Abstract

Much has been written about the interaction of stressors (physical, social, and psychological) and alcohol addiction based on studies in humans and preclinical models. We begin by considering the significance and complexity of alcoholism and the options for effectively modeling it in animals, particularly rodents. We then focus on the following aspects of stress-alcohol interactions: (1) compulsive alcohol consumption, characterized by continued intake despite the presence of stressful or aversive consequences; (2) the possible relationship between acute stress and increased alcohol intake; (3) an apparent cross sensitization of stress and alcohol exposure, which increases both future reactivity to stress and the risk of developing alcohol addiction; and (4) efforts to target stress in therapeutic interventions for alcoholism. We also describe possible neuroadaptations and genetic factors that may interact with stress to increase susceptibility to alcoholism. Throughout, we describe the challenges and inconsistencies inherent in both human and animal studies of alcoholism, its etiology, and its impacts. We believe the relationship between preclinical and human studies is of paramount importance to understand addiction-related behavior in humans and to direct, improve, and expand animal models. It is our hope that a full understanding of the mechanistic bases of pathological alcohol intake will have translational benefits for the development of behavioral and pharmacological therapies.

Key Words: alcoholism; aversion resistance; compulsion; molecular mechanism; neuroadaptation; relapse; risk factor; rodent model; sensitization; stress

Alcoholism has many negative impacts, ranging from crime and domestic violence to lost productivity, impaired military readiness, and hundreds of thousands of avoidable deaths each year (Harwood et al. 1998; Henderson et al. 2009; Killgore et al. 2008; Lieber 1995; Miller and Blencoe 1994; Mokdad et al. 2004; Thomas et al. 2010; Tucker et al. 2009). These social, personal, emotional, legal, and economic costs are borne not only by the alcoholic but also by family, friends, and society in general. It is therefore critical to understand the etiology of alcoholism, in particular the psychological and molecular mechanisms through which stressors may initiate and sustain pathological alcohol drinking.

Strengths and Limitations of Animal Models of Alcohol Intake

Specific Suitability of Animal Models

It is important to determine which areas of human addiction can be modeled in preclinical research and which species to use. Binge drinking and some aspects of poor decision making may be effectively modeled in rodents, whereas some aspects of human behaviors (e.g., drunk driving, denial, and self-delusion) are less amenable. We also consider rodent models excellent for the study of both stress-related neuroadaptations that alter alcohol intake and cellular signaling pathways through which acute stressors can alter alcohol intake or relapse.

Binge drinking is a problem in the treatment of human alcoholics (Banta et al. 2008) as it likely promotes secondary adaptations that anchor alcoholism over the long term. It is also associated with organ damage, higher long-term risk of death (Kauhanen et al. 1997; Standridge et al. 2004), and increased risky behavior such as drunk driving (Zhao et al. 2010).

There are a number of rodent models for binge drinking, including limited access in operant conditions in rats (Simms et al. 2010), excessive drinking in dependent rats and mice (Griffith et al. 2009; Richardson et al. 2008; Sommer et al. 2008), and, in mice, “drinking in the dark”1 (Sparta et al. 2008) and scheduled high access models (Strong et al. 2010), in which limited access promotes excessive alcohol intake. These studies have identified a number of molecular regulators of binge intake, including stress-related molecules (discussed below).

Poor decision making, characterized in part by increased impulsive behavior, is another key problem for the treatment

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1 In this model, mice are allowed 2 hours’ access to ethanol during the middle of their dark cycle, when mice are normally more active.
of alcoholism. Two models of impulsivity are considered comparable across human and animal studies. The first concerns poor response inhibition (inability to withhold a response) and the second poor delayed discounting (inability to delay responding in order to receive a larger reward) (Dick et al. 2010; Lejuez et al. 2010). Greater impulsivity is generally associated with greater alcohol intake in both humans and rodents (Dick et al. 2010; Lejuez et al. 2010; Mitchell et al. 2005; Oberlin and Grahame 2009; Wilhelm and Mitchell 2008). Of particular interest is whether impulsivity precedes or results from alcohol intake; rodent studies have shown both possibilities (Nasrallah et al. 2009; Oberlin and Grahame 2009; Wilhelm and Mitchell 2008), but these are difficult to dissociate conclusively in humans (Dick et al. 2010; Lejuez et al. 2010).

Animal models allow experimental control over exposure to stress and alcohol as well as variables such as age and sex. Although human studies have described a relationship between trauma and subsequent increased risk of addiction (Brown et al. 1995; Enoch 2011; Killgore et al. 2008; Uhart and Wand 2009; Waldrop et al. 2007; Wilk et al. 2010), these are correlational and the cause and effect of stress-alcohol interactions are unclear. Furthermore, the ability of stress to facilitate human addiction may critically involve an interaction between genetic vulnerability and previous exposure to a stressful or traumatic environment (Enoch 2011; Heilig et al. 2010; Saraceno et al. 2009; Schmid et al. 2010; Schwandt et al. 2010). The complex relationship among these potential factors requires preclinical models to disambiguate genetic and environmental factors.

Limitations of Animal Models

There may be important limits to the use of rodents for studies of human alcoholism, especially decision making. For example, compulsive behavior, particularly alcohol seeking despite aversive consequences (addressed in detail below), represents a significant obstacle for treatment of human addiction. In this regard, a few weeks of cocaine exposure are sufficient to impair rodent decision making (Schoenbaum and Shaham 2008), but very long cocaine self-administration is needed for rats to demonstrate compulsive behavior (Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004; for a review of cocaine addiction, see Ahmed and Kenny 2011, in this issue). These studies suggest that drug-related cognitive impairment in rats may be dissociated mechanistically from compulsion, whereas cognitive impairment and compulsion seem to be closely associated in human addiction.

Some concerns related to the use of rodents can be alleviated by the use of primates, whose prolonged development and cortical areas subserving decision making are more like those of humans compared with rodents (Enoch 2011; Schwandt et al. 2010). However, it is not clear that animal models can ever accurately capture the poor decision making inherent in the denial and self-delusion that an alcoholic or other addict uses to justify continued intake (Collins et al. 1996; Larimer et al. 1999). Condition-specific variability further complicates the ability to model human decision making. For example, a recent study found only subtle decision-making impairments associated with recidivist drunk driving (Kasar et al. 2010); alcoholics in this study were not seeking treatment, in contrast to most studies. Thus, there is much to learn about decision making in human addicts to be able to accurately assess the relevance of rodent models.

Overall, studies of human alcoholics remain of paramount importance in efforts to dissect the mechanisms of human pathological behavior. Such studies yield critical information that aids in the design of effective preclinical studies to support the development of therapeutic treatments for alcoholism.

Alcohol Intake Despite Aversive Consequences: A Model for Compulsive Consumption?

The compulsive nature of alcohol and drug intake is widely considered a critical obstacle to the successful treatment of alcoholism and addiction (Anton 2000; Epstein et al. 2006; Koob and Volkow 2010; Larimer et al. 1999; Sanchis-Segura and Spanagel 2006). There is particular interest in aversion resistance during compulsive intake, as human alcoholics continue to seek and consume alcohol despite adverse and sometimes severe social, physical, and legal consequences.

Rodent Models of Aversion Resistance

Rodent models of aversion resistance are considered to represent some aspects of compulsion in humans (Epstein et al. 2006; Everitt and Robbins 2005; Sanchis-Segura and Spanagel 2006). Cocaine intake despite pairing with footshock is considered the most robust model for compulsive addiction (Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004), but to our knowledge similar experiments have not been reported with alcohol. Instead, a number of studies in rodents, using bitter-tasting quinine to examine aversion-resistant alcohol intake, have reported that the animals tolerate alcohol intake while maintaining normal water intake (Hopf et al. 2010; Loi et al. 2010; Spanagel et al. 1996; Spanagel and Holter 1999; Turyabahika-Thyen and Wolffgramm 2006; Vengeliene et al. 2009; Wolffgramm and Heyne 1991; Wolffgramm et al. 2000).

Early studies in rats used a four-bottle choice paradigm (with concurrent access to 20%, 10%, and 5% alcohol, and

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2One general concern about rodent studies is the terminology (e.g., “inflexible,” “maladaptive,” “pathological”) used to describe continued intake despite aversion. We prefer the term “aversion resistance” for preclinical studies, as it is unclear whether such studies effectively represent the inflexibility or loss of control reported in human alcoholics.
water) and showed that quinine-resistant alcohol intake develops after longer-term (>8 months) but not shorter-term (<6 months) alcohol access. Aversion-resistant consumption was accompanied by other addiction-like behaviors such as a switch in preference for higher alcohol concentrations and changes in circadian patterns of alcohol intake (Spanagel et al. 1996; Spanagel and Holter 1999; Turyabahika-Thyen and Wolffgramm 2006; Vengeliene et al. 2009; Wolffgramm and Heyne 1991; Wolffgramm et al. 2000). Some groups have therefore considered continued alcohol intake despite alteration with quinine to model inflexible, compulsive behavior and perhaps represent loss of control over intake despite aversion.

Although aversion-resistant alcohol intake could represent loss of control, rats given a choice of several different alcohol concentrations drink equivalent total amounts of alcohol adulterated with quinine but switch preference from a lower to a higher concentration of alcohol (Turyabahika-Thyen and Wolffgramm 2006; Wolffgramm et al. 2000). This finding could represent adaptive behavior (so that the animal consumes the “preferred” total daily amount of alcohol while minimizing the aversive consequences) rather than loss of control per se.

Some aspects of drinking in human alcoholics may not represent loss of control but instead reflect a maladaptive cognitive process that allows continued alcohol intake (e.g., see discussion of “apparently irrelevant decisions” in Larimer et al. 1999). In addition, it can be upsetting for addicts to focus on the negative consequences of their drinking (Kia-Keating et al. 2009), suggesting perhaps that they know but are attempting to ignore that there are aversive consequences. Human research is critical for helping define the most relevant phenotypes of compulsive behavior for analysis in rodent studies.

Aversion Resistance with Intermittent versus Continuous Access to Alcohol

Our research has demonstrated that quinine-resistant alcohol intake in rats can develop more rapidly than observed in the four-bottle choice studies, with quinine resistance apparent after 3 (but not 1½) months of intermittent access to alcohol (IAA3) (Hopf et al. 2010). Also, a recent drinking in the dark study in mice found development of quinine-resistant alcohol intake after only 2 weeks (Lesscher et al. 2010).

In the IAA model, rats have access to 20% alcohol on 3 of 7 days per week, with at least 1 day between each 24-hour intake session (Hopf et al. 2010; Simms et al. 2008; Wise 1973). We compared results from IAA rats to those from rats with continuous access to alcohol (CAA3). Initial alcohol intake of the two groups was similar, but the IAA rats escalated their intake during the first 4–5 weeks of access to alcohol and drank 6–8 g/kg/24 hr at plateau (Simms et al. 2008), with blood alcohol concentrations greater than 50 mg% (Simms et al. 2008). These acute intake levels are significantly greater than those of CAA rats (Hopf et al. 2010; Simms et al. 2008; Spanagel et al. 1996; Spanagel and Holter 1999; Wolffgramm and Heyne 1991; Wolffgramm et al. 2000) and are similar to those of alcohol-preferring rat strains (e.g., P rats; Bell et al. 2006). Most importantly, we also observed that IAA rats drinking quinine-adulterated alcohol tolerate much greater concentrations of quinine than CAA rats (Hopf et al. 2010), indicating the development of resistance to quinine aversion. Neither group of rats exhibited changes in basic quinine taste reactivity after 3–4 months of intake.

Other studies indicate that the IAA paradigm is a robust animal model with predictive validity for pathological human alcohol intake, as illustrated in the following examples:

- Compounds (e.g., naltrexone and acamprosate; Spanagel 2009) that can reduce alcohol intake in human alcoholics have a greater effect on the excessive intake of IAA rats than on the more moderate intake of CAA animals (Simms et al. 2008).
- IAA but not CAA rats escalate intake during the first month of drinking (Simms et al. 2008); in humans, escalation of intake has been associated with the development of addiction (Koob and Volkow 2010; Uhart and Wand 2009).
- Another model of pathological alcohol intake, the alcohol deprivation effect (ADE3), involves dramatically enhanced alcohol consumption after a protracted period of abstinence from alcohol and is considered a model of human relapse (Sanchis-Segura and Spanagel 2006). IAA rats do not show ADE, whereas CAA rats do (Simms et al. 2008; our unpublished data). We interpret this to indicate that IAA rats may already be at maximum in terms of expression of pathological drinking.
- Finally, a study in an alcohol-preferring rat strain for less than 1 month found relative resistance to quinine adulteration in IAA versus CAA in rats, but still some sensitivity to quinine in the former (Loi et al. 2010). This finding agrees with our study showing some quinine sensitivity at ~1½ months relative to 3–4 months of IAA intake; we used outbred Wistar rats (Hopf et al. 2010), which consume alcohol but are not selected to be alcohol-preferring.

Brain Mechanisms of Aversion Resistance

Relatively little is known about the brain region or molecular mechanisms that support aversion-resistant intake. Human imaging studies suggest that compulsive behavior involves basal hyperactivity across a network of frontal cortical areas, in combination with greater cortical and subcortical activation during exposure to drug-related cues or distress (Filbey

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3Abbreviations that appear ≥3x throughout this article: ADE, alcohol deprivation effect; CAA, continuous access to alcohol; IAA, intermittent access to alcohol
et al. 2008; Kareken et al. 2004; Koob and Volkow 2010; Sinha 2009). In particular, hypofrontality is linked to impulsivity and poor decision making, with some focus on the orbitofrontal cortex as a critical mediator of behavioral flexibility.

A recent study found that rats that self-administer cocaine lost the ability to induce a form of glutamatergic plasticity called long-term depression (LTD) in nucleus accumbens neurons after a few weeks of intake (Kasanetz et al. 2010). When tested after ~7 weeks of self-administration, rats whose cocaine intake was greatly reduced by pairing with shock recovered the ability to generate LTD, whereas those whose cocaine intake was insensitive to pairing with shock did not. The authors suggest that these molecular changes may represent the inability to form new memories and prevent flexible responding (Kasanetz et al. 2010).

**Acute Stressor Exposure and Alcohol Intake**

Acute exposure to stressors may play an important role in promoting drug or alcohol intake; indeed, human alcoholics and addicts often cite stress and negative affect as a reason for relapse or increased intake (Annis et al. 1998; Brown et al. 1995; Dawson et al. 2005; Heilig et al. 2010; Noone et al. 1999; Sinha 2009; Sinha et al. 2009; Uhart and Wand 2009).

More than 50 years ago, Conger (1956) proposed the tension-reduction hypothesis: (1) stress produces an internal state characterized by tension and anxiety and (2) the anxiolytic effects of alcohol reduce such stress. More recently, Koob and colleagues proposed that repeated alcohol or drug intake and the negative experience of withdrawal, perhaps in combination with tolerance to the pleasurable effects of alcohol, result in allostatics (Koob 2003; Koob and Volkow 2010). In contrast to homeostasis, in which adaptive changes reestablish normal, healthy functioning, allostatics represents a maladaptive steady state in which alcohol intake is driven by negative reinforcement (drinking to relieve stress). Allostasis likely reflects both molecular adaptations and learned associations between alcohol intake, its negative consequences, and the ability of alcohol to alleviate the stress resulting from those negative consequences; a cycle of associations that could promote addictive behaviors even during protracted abstinence.

**Acute Stressors and Alcohol Intake in Humans**

Numerous studies of the impact of stressors on human alcohol intake have shown that acute stressors can directly increase alcohol intake (Uhart and Wand 2009) and even that stress-related craving for alcohol (measured in the laboratory) can correlate with drinking levels outside the laboratory over subsequent weeks (Breese et al. 2005a; Sinha 2009).

In general, though, most studies have examined the relationship between stressor exposure and alcohol over weeks or months, making it harder to identify the acute impact of stress on intake. In addition, although many human studies find an association between stress and alcohol intake (Annis et al. 1998; Noone et al. 1999), others do not (Dawson et al. 2005; Pohorecky 1991; Uhart and Wand 2009). As reviewed by Pohorecky (1991) and others, a number of factors may contribute to these mixed results; for example,

- Alcoholics more reliably demonstrate stress-related alcohol intake relative to the general population, suggesting the presence of secondary (behavioral or neuro-) adaptations that promote pathological addiction. But many studies are in heavy social drinkers and may not clearly reflect the impact of stress in alcoholics.
- There are many different types and sources of stressors—acute and chronic, internally and externally generated, and derived from different aspects of life (e.g., job, family, finances, housing)—each of which may influence alcohol intake differently.
- Gender appears to play a role. Females in general show a weaker association between stress and alcohol intake than males, a finding that may reflect gender-related differences in coping skills—women are more likely to seek social support, whereas men are more likely to drink to counteract stress (Dawson et al. 2005; O’Connor et al. 2008; Pohorecky 1991; Udo et al. 2009; Wang et al. 2009; Weinberger et al. 2009).
- Some studies examine drinking and stress in college males, in whom positive expectations of alcohol’s effects may play a greater role in drinking than stress.

Thus, much remains to be learned about the exact parameters of stressful experiences that alter alcohol intake in humans, but the general concept that stress can promote alcohol drinking in alcoholics is likely valid.

**Stressors and Alcohol Intake in Rodent Models of Relapse**

Rodent models of human relapse (Sanchis-Segura and Spanagel 2006) include (1) the ADE, in which alcohol intake is dramatically enhanced after weeks or months of deprivation from alcohol, and (2) reinstatement after extinction, in which operant responding for alcohol (e.g., pressing a lever) is “extinguished” by several weeks during which lever pressing is not associated with alcohol access; lever pressing can then be “reinstated” by an alcohol-related cue or a stressor.

Alcohol intake in these models is increased by stressors such as administration of the anxiogenic yohimbine, footshock, social defeat, or restraint (Bowers et al. 1997; Funk et al. 2004; Le et al. 2000; Liu and Weiss 2002; Simms et al. 2010; but see Dayas et al. 2004) even when no alcohol reward is delivered (perhaps suggesting increased motivation), similar to stress-induced reinstatement for other drugs of abuse (e.g., cocaine, heroin; Epstein et al. 2006; McFarland et al. 2004; Shalev et al. 2010; Vanderschuren and Everitt...
A relatively conserved neural circuit that mediates footshock-induced reinstatement of alcohol seeking in rodents (Epstein et al. 2006; McFarland et al. 2004) is also activated in human alcoholics and addicts by drug- or alcohol-associated cues and stress (Koob and Volkow 2010; Sinha 2009), and the level of brain activation can predict future alcohol intake or relapse in humans (Sinha 2009). Rodent models of relapse may thus be useful for delineating the circuitry through which stress can enhance drug or alcohol intake in humans.

**Mixed Results of Stressors in Rodent Models of Self-Administration**

In contrast to rodent models of relapse, preclinical studies of stressors and alcohol self-administration show more mixed results. In some cases, acute exposure to stressors such as footshock, cold water swim, or brief restraint increase alcohol intake (Fullgrabe et al. 2007; Lynch et al. 1999; Siegmund et al. 2005; Volpicelli et al. 1990), whereas other studies find no effect or even a negative effect of stress on alcohol intake. For example, studies have reported that single or repeated restraint stress or footshock had no effect on alcohol intake (Bowers et al. 1997; Funk et al. 2004; Tambour et al. 2008), or that a reduction in alcohol intake was produced by social defeat stress (Anacker and Ryabinin 2010; Funk et al. 2004; van Erp and Miczek 2001), novelty-related stress (Sabino et al. 2006), restraint stress (Chester et al. 2004; Rockman and Glavin 1986), or cold water swim (Boyce-Rustay et al. 2008). Resolving these mixed results is challenging, as there are many potential differences, such as type of stressor, species or strain of rat or mouse, and paradigm of alcohol exposure, as evidenced in the following examples.

- Rodent strains with lower initial alcohol preference may show a stress-related increase in alcohol intake, whereas those with higher alcohol preference show either no change or a decrease in intake (Chester et al. 2004; Darnaudery et al. 2007; Lowery et al. 2008; Rockman and Glavin 1986; Volpicelli et al. 1990; but see Boyce-Rustay et al. 2008). These divergent results could reflect strain differences in basal stress reactivity rather than alcohol preference per se.
- Stressor exposure can have a delayed effect on alcohol self-administration, with increased alcohol intake evident only days or weeks after stress exposure (Chester et al. 2004; Lowery et al. 2008; and references therein).
- Stress may change the anxiolytic effects of alcohol and thus alter intake (Funk et al. 2004; but see Boyce-Rustay et al. 2008).
- The predictability of a stressor may be another factor. Increased anxiety and negative affect during addiction are hallmarks of the allostatics hypothesis (Koob 2003, 2009; Koob and Volkow 2010). Human nicotine withdrawal, for example, is associated with increased reactiv-

Thus, despite long-standing support for the idea that alcohol intake is driven by the need to relieve stress or anxiety, neither human nor preclinical studies find that acute stressors invariably enhance alcohol intake. Resolving these diverse findings will require a comprehensive and parametric evaluation of different stressors and other variables within the same set of experiments, which will allow better comparison with human studies in which stress-related enhancement of alcohol intake is observed in alcoholics.

**Stress and Alcohol Cross Sensitization**

Many studies have suggested that stress exposure, especially during adolescence, can enhance subsequent development of addictive behaviors, and this correlation has been observed not only in humans (Brown et al. 1995; Cooper et al. 1992; Dawson et al. 2005, 2007; Enoch 2011; Heilig et al. 2010; Helen et al. 2010; Killgore et al. 2008; Richardson et al. 2008; Schafer et al. 2010; Uhart and Wand 2009; Waldrop et al. 2007; Wilk et al. 2010) but also in rodents (Chester et al. 2008; Enoch 2011; Lowery et al. 2008; Spear and Varlinskaya 2010) and nonhuman primates (Enoch 2011; Schwandt et al. 2010). Human studies are correlational, so the cause and effect of stress-alcohol interactions are unclear, whereas animal models can control exposure to stress and alcohol.

As mentioned above, the ability of stress to facilitate human addiction may critically involve an interaction of both genetic vulnerability and exposure to a stressful or traumatic environment (Saraceno et al. 2009; Enoch 2011; Heilig et al. 2010; Schmid et al. 2010; Schwandt et al. 2010), and this gene-stressor-alcohol interaction likely affects future pathological behavior through the development of neuroadaptations.

One type of neuroadaptation is cross sensitization, which occurs when exposure to one type of drug increases activation by subsequent exposure to a different drug, or when exposure to stress increases subsequent drug activation (Robinson and Berridge 2000; Uhart and Wand 2009). This enhanced activation, or “sensitization,” can persist for many months after drug exposure, and the molecular changes that underlie sensitization may drive relapse.
Molecular Mechanisms of Cross Sensitization

Cross sensitization likely involves protracted functional changes in one or more molecules in the brain. Although stress-related molecules could facilitate pathological consumption without any neuroadaptive functional changes, in some cases such changes likely play a central role in pathological alcohol intake.

One interesting possibility is that alcohol and stress act through a common pathway to alter neural function. The resulting neuroadaptations could increase both sensitivity to stress and the propensity for developing addiction (Uhart and Wand 2009). In humans, either stress or early alcohol exposure can increase both future reactivity to stress and the risk of pathological addiction (Heilig et al. 2010; Richardson et al. 2008; Schaefer et al. 2010; Uhart and Wand 2009; Wills et al. 2010).

There is also evidence that exposure to alcohol or drugs can acutely increase signaling of stress-related molecules (Heilig et al. 2010; Richardson et al. 2008; Uhart and Wand 2009; but see Dai et al. 2002), and this stress-related activation may contribute to the feeling of intoxication, at least during the early stages of intake (Sinha 2009; Sinha et al. 2009; Uhart and Wand 2009). Breese and colleagues (2005b) have proposed a “kindling”/stress hypothesis, according to which “stress after repeated alcohol exposures induces an anxiety response not seen in controls” and this anxiety in turn drives alcohol consumption.

Stress and alcohol may thus influence behavior through similar molecular mechanisms during both the development and the expression of addiction. A number of candidate molecules have been suggested from preclinical models of alcohol and/or stress exposure (Heilig et al. 2010; Martin-Fardon et al. 2010; Shalev et al. 2010; Silberman et al. 2009; Uhart and Wand 2009); here, we focus primarily on stress-related molecules (Martin-Fardon et al. 2010; Wills et al. 2010).

Cortisol and the HPA Axis

Considerable literature suggests that regulation of stress responses is disrupted in addicted humans, who exhibit elevated basal cortisol levels but lower neurohormonal response to stress (Adinoff et al. 2005; Brady et al. 2006; Dai et al. 2002; Junghans et al. 2003; Sinha 2009; Sinha et al. 2009).

Alcohol-related cues that increase craving produce a greater increase in cortisol in abstinent alcoholics than in social drinkers (Sinha et al. 2009), and this increase may be important during early stages of alcohol intake (Uhart and Wand 2009). Conversely, although stressors can increase craving, stress-induced cortisol increases are blunted both in abstinent alcoholics versus social drinkers (Sinha et al. 2009) and in alcohol-dependent rats (Richardson et al. 2008; Uhart and Wand 2009). These results indicate that the stress regulatory system may undergo multiple functional changes in relation to stress or alcohol exposure (Heilig et al. 2010; Uhart and Wand 2009).

Furthermore, people with a positive family history of alcoholism show greater stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis (Uhart et al. 2006). Attenuated HPA response in abstinent alcoholics correlates with relapse (Adinoff et al. 2005; Junghans et al. 2003). HPA function has also been shown to affect alcohol self-administration in rats (Nash and Maickel 1988).

It has been suggested that the inability to mount a successful neural and hormonal response to stress could enhance negative affect (Sinha 2009; Sinha et al. 2009) and increase the likelihood of drinking to alleviate that negative affect through restoring HPA function (Richardson et al. 2008). Indeed, pharmacological agents are available to decrease alcohol intake by reducing anxiety or HPA activity (Addolorato et al. 2009; Ciccocioppo et al. 2009; Farook et al. 2009).

In rodents, studies have indicated that stress-induced alcohol reinstatement does not require the HPA axis (Le et al. 2000; Shalev et al. 2010). It would be useful, however, to examine stress effects in other relapse models such as the ADE, since reinstatement involves an extended period of extinction before relapse testing (Sanchis-Segura and Spanagel 2006) and it is unclear whether human alcoholics ever undergo such explicit extinction.

Neuroadaptations in the HPA axis likely contribute to pathological alcohol-related behaviors, but the relationship between stress, alcohol exposure, and HPA function is complex and requires further research.

Corticotrophin-Releasing Hormone and Other Potential Genetic Risk Factors

A heritable endophenotype in humans with low responsiveness to the motor-impairing effects of alcohol has been related to drinking to cope with stress (Schuckit et al. 2008), and there is also a heritable high intoxication response to alcohol (Newlin and Thomson 1990). Thus it seems logical that genetic polymorphisms that increase the reactivity of the stress system could enhance the risk of developing pathological stress-related adaptations.

The corticotrophin-releasing hormone (CRH) is widely considered an important regulator of the neural system that controls stress (Koob 2009; Uhart and Wand 2009). In monkeys, a polymorphism in the CRH promoter increases CRH levels, endocrine and behavioral responses to stress, and the likelihood that early life stress will lead to greater alcohol intake (Barr et al. 2009). These findings seem to confirm cross sensitization between stress and alcohol.

In addition, CRH1 receptor (CRHR1) polymorphisms are associated with stress-induced alcohol intake in humans (Schmid et al. 2010), and high CRHR1 levels in an alcohol-preferring rat strain drive alcohol intake and stress-induced reinstatement (Hansson et al. 2006).

Studies also find alcohol-related neuroadaptations in CRH. Increased levels of CRH peptide and CRHR1 in the central nucleus of the amygdala drive alcohol intake in alcohol-dependent rats (Schmid et al. 2010; Richardson et al. 2008; Schaefer et al. 2010; Uhart and Wand 2009; Wills et al. 2010). The corticotrophin-releasing hormone (CRH) is widely considered an important regulator of the neural system that controls stress (Koob 2009; Uhart and Wand 2009). In monkeys, a polymorphism in the CRH promoter increases CRH levels, endocrine and behavioral responses to stress, and the likelihood that early life stress will lead to greater alcohol intake (Barr et al. 2009). These findings seem to confirm cross sensitization between stress and alcohol.

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inability to tolerate distress (Daughters et al. 2009; Howell and posttraumatic stress disorder patients often exhibit an 2010; Wang et al. 2009). Furthermore, inasmuch as addicts et al. 2006; Mohr et al. 2008; Pohorecky 1991; Volkel et al. 2009; Daeppen et al. 2010; Franko et al. 2008; Fulkerson ment and prevention of alcoholism and addiction (Brady et al. 2006; Killgore et al. 2008; Noone et al. 1999; Pohorecky 1991; Wang et al. 2009). One largely unexplored option for modeling the ability to learn positive coping mechanisms is to give alcohol-related neuroadaptations. 

Finally, decreased striatal dopamine (D2) receptor levels are associated with many forms of human addiction, perhaps by contributing to the hypofrontality that underlies poor decision making (Koob and Volkow 2010). Lower D2 receptor levels in rats predict greater impulsivity and a higher level of drug intake, and may thus represent an innate risk factor (Dalley et al. 2007). At present, however, little is known about any potential relationships between D2 receptor levels, stress reactivity, and addictive behaviors.

Molecular Changes Related to Learning

Stress and alcohol exposure could interact through more ba- sic learning mechanisms. Because stress exposure causes humans to learn through a habit-based rather than a goal- directed system (Schwabe and Wolf 2009), the only adaptation that might be needed to encode stress-driven alcohol consump- tion could be the same as that required for any other type of habit memory. It has also been demonstrated that stress, if not extreme, can enhance learning; for example, it improves learning in a water maze task through glucocorticoid receptor–induced increases in the α-amino-3-hydroxy- 5methyl-4-isoxazoloproprionic acid (AMPA) receptor sub- units in the amygdala (Conboy and Sandi 2010).

Further research is needed to explore the memory sys- tems through which stress can anchor addictions.

Stress Reduction as a Therapeutic Treatment of Alcoholism

One promising area of research in human addiction is the possibility that addicts and alcoholics can enhance their re- covery by learning behavioral strategies to allay the negative behavioral consequences of stressful experiences and stress- related neuroadaptations.

Positive Coping Strategies

A number of human studies highlight the importance of de- veloping positive coping strategies—such as family dinners, mindfulness training, positive thinking—for successful treat- ment and prevention of alcoholism and addiction (Brady et al. 2009; Daeppen et al. 2010; Franko et al. 2008; Fulkerson et al. 2006; Mohr et al. 2008; Pohorecky 1991; Volkow et al. 2010; Wang et al. 2009). Furthermore, inasmuch as addicts and posttraumatic stress disorder patients often exhibit an inability to tolerate distress (Daughters et al. 2009; Howell et al. 2010; Marinkovic et al. 2009), studies have shown that they can reduce their alcohol intake by learning strategies to cope with stress (Armelis et al. 2010; Daeppen et al. 2010; Fulkerson et al. 2006; Garland et al. 2010; Mohr et al. 2008; Pohorecky 1991; Vieten et al. 2010).

One largely unexplored option for modeling the ability to learn positive coping mechanisms is to give alcohol- experienced animals a choice between the intoxicant and a conditioned safety signal or other experience the animal would perceive as positive (e.g., access to a familiar conspe- cific). Such an experiment might enable identification of the underlying circuitry and molecular impact of positive coping strategies.

Impacts of Social Interaction

Research has demonstrated the importance of social support for the prevention and treatment of alcoholism in humans (Anacker and Ryabinin 2010; Brown et al. 1995; Fulkerson et al. 2006; Killgore et al. 2008; Noone et al. 1999; Pohorecky 1991; Wang et al. 2009). Animal models may reveal much about basic aspects of the neural circuitry through which positive and negative social interactions regulate alcohol addiction. Rodent and primate studies have shown that social interaction can buffer stress-related development of addiction and, conversely, that social isolation enhances alcohol intake (Anacker and Ryabinin 2010; Roske et al. 1994; Wolffgramm and Heyne 1991).

There are, however, some caveats to the relationship be- tween social interactions and alcohol intake. Some types of social interactions—both positive and negative—enhance alcohol intake in humans and primates (e.g., when positive interaction with an intoxicated peer increases intake; Anacker and Ryabinin 2010). The impact of stress may also vary with social position (Pohorecky 2010); studies in rodents and pri- mates suggest that a subordinate position in a dominance hierarchy correlates with greater alcohol and cocaine intake (Anacker and Ryabinin 2010; Blanchard et al. 1987; Brady et al. 2009; Funk et al. 2005; Morgan et al. 2002).

Targeting Adolescence as a Time for Learning Emotional Skills

Adolescent alcohol or stress exposure can dramatically pro- mote future alcohol intake both in humans (Dawson et al. 2007; Enoch 2011; King et al. 2009; Pilowsky et al. 2009) and in preclinical rodent models (Fullgrabe et al. 2007; Schramm-Sapyta et al. 2008; Spear and Varlinskaya 2010; Wills et al. 2010). Adolescence is thus a time of particular risk and an important period for targeted intervention.

It may be particularly important to learn strategies to buffer shame (Mohr et al. 2008) and hostility and anger (Berman et al. 2009; Friedman et al. 2007; Kelly et al. 2010; Thomas et al. 2010), which can promote negative affect, stress, and the urge to seek relief from distress. Brady and colleagues (2009) found that adolescents with better cogni- tive coping skills (e.g., addressing stress by problem solving
and focusing on the positive) were less likely to engage in substance abuse after bullying. Conversely, responding to stress with rumination and dwelling on the negative increases the risk of substance abuse in adolescents (Skitch and Abela 2008). As described above, a sense of control can also decrease the impact of stressors; thus, teaching adolescents to take days off from smoking (Wileyto et al. 2009) or to recognize that the ability to binge drink is a risk factor rather than a source of pride (Spear and Varlinskaya 2010) may enable them to counteract social stressors that promote these addictive behaviors.

Given the complexities of human social interactions, some aspects of the mechanisms through which social support can help humans overcome addictive drives may be difficult to model with certainty in rodents. For example, the emotional, cognitive, and relational support that regular family dinners may afford probably requires investigation primarily in humans (Franko et al. 2008; Fulkerson et al. 2006). But preclinical experiments that systematically vary the relative amounts of stress and social contact and determine the resulting impact on alcohol intake would be useful (cf. Anacker and Ryabinin 2010).

New animal models may help to elucidate an addicted individual’s decision to resist alcohol or drugs, the cognitive effort necessary for success in such efforts, and the capacity to learn new behaviors to help overcome old habits.

Conclusions

Alcoholics likely have molecular neuroadaptations that underlie both their sensitivity to stress and their susceptibility to pathological drinking. These adaptations may result from a combination of genetic predisposition and early exposure to stress and/or alcohol. From a translational perspective, most alcoholics and addicts likely already have neuroadaptations in place, and preclinical work should identify them to support the development of pharmacological therapies to counteract the resulting functional changes.

Animal models enable study of the molecular mechanisms that underlie binge intake, greater drinking in dependent animals, aversion-resistant intake, drinking in response to stress, and the consequences of stress and/or alcohol exposure on subsequent stress reactivity and alcohol intake. These models are not only tremendously valuable in efforts to identify and understand the mechanistic bases of pathological alcohol-related behaviors, they also yield important insights that would be very challenging to discern in human studies. Further research is necessary to determine whether animal models can be developed for more complex aspects of human addiction, such as self-delusion or the development of coping strategies to increase tolerance for stress.

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