fig. 3).

An overall conceptual theme argued here is that drug addiction represents a break with homeostatic brain regulatory mechanisms that regulate the emotional state of the animal. The dysregulation of emotion begins with the binge and subsequent acute withdrawal, but leaves a residual neuroadaptive trace that allows rapid "re-addiction" even months and years after detoxification and abstinence. Thus, the emotional dysregulation of alcohol addiction represents more than simply a homeostatic dysregulation of hedonic function—it also represents a dynamic break with homeostasis of this system that has been termed *allostasis* (Koob 2003).

Allostasis, originally conceptualized to explain persistent morbidity of arousal and autonomic function, can be defined simply as "stability through change" (Sterling and Eyer 1988). Allostasis is different from homeostasis. Allostasis involves a feed-forward mechanism rather than the negative feedback mechanisms of homeostasis. Allostasis involves a changed set point with continuous re-evaluation of need and continuous readjustment of all parameters toward new set points. The set point in question here is emotional state. An *allostatic state* can be defined as a state of chronic deviation of the reward system from its normal (homeostatic) operating level. *Allostatic load* has been defined as the "long-term cost of allostasis that accumulates over time and reflects the accumulation of damage that can lead to pathological states" (McEwen 2000). Although the concept of allostatic state has not received much attention, the argument here is that alcoholism reflects largely a movement to an allostatic state, often before sufficient

pathology has ensued to produced allostatic load sufficient for physical pathology (Koob and Le Moal 2001).

Allostatic mechanisms have been hypothesized to be involved in maintaining a functioning brain reward system that has relevance for the pathology of addiction (Koob and Le Moal 2001). Two components are hypothesized to adjust to challenges of the brain produced by drugs of abuse: underactivation of brain reward transmitters and circuits and recruitment of the brain anti-reward or brain stress systems (Fig. 4). Thus, the very physiological mechanism that allows rapid responses to environmental challenge becomes the source of pathology if adequate time or resources are not available to shut off the response (one example is the interaction between CRF and norepinephrine in the brainstem and basal forebrain that could lead to pathological anxiety; Koob 1999).

Repeated challenges, such as with repeated alcohol binges, lead to attempts of the brain via molecular, cellular, and neurocircuitry changes to maintain stability but at a cost. For the alcoholism framework elaborated here, the residual deviation from a normal emotional state is termed the *allostatic state*. This state represents a combination of chronic elevation of the reward set point fueled by decreased function of reward circuits and recruitment of anti-reward systems, both of which lead to the compulsivity of alcohol-seeking and alcohol taking. How these systems are modulated by other known brain emotional systems localized to the basal forebrain, where the ventral striatum and extended amygdala project to convey emotional valence, how the dysregulation of brain emotional systems impacts on the cognitive domain linked to impairments in executive function, and how individuals differ at the molecular-genetic level of analysis to convey loading on these circuits remain challenges for future research (George and Koob 2010).

As such, the present thesis does not preclude a key role for other systems associated with the addiction process, including the mesolimbic dopamine system involved in incentive salience, the dorsal striatum involved in habit formation, the parabrachial amygdala and spinothalamocortical systems involved in pain, and the prefrontal cortex involved in decision-making (Koob and Volkow 2010; George and Koob 2010). Such modules are driven by bottom-up signals from both the external world and interoceptive signals and by top-down signals from higher-order systems mediating cognitive control. Indeed, the failure of a specific module may differ from one individual to another and may represent a neuropsychobiological mechanism underlying individual differences in the vulnerability to drug addiction. For example, we have hypothesized that individual differences in the function of the incentive salience mesolimbic dopamine system and the habit/striatum modules may be particularly important for craving-type 1 (or reward craving), defined as craving for the rewarding effects of alcohol and usually induced by stimuli that have been paired with alcohol self-administration, such as environmental cues. Additionally, hypoactivity of the decision-making/prefrontal cortex module may lead to a loss of control over drug intake despite negative consequence because of impaired inhibitory control and decision-making leading to choices of immediate rewards over delayed rewards (Goldstein and Volkow 2002).

Nevertheless the hypothesis outlined here is that a core component of alcoholism involves hyperactivity of the negative emotional state/extended amygdala system that is associated with increased emotional pain and stress and might be a risk factor for drug use as self-medication for emotional pain, dysphoria, and stress (Khantzian 1997). A subhypothesis is that vulnerability in the emotional pain parabrachial-amygdala system (Besson 1999; Shurman et al. 2010) may lead to increased emotional pain during withdrawal and intense craving-type 2 (or withdrawal relief craving), which is conceptualized as an excessive motivation for the drug to obtain relief from a state change characterized by anxiety and

dysphoria after protracted abstinence (Heinz et al. 2003), thus contributing to the preponderant role of the *withdrawal/negative affect* stage that characterizes alcoholism. Increased reactivity of the stress/hypothalamic-pituitary-adrenal axis module may be critical in the initiation of alcohol intake and for the maintenance of drug intake which have little initial rewarding value, such as nicotine. Activation of the hypothalamic-pituitary-adrenal axis can potentiate the reinforcing effects of drugs (Piazza and Le Moal 1998). However, this activation can in turn drive amygdala CRF. further exacerbating the development of negative emotional states (Koob and Kreek 2007). Although the initial deficit in a specific functional circuit that drives excessive drinking might be specific to one stage of the addiction cycle, as the transition to addiction progresses, an individual is ultimately likely to show a progressive and generalized loss of control over many, if not all, systems. However, the thesis argued here is that as excessive alcohol intake progresses to Substance Dependence on Alcohol (Alcoholism), a common dysregulated functional element is a reward system deficit.

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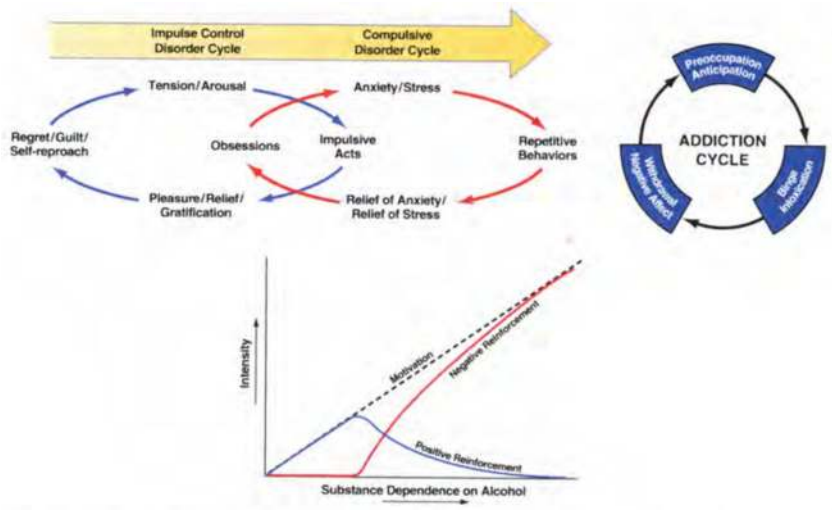

Fig. 1.

(Top left) Diagram showing the stages of impulse control disorder and compulsive disorder cycles related to the sources of reinforcement. In impulse control disorders, an increasing tension and arousal occurs before the impulsive act, with pleasure, gratification, or relief during the act. Following the act, there may or may not be regret or guilt. In compulsive disorders, there are recurrent and persistent thoughts (obsessions) that cause marked anxiety and stress followed by repetitive behaviors (compulsions) that are aimed at preventing or reducing distress (American Psychiatric Association 1994). Positive reinforcement (pleasure/gratification) is more closely associated with impulse control disorders. Negative reinforcement (relief of anxiety or relief of stress) is more closely associated with compulsive disorders. *(Top right)* Collapsing the cycles of impulsivity and compulsivity results in the addiction cycle, conceptualized as three major components: *preoccupation/ anticipation, binge/intoxication,* and *withdrawal/negative affect* (Taken with permission from Koob 2008b.)*(Bottom)* Change in the relative contribution of positive and negative reinforcement constructs during the development of substance dependence on alcohol

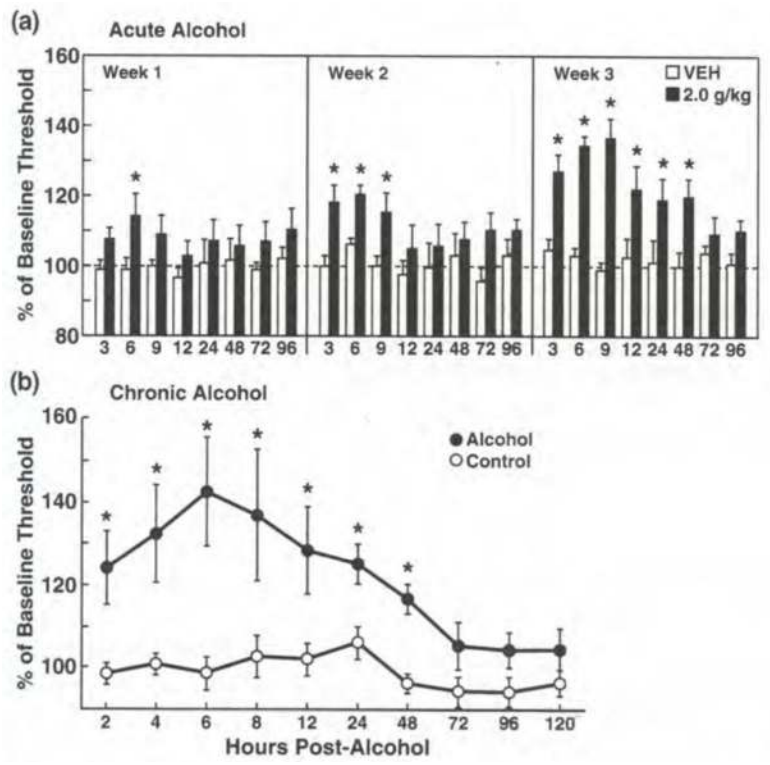

Fig. 2.

a Withdrawal from a single boul of acute ethanol intoxication (week 1) resulted in a significant but transient increase in brain reward threshold only with the highest dose of ethanol tested (2.0 g/kg: $^{a}P < 0.05$, compared with vehicle controls at given time-point post-injection). The effect was significant at 6 hours, a time when blood alcohol levels had declined to virtually undetectable levels following this dose of ethanol. Repeated treatment with this dose for two additional weeks resulted in a progressive broadening of the duration of significant threshold elevations. By comparison, treatment with 1.5 g/kg ethanol resulted in significant but transient elevations only after three repeated bouts of intoxication/withdrawal, and no statistically reliable changes were seen after one or two treatments (data not shown). Treatment with 1.0 g/kg did not produce any statistically reliable threshold changes regardless of treatment week (data not shown). Data are expressed as mean ± SEM percentage of baseline threshold, $n = 8–10$ per dose group. [Taken with permission from Schulteis and Liu 2006.] **b** Time-dependent elevation of intracranial self-stimulation thresholds during ethanol withdrawal. Mean blood alcohol levels were 197.29 mg%, Data are expressed as mean ± SEM percentage of baseline threshold, $^{a}p < 0.05$, thresholds that were significantly elevated above control levels at 2–48 hours post-ethanol. Open circles indicate the control condition. Closed circles indicate the ethanol withdrawal condition. [Taken with permission from Schulteis et al. 1995.]

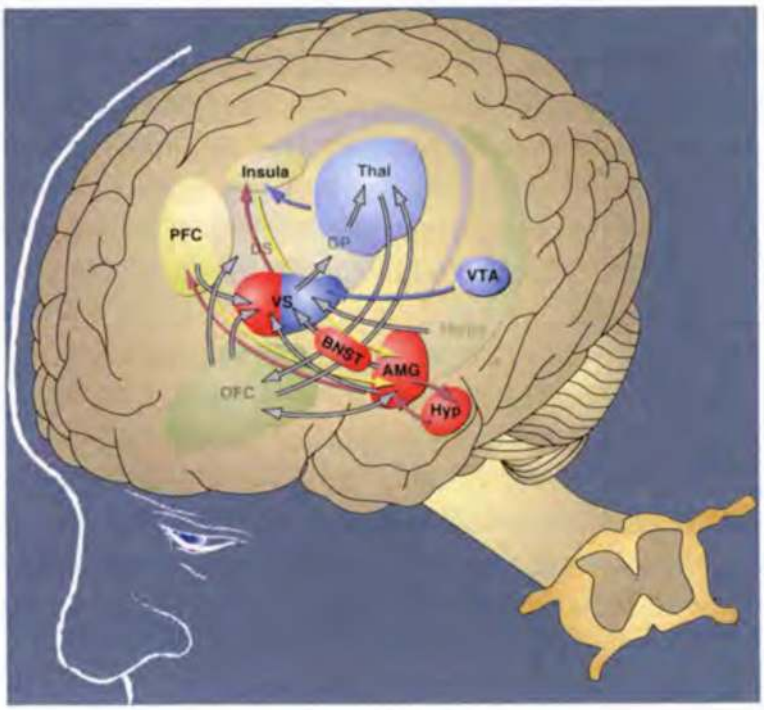

Fig. 3.

Pathways for key elements of addiction circuitry implicated in negative emotional states. Addiction circuitry is composed of structures involved in the three stages of the addiction cycle: *binge/intoxication* (ventral striatum, dorsal striatum and thalamus), *withdrawal/ negative affect* (ventral striatum, bed nucleus of the stria terminalis and central nucleus of the amygdala), *preoccupation/anticipation* (prefrontal cortex, orbitofrontal cortex and hippocampus). Highlighted here for the *withdrawal/negative affect* stage is increased activity in the extended amygdala and decreased activity in the reward system, illustrated with the use of imaging colors (i.e., *red* for high activity and *blue* for low activity). Modified with permission from Blackburn-Munro and Blackburn-Munro (2003) and Koob et al. (2008). AMG, amygdala; BNST, bed nucleus of the stria terminalis; DS, dorsal striatum; GP, globus pallidus; Hippo, hippocampus; Hyp, hypothalamus; Insula, insular cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; Thal, thalamus; VS, ventral striatum; and VTA, ventral tegmental area. [Modified with permission from Zald and Kim 2001]

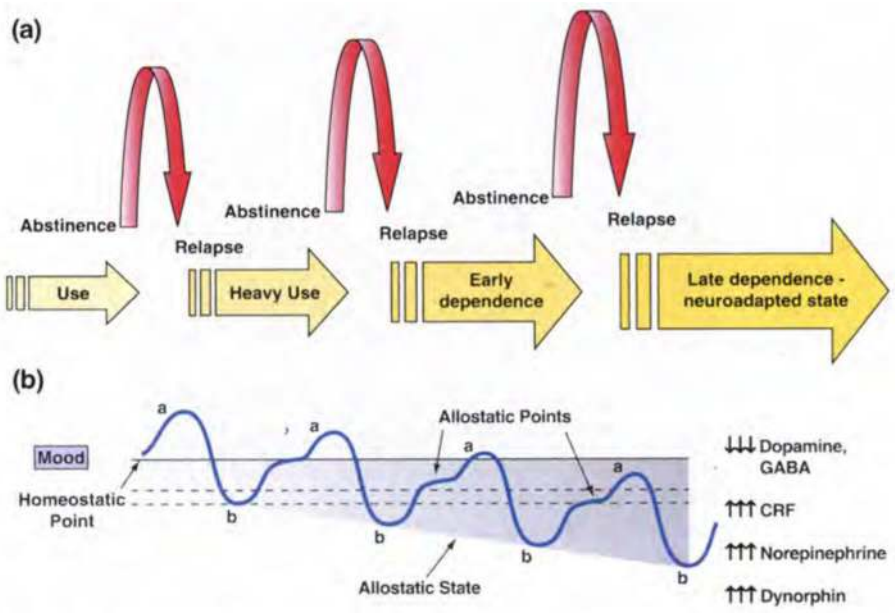

Fig. 4.

a Schematic of the progression of alcohol dependence over time, illustrating the shift in underlying motivational mechanisms. From initial, positive reinforcing, pleasurable alcohol effects, the addictive process progresses over time to being maintained by negative reinforcing relief from a negative emotional state. Data presented in this paper suggest that neuroadaptations encompassing the recruitment of extrahypothalamic CRF systems are key to this shift. (Taken with permission from Heilig and Koob 2007.) **b** The *a-process* represents a positive hedonic or positive mood state, and the *b-process* represents the negative hedonic or negative mood state. The affective stimulus (state) has been argued to be the sum of both the *a-process* and *b-process.* An individual who experiences a positive hedonic mood state from a drug of abuse with sufficient time between re-administering the drug is hypothesized to retain the *a-process.* An appropriate counteradaptive opponent process *(b-process)* that balances the activational process *(a-process)* does not lead to an allostatic state. The changes in the affective stimulus (state) in an individual with repeated frequent drug use may represent a transition to an allostatic state in the brain systems and, by extrapolation, a transition to addiction (*see* text). Notice that the apparent *b-process* never returns to the original homeostatic level before drug taking begins again, thus creating a greater and greater allostatic state in the brain emotional systems. The counteradaptive opponent-process *(b-process)* does not balance the activational process *(a-process)* but in fact shows a residual hysteresis. Although these changes illustrated in the figure are exaggerated and condensed over time, the hypothesis is that even during post-detoxification (a period of "protracted abstinence"), the brain emotional systems still bear allostatic changes (*see* text). The following definitions apply: *alkalosis,* the process of achieving stability through change; *allostatic state,* a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level: *allostatic load,* the cost to the brain and body of the deviation, accumulating over time, and reflecting in many cases pathological states and accumulation of damage. [Modified with permission from Koob and Le Moal 2001.]

Table 1

Effects of intravenous self-administration of D-amphetamine, cocaine, and heroin and oral self-administration of alcohol on extracellular dopamine levels in the nucleus accumbens using in vivo microdialysis

Drug	% Increase in Dopamine over Baseline	Reference
D-Amphetamine	700%	Di Ciano et al (1995)
Cocaine	200–500%	Di Ciano et al (1995); Weiss et al (1992a)
Alcohol	25–50%	Weiss et al (1992b, 1996)
Heroin	<20%	Hemby et al (1995)

Table 2

Role of corticotropin-releasing factor in dependence

Drug	CRF antagonist effects on withdrawal-induced anxiety-like responses	Withdrawal-induced changes in extracellular CRF in CeA	CRF antagonist effects on dependence-induced increases in self-administration
Cocaine	↓	↑	↓
Opioids	↓[a]	↑	↓
Ethanol	↓	↑	↓
Nicotine	↓	↑	↓
Δ^9-Tetrahydrocannabinol	↓	↑	nt

[a]Aversive effects with place conditioning

nt, not tested

CeA, central nucleus of the amygdala