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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Alcoholism: Allostasis and Beyond

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Alcoholism is a chronic relapsing disorder characterized by compulsive drinking, loss of control over intake, and impaired social and occupational function. Animal models have been developed for various stages of the alcohol addiction cycle with a focus on the motivational effects of withdrawal, craving, and protracted abstinence. A conceptual framework focused on allostatic changes in reward function that lead to excessive drinking provides a heuristic framework with which to identify the neurobiologic mechanisms involved in the development of alcoholism. Neuropharmacologic studies in animal models have provided evidence for specific neurochemical mechanisms in specific brain reward and stress circuits that become dysregulated during the development of alcohol dependence. The brain reward system implicated in the development of alcoholism comprises key elements of a basal forebrain macrostructure termed the extended amygdala that includes the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and a transition zone in the medial (shell) part of the nucleus accumbens. There are multiple neurotransmitter systems that converge on the extended amygdala that become dysregulated during the development of alcohol dependence, including gamma-aminobutyric acid, opioid peptides, glutamate, serotonin, and dopamine. In addition, the brain stress systems may contribute significantly to the allostatic state. During the development of alcohol dependence, corticotropin-releasing factor may be recruited, and the neuropeptide Y brain antistress system may be compromised. These changes in the reward and stress systems are hypothesized to maintain hedonic stability in an allostatic state, as opposed to a homeostatic state, and as such convey the vulnerability for relapse in recovering alcoholics. The allostatic model not only integrates molecular, cellular, and circuitry neuroadaptations in brain motivational systems produced by chronic alcohol ingestion with genetic vulnerability but also provides a key to translate advances in animal studies to the human condition.

Key Words: Alcoholism, Allostasis, Extended Amygdala, Corticotropin-Releasing Factor, Neuropeptide Y.

ALCOHOLISM CAN BE defined as a complex behavioral disorder characterized by preoccupation with obtaining alcohol and a narrowing of the behavioral repertoire toward excessive consumption and compulsive use (loss of control over consumption). It is characterized by excessive ingestion of alcohol, the development of tolerance and withdrawal, and impairment in social and occupational functioning (American Psychiatric Association, 1994). For the purposes of this review, substance dependence on alcohol, as defined by the DSM-IV, will be considered to be operationally equivalent to the syndrome of alcoholism. This review will explore understanding the neurobiology of alcoholism with a focus on the neuroadaptive changes in specific basal forebrain neuronal circuits associated with development of dependence and with the residual neuroadaptive changes that convey vulnerability to relapse. It is recognized that animal models of a complete syndrome of alcoholism are difficult, if not impossible, to achieve. However, it is clear that validated animal models exist for most of the components of the syndrome, particularly the motivational effects of withdrawal, craving, and relapse. Such models provide a heuristic means with which to pursue the underlying neurobiological basis of the disorder.

The compulsive use of ethanol has been hypothesized to be driven by multiple sources of reinforcement that change with an individual's movement from social use to abuse and dependence on ethanol (Fig. 1). Koob and Le Moal (1997) conceptualized addiction, including alcoholism, as a continuous process of hedonic homeostatic dysregulation. This homeostatic dysregulation has been expanded conceptually to the realm of allostasis, the ability to attain stability but at an altered, potentially pathologic set point (Koob and Le Moal, 2001). Multiple sources of reinforcement were identified in a spiraling cycle of addiction that provided a heuristic framework for the self-regulation failures associated with addiction-like behavior, the phenomenology of current psychiatric diagnoses of addiction, and the neurobiological changes that accompany the development of ad-

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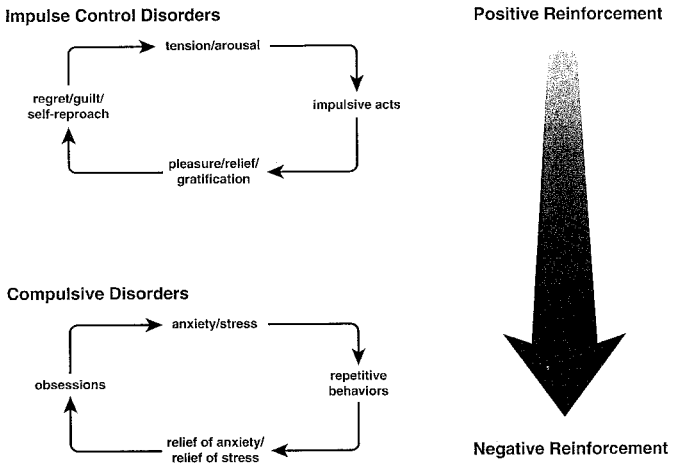

Fig. 1. Diagram showing stages of impulse control disorder and compulsive disorder cycles related to the sources of reinforcement. In impulse control disorders, an increasing tension and arousal occurs before the impulsive act, with pleasure, gratification, or relief during the act. Following the act, 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.

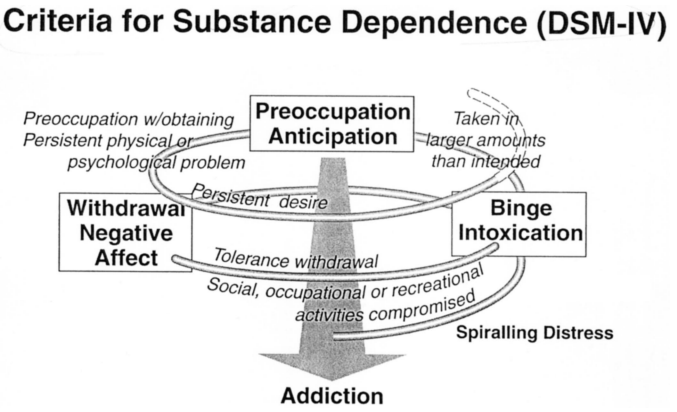

Fig. 2. Diagram describing the spiraling distress/addiction cycle from a psychiatric perspective. The addiction cycle is conceptualized as a spiral that increases in amplitude with repeated experience, ultimately resulting in the pathologic state known as addiction. The three major components of the addiction cycle–preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect–are shown with the different criteria for substance dependence incorporated from the *Diagnostic and Statistical Manual of Mental Disorders IV* (American Psychiatric Association, 1994). (Taken with permission from Koob and Le Moal, 1997.)

diction (Koob and Le Moal, 1997) (see Fig. 2). Three stages of addiction were derived from the social psychological elements of failure to self-regulate observed not only in addiction to drugs but also addiction-like patterns of behavior observed in other atypical impulse control disorders. These stages include preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect. Critical for the conceptual framework outlined by Koob and Le Moal (1997) was the withdrawal/negative affect stage which was hypothesized to grow larger and larger and to lead to a major motivational impetus for compulsive ethanol intake.

Indeed, some have argued that the presence of a negative affective state is the defining feature of 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).

Such a negative affective state presumably would be the basis for the negative reinforcement that has classically defined the addiction process.

Previous work has identified critical neurotransmitters involved in the acute positive reinforcing effects of ethanol and has shown how alterations of these neurotransmitter systems during the development of dependence contribute to the negative reinforcing effects of ethanol. Important roles in the acute reinforcing effects of ethanol have been determined for dopamine, opioid peptides, gamma-aminobutyric acid (GABA), and glutamate and have been established in specific brain sites that comprise a forebrain macrostructure termed the extended amygdala (Koob et al., 1998). Motivational roles for GABA, glutamate, and dopamine have been shown during the development of dependence, but most importantly for the present review, preliminary evidence has shown a key role for dysregulation of the brain stress systems during the development of dependence. More specifically, evidence shows motivationally significant recruitment of brain corticotropin-releasing factor (CRF) activity during the development of dependence that persists into protracted abstinence. Data from our laboratory and others also suggest a role for neuropeptide Y (NPY) in stress modulation opposite to that of CRF. The present review will explore the studies on the mechanisms of neuroadaptation within ethanol reinforcement systems during the development of dependence and during prolonged abstinence (protracted abstinence) with a focus on CRF and NPY within the neurocircuitry of the extended amygdala.

The overall hypothesis in the present review is that specific neurotransmitter elements related to brain stress systems within the extended amygdala macrostructure of the basal forebrain are responsible for the allostatic changes in ethanol reward associated with acute withdrawal and protracted abstinence. More specifically, it is hypothesized that increased CRF activity and decreased NPY activity in the central nucleus of the amygdala and/or bed nucleus of the stria terminalis (BNST) are responsible for the enhanced drinking associated with acute withdrawal and protracted abstinence.

ANIMAL MODELS OF ETHANOL REINFORCEMENT, DEPENDENCE, AND PROTRACTED ABSTINENCE: EVIDENCE FOR AN ALLOSTATIC MECHANISM

Animal models have been developed not only for the acute 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 (self-medication from the aversive effects of abstinence from chronic ethanol or self-medication of a pre-existing negative affective state) (Koob et al., 1993). For the positive reinforcing effects of ethanol, early paradigms which assessed the reinforcing effects of ethanol typically used an oral preference paradigm where animals were allowed to drink ethanol or water. A major breakthrough in this area 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 (Samson, 1987). Recent work has not only replicated the Samson procedures but extended these procedures to measures of self-administration in dependent rats and postdependent rats (Roberts et al., 1996, 2000) (Figs. 3 and 4). Reliable self-administration of ethanol in dependent animals has been characterized, where animals exhibit blood alcohol levels in the 100–150 mg/100 ml range (Roberts et al., 1999, 2000). Similarly, rats with a history of ethanol dependence show increased self-administration of ethanol, even weeks after acute withdrawal (Roberts et al., 2000). More recent results have shown that intermittent exposure to chronic ethanol using ethanol vapor chambers (14 hr on/10 hr off) produces more rapid escalation to increased ethanol intake and higher amounts of intake (O'Dell, Roberts, and Koob, 2002, unpublished results).

Ethanol studies with inbred lines and selected breeding have established a number of selected lines for high ethanol consumption that have been based on the phenotype of free-choice drinking. Numerous lines of rats and mice have been selected and characterized (Li et al., 1993). For rats, these lines include preferring (P) and non-preferring (NP); high-alcohol-drinking (HAD) and low-alcohol-drinking (LAD); Sardinian preferring (SP) and Sardinian non-preferring (SNP); and Alko alcohol (AA) and Alko nonalcohol (ANA). For mice, these lines include high-alcohol-preference (HAP) and low-alcohol-preference (LAP). In general, P rats tend to have a low sensitivity to ethanol and alterations in neurotransmitter systems known to be involved in the positive reinforcing effects of ethanol such as serotonin and dopamine (McBride and Li, 1998). The P rats also show evidence of increased anxiety-like behavior (Stewart et al., 1993). Recent work has been done to characterize these strains in the context of environmental challenges that lead to excessive drinking. The P strain shows a very robust increase in alcohol consumption following repeated alcohol deprivations, ingesting up to 16–18 g/kg over 24 hr (Rodd-Henricks et al., 2001). Under limited access conditions with repeated deprivations, the P rats can drink as much as 6–8 g/kg, reaching the point of actually becoming comatose (Rodd-Henricks et al., 2001). These results suggest that drinking in rodents to clearly excessive levels can be obtained by both environmental and genetic manipulations and, in certain cases, the interaction can be particularly effective in escalating intake, an observation

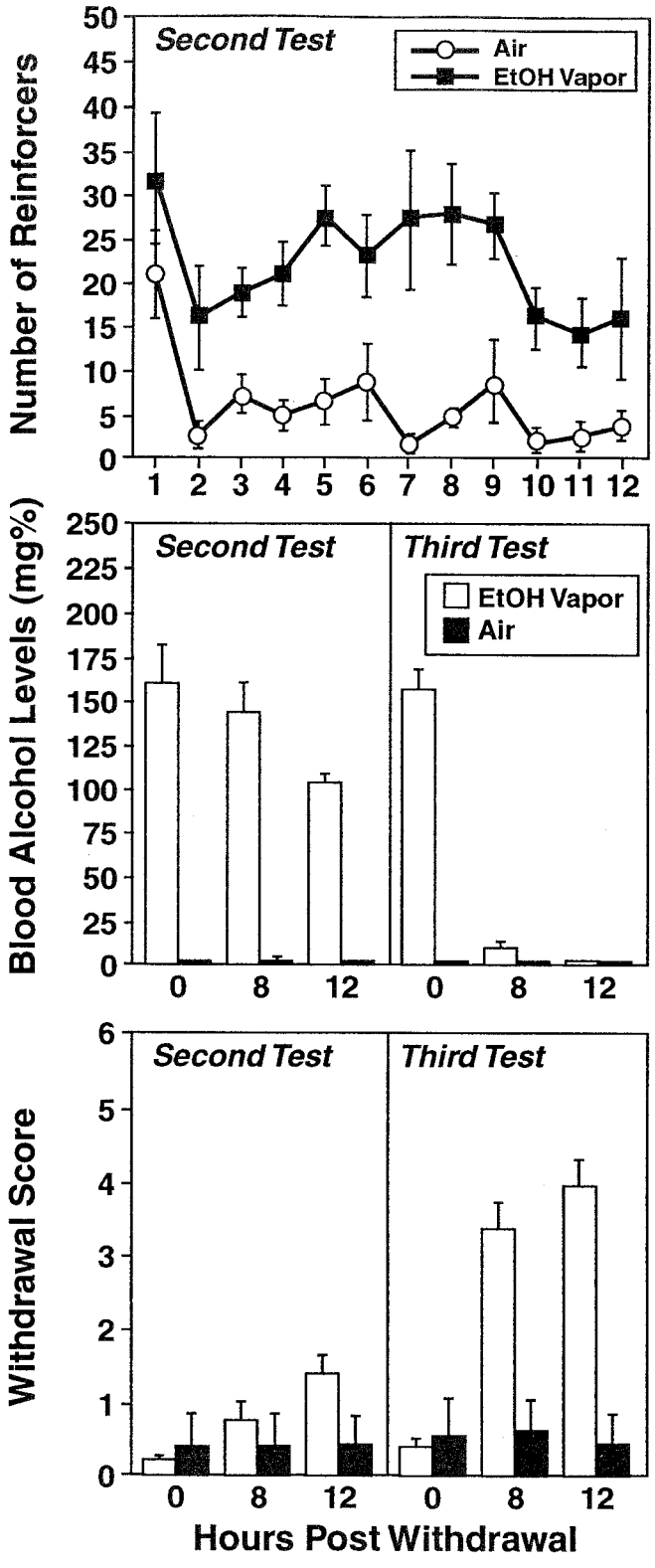

Fig. 3. Operant responding for ethanol (EtOH) across a 12-hr test period by air-exposed and ethanol-vapor-exposed rats (top). In addition, blood alcohol levels (middle) and ethanol withdrawal severity (bottom) obtained while rats were allowed access to ethanol in the operant boxes and while in their home cages are shown. Data are expressed as mean ± SEM. (Taken with permission from Roberts et al., 1996.)

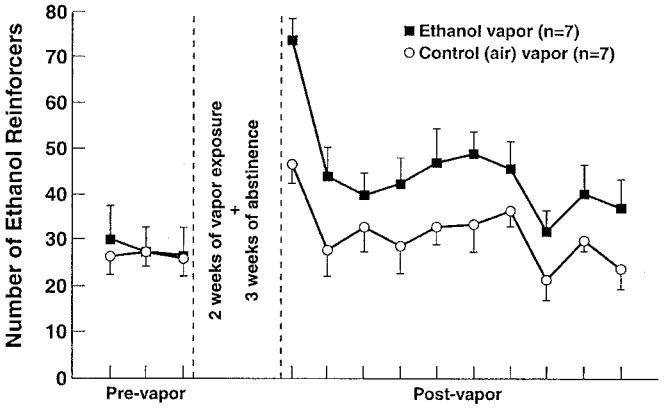

Fig. 4. Operant responding for oral ethanol across 10 days of 30-min test sessions in rats exposed to 2 weeks of ethanol vapor ($n = 6$) or air ($n = 6$). The three prevapor test sessions were used for group selection. Daily operant test sessions were resumed 2 weeks following removal from the vapor chambers. Numbers of deliveries are represented as mean ± SEM. Asterisks (*) indicate a significant difference between the ethanol and control groups ($p < 0.05$). (Taken with permission from Roberts et al., 2000.)

which has face validity with the human condition of alcoholism.

EXTENDED AMYGDALA: FUNCTIONAL ATTRIBUTES OF A BASAL FOREBRAIN MACROSTRUCTURE AS A FOCAL POINT FOR ALCOHOL REINFORCEMENT

The term extended amygdala represents a macrostructure that shares similarities in morphology, neurochemistry, and connectivity and is composed of several basal forebrain structures: the BNST, the central and medial amygdala, the area termed the sublenticular substantia innominata, and a transition zone in the posterior medial part of the nucleus accumbens (e.g., shell) (Heimer and Alheid, 1991). This system receives afferents from limbic and olfactory cortices and projects heavily to the hypothalamus and midbrain. As such, the extended amygdala links the basal forebrain to the classical reward systems of the lateral hypothalamus via the medial forebrain bundle reward system. A guiding hypothesis is that many of the neuropharmacological effects of ethanol, including its rewarding and anxiolytic or tension-reducing effects may be mediated by this circuitry. Neuroadaptive changes in this reward circuit also may provide the motivation for excessive drinking characterized by dependence and relapse (see below) (Koob et al., 1998).

Further examination of this anatomic system reveals two major divisions: the central division and the medial division (Figs. 5 and 6). These two divisions have important differences in structure and afferent and efferent connections (Alheid et al., 1995) that may be of heuristic value for the present review. The central division of the extended amygdala includes the central nucleus of the amygdala, the central sublenticular extended amygdala, the lateral BNST, and a transition area in the medial and caudal portions of the nucleus accumbens and medial portions of the olfactory tubercle. These structures contain nuclei that have an overall cytoarchitectural similarity to the central nucleus of the amygdala and have close interconnections with the lateral rather than the medial hypothalamus and interconnections with the ventral tegmental area. Prominent afferents to the central division include the posterior basolateral amygdala, subparafascicular thalamus, and insular and medial frontal cortices. Notable efferents from the central division include the lateral hypothalamus, ventral tegmental area, tegmental pedunculopontine nucleus, and various brainstem nuclei.

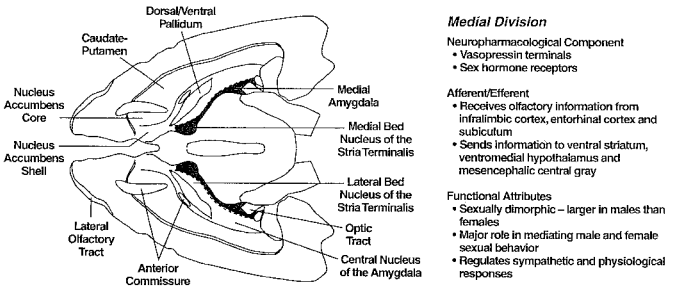

Fig. 5. Diagram illustrating the medial extended amygdala, its neuropharmacological components, afferent and efferent connections, and functional attributes. Based on anatomic integration of Alheid et al., 1995; Heimer and Alheid, 1991.

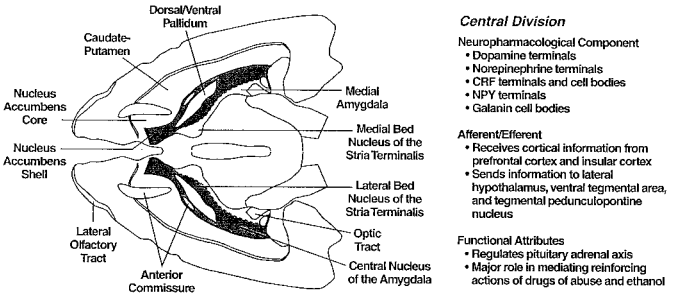

Fig. 6. Diagram illustrating the central extended amygdala, its neuropharmacological components, afferent and efferent connections, and functional attributes. Based on anatomic integration of Alheid et al., 1995; Heimer and Alheid, 1991.

The medial division of the extended amygdala includes the medial BNST, medial nucleus of the amygdala, and the medial sublenticular extended amygdala. These structures have been defined largely as the medial division by their network of intrinsic associative connections and extensive relations to the medial hypothalamus (Alheid et al., 1995). Prominent afferents to the medial division include the anterior olfactory nucleus, agranular insular cortex, accessory olfactory nucleus and infralimbic cortex, ventral subiculum, and basomedial amygdala. Notable efferents from the medial division include the ventral striatum, the ventromedial hypothalamus, and mesencephalic central gray. The lateral BNST which forms a key element of the central division of the extended amygdala has high amounts of dopamine and norepinephrine terminals, CRF terminals, CRF cell bodies, NPY terminals, and galanin cell bodies and receives afferents from the prefrontal cortex, insular cortex, and amygdalopiriform area. The medial BNST, in

contrast, contains high amounts of vasopressin, is sexually dimorphic, and receives afferents from structures such as the infralimbic cortex, entorhinal cortex, and subiculum (Allen et al., 1984; Dong et al., 2001; Gray and Magnuson, 1992; Kozicz, 2001; McDonald et al., 1999; Phelix and Paull, 1990).

Evidence suggests that the lateral BNST may be involved in receiving cortical information and regulating the hypothalamic pituitary adrenal axis (Gray et al., 1993), whereas the medial BNST may be more involved in sympathetic and physiologic responses and receiving olfactory information (Lesur et al., 1989; Nijsen et al., 2001; Pompei et al., 1991). To date, most motivational manipulations resulting in modification of the reinforcing effects of ethanol and other drugs have been in the central nucleus of the amygdala and the lateral nucleus of the BNST.

NEUROBIOLOGY OF THE ACUTE REINFORCING EFFECTS OF ETHANOL

Ethanol has been hypothesized neuropharmacologically to interact with a number of ligand-gated ion channels and its action on the GABA receptor system long has been linked to ethanol reinforcement (Deitrich et al., 1989; Tabakoff and Hoffman, 1992). The in vitro actions of ethanol on the GABA-A receptor are some of its most potent effects, with doses as low as 1–3 mM being effective at altering GABA-gated current measures (Sundstrom-Poromaa et al., 2002). At the pharmacological level, one can antagonize the effects of ethanol with GABA antagonists. In addition, a very potent GABA antagonist, SR95531, when microinjected into the basal forebrain, significantly decreased ethanol consumption (Hyytia and Koob, 1995), the antagonist being most active in the central nucleus of the amygdala compared with the nucleus accumbens and BNST.

Significant evidence also supports a role for other reward transmitters at basal forebrain sites such as the nucleus accumbens and central nucleus of the amygdala in ethanol reinforcement. Very low doses of the dopamine antagonist fluphenazine injected into the nucleus accumbens will block ethanol self-administration (Rassnick et al., 1992). Ethanol self-administration increases extracellular levels of dopamine in the nucleus accumbens in nondependent rats (Weiss et al., 1993). Such increases occur not only during the actual self-administration session but precede the self-administration session, possibly reflecting the incentive motivational properties of cues associated with ethanol (Weiss et al. 1993). Injections of an opiate antagonist into the central nucleus of the amygdala also significantly reduce ethanol consumption at lower doses than for other sites such as the nucleus accumbens or lateral ventricle (Heyser et al., 1999), suggesting a role for opioid peptides in the extended amygdala in the acute reinforcing actions of ethanol.

Modulation of various aspects of serotonergic transmission, including increases in the synaptic availability of serotonin with precursor loading and blockade of serotonin reuptake, can decrease ethanol intake (Sellers et al., 1992). Antagonists of several serotonin receptor subtypes can decrease ethanol self-administration. Serotonin-3 receptor antagonists decrease ethanol self-administration (Fadda et al., 1991; Hodge et al., 1993), and serotonin-2 receptor antagonists, including some with both serotonin-1A agonist activity and serotonin-2 antagonist action, can selectively decrease acute ethanol reinforcement (Roberts et al., 1998).

Modulation of the NMDA receptor also may contribute to the intoxicating effects of ethanol (Hoffman et al., 1989; Lovinger et al., 1989) and perhaps to the dissociative effects seen in people with high blood alcohol levels (Tsai et al., 1995). Thus, multiple neurotransmitters have been implicated in the acute reinforcing effects of ethanol.

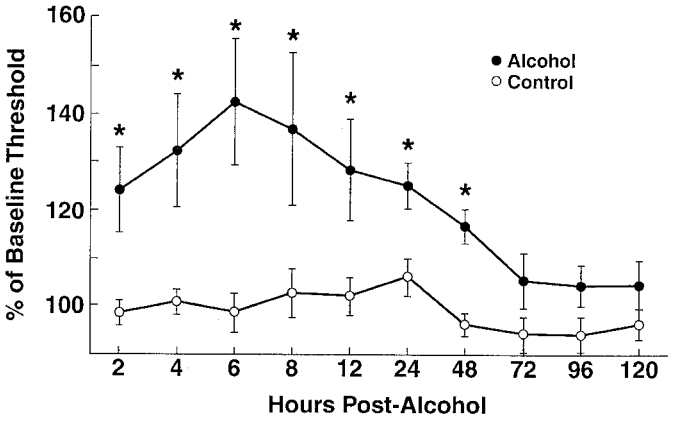

Fig. 7. Time-dependent elevation of intracranial self-stimulation thresholds during ethanol withdrawal. Mean blood alcohol levels achieved were 197 mg/100 ml. Data are expressed as mean ± SEM percentage of baseline threshold. Asterisks (*) indicate thresholds that were significantly elevated above control levels at 2–48 hr post-ethanol ($p < 0.05$). Open circles indicate the control condition. Closed circles indicate the ethanol withdrawal condition. (Taken with permission from Schulteis et al., 1995.)

NEUROBIOLOGY OF THE NEGATIVE REINFORCEMENT ASSOCIATED WITH ETHANOL WITHDRAWAL: DYSREGULATION OF NEUROTRANSMITTER SYSTEMS ASSOCIATED WITH POSITIVE REINFORCING EFFECTS OF ETHANOL

The neurobiological basis for the negative reinforcement important for the development of alcoholism and the vulnerability to relapse has been argued to include counteradaptive neurochemical events within the brain emotional systems normally used to maintain emotional homeostasis (Koob and Le Moal, 2001). Key to this hypothesis is the observation that during acute withdrawal from ethanol there is a compromised brain reward system as reflected in an increase in brain reward thresholds (Schulteis et al., 1995) (Fig. 7) which is opposite in direction to the threshold-lowering action of acute ethanol (Bespalov et al., 1999; De Witte and Bada, 1983; Kornetsky et al., 1988).

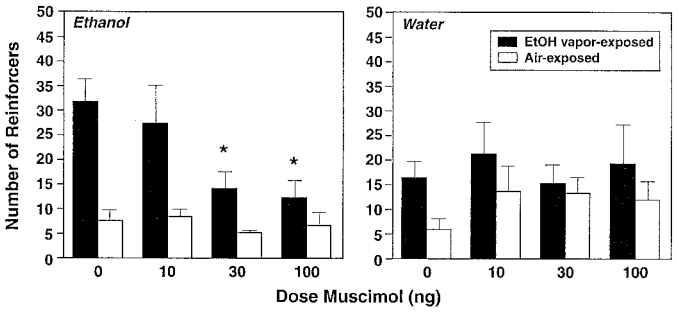

Fig. 8. Operant responding for ethanol and water in ethanol-vapor-exposed and air-exposed rats after intra-amygdala administration of muscimol, a GABA-A receptor agonist. Data are the mean ± SEM of hr 7 and 8 postwithdrawal of 12-hr withdrawal sessions where animals had access to ethanol self-administration for all 12 hr. Asterisks (*) indicate significant difference ($p < 0.05$). (Taken with permission from Roberts et al., 1996.)

Rats made dependent on ethanol using ethanol vapor that results in blood ethanol levels of 150–200 mg/100 ml show elevations in reward thresholds during withdrawal from ethanol that persist up to 72 hr postexposure (Schulteis et al., 1995). More and more evidence has accumulated in animal models of elevations in reward thresholds following acute withdrawal from all major drugs of abuse [nicotine: (Epping-Jordan et al., 1998); ethanol: (Schulteis et al., 1995); amphetamine: (Paterson et al., 2000); cocaine: (Markou and Koob, 1991); opiates: (Schulteis et al., 1994)].

These changes in reward function are accompanied by changes in neurochemical systems within the extended amygdala that include decreases in neurotransmitter function implicated in the acute reinforcing effects of alcohol (e.g., GABAergic, opioid peptidergic, dopaminergic, serotonergic, and glutamatergic systems). Neuropharmacological studies have shown that the enhanced ethanol self-administration during acute withdrawal can be reduced dose-dependently by intracerebral pretreatment of a GABA agonist into the central nucleus of the amygdala (Roberts et al., 1996) (Fig. 8). Acamprosate, a hypothesized partial agonist or antagonist at brain glutamate systems also decreases excessive drinking associated with dependence and abstinence in rats (Boismare et al., 1984; Gewiss et al., 1991; Heyser et al., 1998; Holter et al., 1997; Le Magnen et al., 1987; Spanagel et al., 1996), and intracerebral administration of acamprosate suggests the BNST is a particularly sensitive site (Morse and Koob, 2002, unpublished data). Identical doses and administration of these neuropharmacological agents to nondependent rats had no effect on self-administration of ethanol.

Dopaminergic function also is compromised during acute ethanol withdrawal. Animals sustained on a liquid diet show a decrease in extracellular levels of dopamine in the nucleus accumbens (Weiss et al., 1996). Similar effects have been observed for virtually all major drugs of abuse. Particularly compelling in the above study, however, was the observation that when animals were allowed to self-administer ethanol during acute withdrawal, the animals self-administered just enough ethanol to return extracellular dopamine levels in the nucleus accumbens back to predependence baseline levels. Overall, these observations suggest that the classical neurotransmitters associated with regulating the positive reinforcing properties of drugs of abuse, including ethanol, are compromised during ethanol withdrawal.

NEUROBIOLOGY OF NEGATIVE REINFORCEMENT ASSOCIATED WITH ETHANOL REINFORCEMENT: ENGAGEMENT OF BRAIN STRESS SYSTEMS

Other driving forces for the changes in reward function associated with ethanol dependence have been hypothesized to include dysregulation of the brain stress systems. Increased activity of the extended amygdala CRF system has been observed during acute withdrawal from virtually all major drugs of abuse (Merlo-Pich et al., 1995; Olive et al., 2002; Richter and Weiss, 1999; Rodriguez de Fonseca et al., 1997; Zorrilla et al., 2001) and evidence is accumulating for changes in NPY systems with development of dependence (Roy and Pandey, 2002; Slawecki et al., 1999).

CRF is a 41 amino acid polypeptide with a wide distribution throughout the brain with particularly high concentrations of cell bodies in the paraventricular nucleus of the hypothalamus, the basal forebrain (notably the extended amygdala), and the brainstem (Swanson et al., 1983). Central administration of CRF mimics the behavioral response to activation and stress in rodents, with the types of behavior elicited depending upon the baseline state of the animal. CRF increases brain reward thresholds (reduces reward) (Macey et al., 2000) and produces both taste and place aversion (Heinrichs et al., 1991). Two distinct mammalian G-protein-coupled CRF receptors have been identified. The type 1 CRF receptor (CRF-1) is found mainly in the pituitary, amygdala, BNST, hippocampus, cerebellum, and cortex and generally is associated with increases in anxiety-like behavior (Koob and Heinrichs, 1999). The type 2 CRF receptor (CRF-2) is found mainly in the lateral septum, ventromedial hypothalamus, corticomedial amygdala, BNST, nucleus tractus solitarius, and choroid plexus (Chalmers et al., 1995; Perrin et al., 1995; Van Pett et al., 2000) and generally appears to be more associated with appetite suppression than stress-like responses (Pelley-mounter et al., 2000; Spina et al., 1996).

Ethanol also is a powerful modulator of stress systems, an effect that may be crucial in the understanding of dependence and relapse. Both acute and chronic ethanol activate the hypothalamic-pituitary adrenal axis, and this appears to be the result of release of CRF in the hypothalamus to, in turn, activate the classic neuroendocrine stress response (Rasmussen et al., 2000; Rivier et al., 1984). However, recent evidence suggests that chronic ethanol also may interact with an extensive extrahypothalamic, extra-neuroendocrine CRF system implicated in behavioral responses to stress (Koob et al., 1994). The anxiogenic-like effect of ethanol withdrawal can be reversed by intracere-

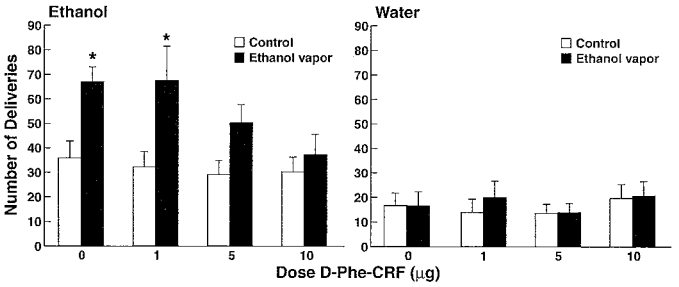

Fig. 9. Effects of the CRF receptor antagonist D-Phe-CRF_{12-41} on responding for ethanol and water 2 hr following chronic ethanol vapor exposure. Control rats were exposed to air vapor. Rats were microinjected icv with 0–10 μg of D-Phe-CRF_{12-41} (n = 10–12 per group) using a within-subjects Latin square design 2 hr after removal from the vapor chambers. The number of lever presses for ethanol and water ± SEM were measured for 60 min, 10 min after injection. Each rat had access to ethanol for only 60 min, 2 hr into withdrawal. Following the initial test session, rats were re-exposed to ethanol vapor or air, and the procedures were repeated until the Latin square design was complete. * $p < 0.05$, Tukey's test, compared with controls. (Taken with permission from Valdez et al., 2002.)

bral administration of the CRF antagonist into the central nucleus of the amygdala (Rassnick et al., 1993). Increases in extracellular levels of CRF are observed in the amygdala and BNST during ethanol withdrawal (Merlo-Pich et al., 1995; Olive et al., 2002). Even more compelling is the observation that a competitive CRF antagonist that has no effect on ethanol self-administration in nondependent rats effectively eliminates excessive drinking in dependent rats (Valdez et al., 2002) (Fig. 9).

NPY is a 36 amino acid polypeptide distributed widely throughout the central nervous system but with high concentrations within the extended amygdala (Adrian et al., 1983). Central administration of NPY increases feeding behavior (Clark et al., 1984; Levine and Morley, 1984), reduces anxiety-like behavior (Kask et al., 1998), and potentiates the effects of sedative hypnotics (Heilig and Murison, 1987; Heilig et al., 1989). As with CRF receptors, multiple NPY receptor subtypes have been identified (Y-1, Y-2, Y-4, Y-5, and Y-6) with the Y-1 receptor hypothesized to be most involved in emotional behavior. The Y-1 receptor has a wide distribution throughout the rat brain, where it is most abundantly found in the cortex, olfactory tubercle, hippocampus, hypothalamus, and thalamus (Parker and Herzog, 1999) and has been the receptor most associated with the antistress effects of NPY (Heilig et al., 1993). Such antistress effects of NPY are reversed by co-administration of a Y-1 receptor antagonist (Sajdyk et al., 1999) and antisense inhibition of Y-1 receptor expression (Heilig and Widerlov, 1995).

Acute withdrawal from ethanol is associated with decreases in the levels of NPY in the central and medial nuclei of the amygdala and the piriform cortex (Roy and Pandey, 2002), and Wistar rats show a blunted electrophysiological response to central injections of NPY in the amygdala following chronic alcohol exposure (Slawecki et al., 1999). These studies suggest that alcohol-induced changes in NPY activity in the amygdala may be involved not only in stress responses but also in the motivational effects of ethanol. One hypothesis is that decreased activity of NPY, parallel to increased activity of CRF, may provide a motivational basis for alcohol self-administration during alcohol withdrawal. These results suggest not only a change in function of neurotransmitters associated with the acute reinforcing effects of ethanol, such as GABA, during the development of dependence, but also recruitment of the CRF brain stress system and decreased activity of the NPY brain antistress system.

NEUROBIOLOGICAL BASIS FOR MOTIVATIONAL EFFECTS OF PROTRACTED ABSTINENCE FROM ETHANOL

The neurotransmitter systems in specific reward or emotional circuits are hypothesized to function in a normal state in a homeostatically regulated hedonic system such that their function is modified by positive and negative stimuli to return to a homeostatic baseline. However, such a hedonic system has been hypothesized to have limited resources (Koob and Le Moal, 1997), and dysregulation of this homeostatic system–either by constitutive elements (genetics or development history) or by a history of drug taking–is hypothesized to lead to an allostatic state of elevated thresholds for drug reward (decreased reward) following or during dependence. This allostatic state in the brain reward system is hypothesized not only to produce vulnerability to become addicted but also to perpetuate addiction and vulnerability to relapse during protracted abstinence (Koob and Le Moal, 2001). Protracted abstinence from ethanol so defined in the rat spans a period when acute physical withdrawal has disappeared where elevations in ethanol intake over baseline and increased stress responsivity persist 2–8 weeks postwithdrawal from chronic ethanol (Roberts et al., 2000; Valdez et al., 2002).

The increased self-administration of alcohol observed during protracted abstinence also was blocked by a competitive CRF antagonist. Rats trained to self-administer alcohol in 30-min daily sessions and subsequently made dependent with chronic continuous exposure to ethanol vapor were withdrawn from alcohol and retested in 1-hr sessions 2–5 weeks following removal from ethanol vapor. A CRF antagonist dose-dependently reduced self-administration only in the rats with a history of dependence (Valdez et al., 2002) (Fig. 10). Rats similarly made dependent with chronic continuous exposure to ethanol vapor showed anxiety-like behavior on the elevated plus-maze at 4 weeks following withdrawal (Valdez et al., 2002). These results suggest that brain CRF systems remain hyperactive during protracted abstinence and this hyperactivity is of motivational significance for excessive drinking of alcohol.

NPY not only has a well-documented orexigenic action and antianxiety-like action in rodents but also has been shown to oppose functionally the actions of CRF (Heilig et al., 1994; Heinrichs et al., 1993). Studies involving molecular genetic manipulations in mice and selective breeding studies in rats also implicate NPY as a mechanism in the

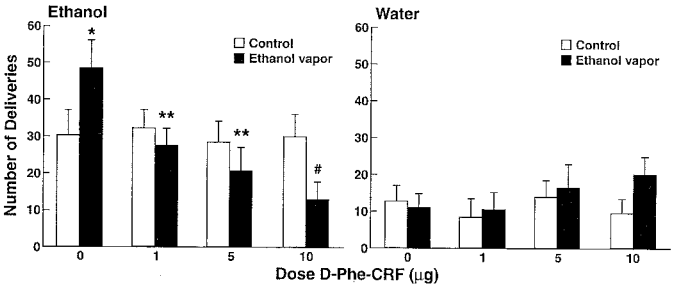

Fig. 10. Effects of the CRF receptor antagonist D-Phe-CRF_{12-41} on responding for ethanol and water 2 to 5 weeks following chronic ethanol vapor exposure. Control rats were exposed to air vapor. Rats were microinjected icv with 0–10 μg of D-Phe-CRF_{12-41} ($n = 8$ per group) using a within-subjects Latin square design 2 weeks after removal from the vapor chambers. The number of lever presses for ethanol and water ± SEM were measured for 60 min, 10 min after injection. Each rat had access to ethanol for only a 60-min test session. Following the initial test session, rats were returned to their home cages and left undisturbed. The testing procedures were repeated over the next 3 weeks until the Latin square design was complete. * $p < 0.05$, Tukey's test, compared with controls; ** $p < 0.05$, Tukey's test, compared with ethanol-exposed rats injected with 0 μg of D-Phe-CRF12–41; # $p < 0.05$, Tukey's test, compared with ethanol-exposed rats injected with 0 μg of D-Phe-CRF_{12-41} and controls. (Taken with permission from Valdez et al., 2002.)

regulation of alcohol consumption that has implications for vulnerability to alcoholism and the concept of protracted abstinence. NPY knockout mice self-administer significantly higher amounts of alcohol compared with wild-type controls (Thiele et al., 1998). These mice are less sensitive to the sedative effects of alcohol; they are able to recover from alcohol-induced inactivity faster than wild-type controls with similar blood alcohol concentrations (Thiele et al., 1998). NPY-overexpressing mice show a lower preference for alcohol and are more sensitive to the sedative effects of alcohol compared with controls (Thiele et al., 1998). Selectively bred P rats show lower concentrations of NPY-like immunoreactivity in the amygdala, hippocampus, and frontal cortex compared with selectively bred NP rats (Ehlers et al., 1998), and P rats and HAD rats show similar concentrations of NPY-like immunoreactivity in the central nucleus of the amygdala, which is significantly lower compared with both NP and LAD rats (Hwang et al., 1999). Perhaps more compelling, NPY administered intracerebroventricularly decreases ethanol self-administration in P rats at doses that do not affect responding for ethanol in NP rats (Badia-Elder et al., 2001). Thus, the hypothesis generated here is that the extended amygdala NPY system is compromised during the development of dependence and, combined with an activated extended amygdala CRF system, provides a powerful contribution to the negative affective state that drives the negative reinforcement of acute withdrawal and protracted abstinence.

ALLOSTASIS AND BEYOND

Allostasis, simply defined as the process of achieving stability through change, originally was formulated as a hypothesis to explain the physiologic basis for changes in patterns of human morbidity and mortality associated with modern life (Sterling and Eyer, 1988). High blood pressure and other pathology was linked to social disruption by a brain–body interaction. Using the arousal/stress continuum as their physiologic framework, Sterling and Eyer (1988) argued that homeostasis was not adequate to explain such brain–body interactions, and that the concept of allostasis has several unique characteristics that give it more explanatory power than homeostasis in characterizing the physiologic responses required in an ever changing environment. These characteristics include a continuous re-evaluation of the organism's need and continuous readjustments to new set points, depending on demand. Homeostatic systems, in contrast, cannot anticipate need or make adjustments in advance but, in fact, react only to deviations from the normal range by forcing a parameter to a specific set point (e.g., the average or normal set point) (Sterling and Eyer, 1988). The remarkable capacity to adjust and fine tune physiologic responses in an allostatic system, however, has a dark side when arousal (demand) becomes excessive. Allostasis as a concept was extended to the domains of stress and the hypothalamic pituitary axis by McEwen (1998, 2000) and anxiety disorders and central CRF by Schulkin et al., (1994). The concept of allostatic load was introduced, which is the price the body pays to adapt to adverse psychosocial or physical situations (McEwen, 2000). Allostatic load represents either external demands, such as too much stress, or internal demands, such as inefficient operation of the stress hormone response system. Allostatic load was defined as the cost to the brain and body of the deviation, accumulating over time and reflecting, in many cases, pathologic states and accumulation of damage. Allostatic state was introduced to explain the concept of how movement of physiologic parameters out of the homeostatic range could lead to a chronic condition of heightened vulnerability to pathology such as alcoholism (Koob and Le Moal, 2001). An allostatic state can be defined as a state of chronic deviation of the regulatory systems from their normal state of operation with establishment of a new set point.

Such an allostatic model is far more complex than homeostasis because all parameters of a given domain (e.g., blood pressure or, for the present review, reward function in the central nervous system) are controlled by numerous mutually interacting signals. When demands become chronic, the brain–body system tonically adapts at essentially all levels of organization implying widespread changes in set points; entry into a relaxed condition may create an unpleasant state of withdrawal from one's physiologic regulation. Such changes in hormone and neurotransmitter function provide a physiologic basis for the individual to continue to seek a condition of high demand (Sterling and Eyer, 1988) and a stabilized new level of activity far from homeostatic equilibrium. However, when chronic arousal, repeated stress, and negative affective states impose prolonged regulations far from normality, there is no margin left for responding to additional challenges, no opportunity for relaxation, and no capacity for more responsiveness.

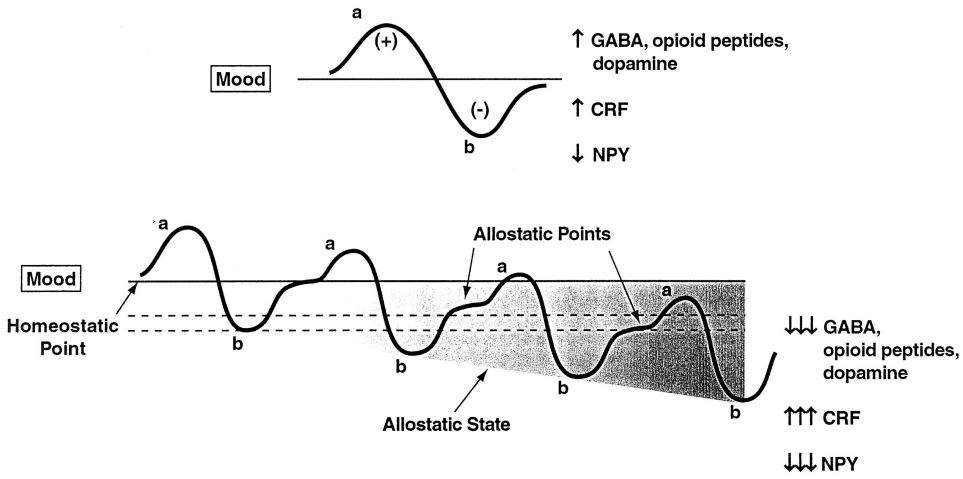

Fig. 11. Diagram illustrating an extension of Solomon and Corbit's (1974) opponent-process model of motivation to outline the conceptual framework of the allostatic hypothesis. Both panels represent the affective response to the presentation of a drug. (Top) This diagram represents the initial experience of a drug with no prior drug history. 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 a sum of both an a-process and a b-process. (Bottom) The changes in the affective stimulus (state) in an individual with repeated frequent drug use that may represent a transition to an allostatic state in the brain reward systems and, by extrapolation, a transition to addiction. Note that the apparent b-process never returns to the original homeostatic level before drug-taking is reinitiated, thus creating a greater and greater allostatic state in the brain reward system (see text). Small up- and down-arrows refer to increased or decreased functional activity of the neurotransmitters. DA, dopamine; CRF, corticotropin-releasing factor; GABA, gamma-aminobutyric acid; NPY, neuropeptide Y. (Modified with permission from Koob and Le Moal, 2001.)

This stabilized new level of activity far from homeostatic equilibrium forms an allostatic state.

Changes in the brain systems associated with the development of motivational aspects of withdrawal are hypothesized to be a major source of potential allostatic changes that drive and maintain alcoholism. Acute withdrawal from alcohol produces changes in reward neurotransmitters opposite to those experienced during acute positive reinforcement in specific elements of reward circuitry associated with the extended amygdala as well as recruitment and disruption of brain stress systems that motivationally oppose the hedonic effects of drugs of abuse. In this context, allostasis from the drug addiction perspective is the process of maintaining apparent reward function stability through changes in reward and stress system neurocircuitry. Decreases in the function of dopamine, serotonin, and opioid peptides are hypothesized to contribute to a shift in reward set point as well as recruitment of the CRF brain stress system and disruption of the NPY brain antistress system (Koob, 2002) (Fig. 11). All of these changes are hypothesized to be focused on a dysregulation of function within the neurocircuitry of the basal forebrain macrostructure of the extended amygdala.

The present formulation forms an extension of the opponent process theory proposed by Solomon and Corbit (1974) to an allostatic framework with a hypothesized neurobiologic mechanism (Koob, 2002; Koob and Le Moal, 2001) (Fig. 11). Here, the counteradaptive opponent process (originally described as the b-process; see Fig. 11) does not balance the activational process (a-process) but, in fact, shows a residual hysteresis which can be hypothesized to involve not only decreases in reward neurotransmission such as dopamine, GABA, and opioid peptides but also recruitment of the CRF brain stress systems and dysregulation of the NPY brain antistress system (Fig. 11). These opponent process-like neurochemical/neurocircuitry changes associated with withdrawal therefore may contribute to the increased motivational properties of ethanol during protracted abstinence, thereby providing the driving force for relapses and the cycles of ethanol abuse and addiction.

PSYCHODYNAMIC VIEW OF ADDICTION: A DEFICIT IN AFFECTIVE STATE AND SELF-CARE

A cogent and scholarly argument for a psychodynamic view of addiction with a focus on what factors lead to the vulnerability for addiction can be found in the work of Edward Khantzian. The core element of Khantzian's psychodynamic perspective is a dysregulated emotional system in individuals vulnerable to addiction and a dysregulation in how the emotions are expressed, experienced, and corrected (Khantzian, 1985, 1990, 1997). Two critical elements have been identified–disordered emotions and disordered self-care–which interact with two contributory elements–disordered self-esteem and disordered relationships. A self-medication hypothesis has been postulated where individuals with substance use disorders are hypothesized to take drugs as a means to cope with painful and threatening emotions. Addicted individuals are further hypothesized to experience states of subjective distress and suffering that may or may not be associated with conditions meeting DSM-IV criteria for a psychiatric diagnosis (American Psychiatric Association, 1994) and consist mainly of feelings that are overwhelming and unbearable but also may consist of a life that is absent and nameless.

In this context, drug addiction is viewed as an attempt to medicate such a negative affective state, and significant psychodynamic evidence has been marshaled not only for the existence of the negative affective state but also for self-medication. In addition, such self-medication may be state-specific (anxiety, irritability, dysphoria, anger) and drug-specific in that 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 and energizing agents for low energy individuals, and depressants 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) of such individuals. Disordered self-care is hypothesized to combine malignantly with the disordered emotional life to become a principal determinant of substance use disorders.

This psychodynamic approach resonates well with the evidence for a critical role of dysregulated brain reward and stress systems described above. However, from a neurobiological perspective, drugs of abuse such as ethanol would interact with personality and character traits that lead to addiction and, by their action on the brain, reward and stress systems not only would perpetuate such character flaws but actually may create them.

NEUROCIRCUITRY OF THE EXTENDED AMYGDALA AS A FOCAL POINT FOR ALLOSTATIC CHANGES ASSOCIATED WITH ALCOHOLISM

Allostasis from the addiction perspective has been defined as the process of maintaining apparent reward function stability through changes in brain reward mechanisms. The allostatic state represents a chronic deviation of reward set point that often is not overtly observed while the individual is actively taking drugs. The allostatic state is fueled not only by dysregulation of reward circuits per se but also by the activation of brain and hormonal stress responses. From the perspective of alcoholism, it is unknown whether the hypothesized reward dysfunction is specific to alcoholism, common to all addictions, or a combination of both perspectives. However, from the data generated to date, and the established anatomic connections, the manifestation of this allostatic state as compulsive ethanol-taking and loss of control over ethanol-taking is hypothesized to be critically based on dysregulation of specific neurotransmitter function in the central division of the extended amygdala. It is further hypothesized that the pathology of this neurocircuitry is the basis for the emotional dysfunction long associated with alcoholism in humans and some of this neurocircuitry pathology persists into protracted abstinence, thereby providing a strong motivational basis for relapse. The view that alcoholism is the pathology that results from an allostatic mechanism that usurps the circuits established for natural rewards provides a realistic approach to identifying the neurobiological factors that produce vulnerability to addiction and relapse.

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