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REVIEW

Effects of stress on alcohol drinking: a review of animal studies

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Abstract
Rationale While stress is often proposed to play a significant role in influencing alcohol consumption, the relationship between stress and alcohol is complex and poorly understood. Over several decades, stress effects on alcohol drinking have been studied using a variety of animal models and experimental procedures, yet this large body of literature has generally produced equivocal results.
Objectives This paper reviews results from animal studies in which alcohol consumption is evaluated under conditions of acute/sub-chronic stress exposure or models of chronic stress exposure. Evidence also is presented indicating that chronic intermittent alcohol exposure serves as a stressor that consequently influences drinking.
Results The effects of various acute/sub-chronic stress procedures on alcohol consumption have generally been mixed, but most study outcomes suggest either no effect or decreased alcohol consumption. In contrast, most studies indicate that chronic stress, especially when administered early in development, results in elevated drinking later in adulthood. Chronic alcohol exposure constitutes a potent stressor itself, and models of chronic intermittent alcohol exposure reliably produce escalation of voluntary alcohol consumption.
Conclusions A complex and dynamic interplay among a wide array of genetic, biological, and environmental factors govern stress responses, regulation of alcohol drinking, and the circumstances in which stress modulates alcohol consumption. Suggestions for future directions and new approaches are presented that may aid in developing more sensitive and valid animal models that not only better mimic the clinical situation, but also provide greater understanding of mechanisms that underlie the complexity of stress effects on alcohol drinking.

Keywords Stress · Alcohol drinking · Animal models

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Introduction

The term stress typically refers to an internal or external (environmental) event that disrupts normal homeostasis (Selye 1936). Stressful events evoke an extensive multi-system and highly integrative physiological response (Goldstein and Kopin 2007; Kopin 1995). The activation of the hypothalamic–pituitary–adrenocortical (HPA) axis constitutes a major component of the neuroendocrine stress response (Smith and Vale 2006). Alcohol stimulates the HPA axis at several levels, with the magnitude and response profile influenced by a host of variables including genotype, gender, and dosing parameters (Rivier 2000; Wand 2000). Further, both clinical and preclinical studies have documented profound disturbances in HPA axis function following chronic alcohol exposure and withdrawal, and in many instances, these perturbations persist for a protracted period of time. The dysregulation of HPA axis function along with alterations in the activity of extrahypothalamic

stress systems in the brain are postulated to significantly influence motivation for alcohol self-administration behavior (Koob and Kreek 2007; Koob and Le Moal 2001).

The relationship between stress and alcohol consumption is complex and poorly understood. On one hand, alcohol is known to be an effective anxiolytic and, hence, motivation for drinking may be guided by its ability to alleviate stress. On the other hand, alcohol is known to activate HPA axis and extrahypothalamic stress systems and, thus, can serve as a stressor itself. Given this reciprocal, yet paradoxical relationship between stress and alcohol, perhaps it is not surprising that there is no clear consensus regarding the circumstances and manner in which stress influences alcohol drinking behavior.

The anxiolytic effects of alcohol are well established in humans and animal models, and this serves as the cornerstone of the tension (stress)-reduction hypothesis (Brady and Sonne 1999; Cappell and Greeley 1987; Pohorecky 1991; Sayette 1999). However, in clinical studies, support for this notion has not been universal (Chutuape and de Wit 1995; Wand et al. 1998). In a similar vein, the self-medication hypothesis stems from the idea that individuals suffering with affective illness use alcohol to relieve dysphoric/stress symptoms associated with the disorder (Carrigan and Randall 2003; Markou et al. 1998). While there is a relatively high prevalence of comorbidity of alcoholism and mood and anxiety disorders, such individuals do not uniformly endorse alcohol use as a means of coping with (medicating) symptoms of the disorder (Battista et al. 2010). Additionally, several clinical studies indicate a dissociation between physiological and subjective effects of alcohol (de Wit et al. 2003; Lewis and Vogeltanz-Holm 2002; Soderpalm and de Wit 2002). Thus, it cannot be said that stress alleviation serves as the sole motivation for alcohol consumption in all individuals. Preexisting psychiatric conditions, the nature and intensity of stress as well as the context in which stress is experienced, and whether stress is associated with and/or resultant from heavy alcohol use are important variables that impact alcohol drinking behavior. Further, there clearly exist individual differences in sensitivity, perception, and responsiveness to stress and, no doubt, these differences will be reflected in drinking behavior. Indeed, both clinical and preclinical evidence indicate that genetic factors play an important role in shaping the nature of the relationship between stress and alcohol drinking (Clarke et al. 2008; Uhart and Wand 2009). Collectively, current evidence suggests that while some individuals may drink alcohol to alleviate perceived stress and dysphoria, many do not drink for this reason.

As previously noted, at the same time that alcohol consumption may be perceived by some as having a calming effect, for other individuals, activation of stress systems along with resultant elevation of circulating corticosteroids may relate to the energizing and euphoric effects of alcohol. There is some evidence indicating that elevated levels of corticosteroid hormones interact with the reinforcing effects of alcohol to enhance propensity to drink. For example, systemic or central administration of corticosterone has been reported to modestly increase alcohol self-administration (Fahlke et al. 1994a, 1996; Fahlke and Hansen 1999), while adrenalectomy or pharmacological inhibition of corticosterone synthesis reduced drinking in rats (Fahlke et al. 1995, 1994b; Lamblin and De Witte 1996). The fact that rats will self-administer corticosterone suggests that this stress hormone may have positive reinforcing effects in its own right (Deroche et al. 1993; Piazza et al. 1993). Further, evidence from studies in animals and humans suggest that stress-related elevations in glucocorticoids interact with mesolimbic reward circuitry to increase drug self-administration behavior (Cleck and Blendy 2008; Melis et al. 2009; Miczek et al. 2008; Sinha 2008; Uhart and Wand 2009). While this is a plausible mechanistic explanation for how stress may increase alcohol drinking, much of the supporting evidence comes predominantly from preclinical and clinical investigations involving psychostimulants. Additionally, it is important to recognize that the ability of alcohol to activate the HPA axis is dose-dependent (Pohorecky 1990, 1991) and, similarly, the ability and manner in which stress modulates neurobiological systems that underlie motivational aspects of alcohol-related behaviors depend on the nature as well as the intensity of the stressor (Kopin 1995; Miczek et al. 2008; Pacak and Palkovits 2001).

The influence of stress on alcohol drinking is further complicated by a host of alcohol-related factors (history of use, level and pattern of drinking, and timing of accessibility of alcohol) and stress-related factors (type, chronicity, intermittency, predictability, and controllability) that intersect with a number of biological variables (genetics, age, and sex). The dynamic interaction of these variables along with experiential factors plays a critical role in defining subjective aspects of stress (i.e., perception and appraisal of a stressful event) as well as how response to stress impacts decisions about alcohol drinking and alcohol consumption alters stress responsiveness. The large number of variables at play along with the dynamic and variable nature in which they interact has certainly contributed to clouding consensus regarding questions of how and when stress influences alcohol drinking in humans. This, in turn, has undoubtedly made the task of developing animal models that accurately reflect the clinical situation especially challenging.

Despite the complexity of the interaction between stress and alcohol reflected in varied clinical study outcomes, it is generally acknowledged that stressful life events play a prominent role in influencing alcohol drinking and, in particular, triggering relapse (Brady and Sonne 1999; Sinha 2001, 2008). This continues to be the major impetus for

using animal models to examine stress–alcohol interactions under more controlled conditions as well as elucidate underlying mechanisms. The circumstances and manner in which stress influences drinking behavior in animal models have been extensively studied under a variety of conditions (Pohorecky 1990; Sillaber and Henniger 2004). Unfortunately, this large body of literature has yielded equivocal results, with evidence for stress increasing, decreasing, or not changing alcohol ingestion. This review surveys this literature, with special attention given to the plethora of aforementioned variables that may contribute to discrepancies in results.

An animal model that has been extensively used to study stress–alcohol interactions involves examining the effects of stress on operant alcohol self-administration behavior following a period of abstinence (relapse). In this operant reinstatement model, animals are first trained to respond for alcohol reinforcement. Once stable levels of responding and alcohol intake are established during daily sessions, alcohol-reinforced responding is then extinguished by removing alcohol as a reinforcer, even when the animals appropriately respond for it. Exposing animals to stress (typically footshock) has been shown to reinstate alcohol responding in rats, an effect mediated, at least in part, by extrahypothalamic corticotropin-releasing factor (CRF) activity (Le et al. 1998, 1999, 2000, 2002; Liu and Weiss 2002; Martin-Fardon et al. 2000). While this effect is fairly robust and applicable to several drugs (Shaham et al. 2003; Shalev et al. 2010, 2002), it is important to note that the effect of stress on alcohol/drug responding is examined under conditions of extinction. Since animals are typically not given the opportunity to drink alcohol during test sessions when stress is administered, the reinstatement procedure does not involve examining whether stress alters alcohol consumption. Thus, this model assesses stress effects on alcohol "seeking," not alcohol drinking.

Since this review is restricted to animal studies investigating stress effects on alcohol consumption, studies involving stress and operant reinstatement procedures are not included in the discussion. Rather, the following highlights results from animal studies in which alcohol consumption is evaluated under conditions when acute/sub-chronic stress exposure is administered during periods when alcohol is available for consumption, and when chronic stress exposure occurs before or during periods of alcohol accessibility. Evidence also is presented from studies indicating that chronic alcohol exposure and withdrawal experience serves as a unique stressor that consequently influences motivation to drink. Finally, suggestions for future directions and new approaches are presented that may aid in developing more sensitive and valid animal models that not only better mimic the clinical situation, but also provide greater understanding of mechanisms that underlie the complexity of stress effects on alcohol drinking.

Acute/sub-chronic stress exposure during alcohol access

A large body of literature has centered around examining the effects of acute or repeated stress exposure on alcohol consumption. Studies of this nature have been organized in Table 1, according to the species employed (i.e., rat or mouse), type of stressor tested, and the direction of the influence of stress on alcohol intake. For the most part, these studies have involved initially providing animals with an opportunity to drink an alcohol solution in order to establish a baseline level of consumption, most commonly in a continuous-access choice situation in which alcohol is offered in an unrestricted fashion as a two-bottle choice, with a control solution such as tap water or saccharin serving as an alternative fluid. Subsequently, stress procedures were administered with alcohol access usually available during this phase to examine alterations in alcohol consumption. In some studies, assessment of intake was continued for a period of time after exposure to the stressor was terminated, allowing for examination of post-stress changes in intake. It should be noted that results from this body of work have been categorized in Table 1 as "Decreased Intake", "No Change", or "Increased Intake" based on overall findings in the studies. In several studies, multiple strains, genetic lines, and/or both sexes were examined. When mixed results were reported as a function of these subject variables, results are categorized in the table according to the direction of effects observed for the majority of stressed subjects. Additionally, if in a particular study stress did not significantly alter alcohol intake during the stress phase itself, that study was listed in the "No Change" column of Table 1. Therefore, studies in which stress-related increases in alcohol intake were reported only during a post-stress measurement phase were placed in the "No Change" column. Further, while it would be optimal in studies of this nature to compare alcohol consumption in stressed and non-stressed subjects, in some instances non-stressed controls were not included in the study design (i.e., stress-induced changes in intake were assessed relative to a period of time prior to stress application). Notably, there are some limited studies in which neither baseline intake nor non-stressed controls were included in the study, thus precluding conclusions regarding the influence of stress on alcohol intake—these studies are not included in Table 1.

As shown in Table 1, a large number of studies examining the influence of various acute/sub-chronic stress procedures on alcohol consumption have produced equivocal findings. The preponderance of outcomes suggests that stress either does not significantly change or decreases alcohol consumption, although there is some evidence for increased alcohol intake. Notable features of these studies are highlighted below.

Inescapable footshock Historically, inescapable footshock was one of the first stressors used in which investigators reported that exposure to stress was capable of eliciting an increase in alcohol consumption relative to a group of similarly treated controls without shock exposure and/or relative to a period of unstressed baseline ethanol consumption (e.g., Anisman and Waller 1974; Kinney and Schmidt 1979; Mills et al. 1977; Volpicelli et al. 1990). For example, when adult male Holtzman rats were exposed to either 6 or 12 h alternating periods of unsignalled inescapable footshock presented on either a fixed or random interval schedule, alcohol intake was found to significantly increase relative to non-shocked controls (Anisman and Waller 1974). More recently, other studies utilizing footshock exposure have reported a similar stress-induced increase in alcohol intake (Fullgrabe et al. 2007; Siegmund et al. 2005; Vengeliene et al. 2003).

However, upon closer inspection, many of these outcomes were not especially robust. For example, in the Kinney and Schmidt (1979) study, while cued delivery of inescapable footshock significantly increased alcohol intake compared to non-stressed controls, this increase was only significant during one of the four time periods in which footshock and alcohol access were concurrently experienced. Furthermore, another group of animals in the same study that was exposed to unsignalled footshock failed to significantly increase their alcohol consumption. While Mills et al. (1977) also reported that footshock increased alcohol consumption, this effect was

Table 1 Acute/sub-chronic stress exposure during alcohol access

Stressor	Species	Decreased intake	No change	Increased intake
FS	Rat	Bond 1978[b]	Casey 1960[d]	Myers and Cicero 1969
		Champagne and Kirouac 1987	Powell et al. 1966[c]	Anisman and Waller 1974
		Darnaudery et al. 2007[b]	Myers and Holman 1967	Mills et al. 1977
			Cicero et al. 1968[g]	Mills and Bean 1978
			Von Wright et al. 1971[d]	Kinney and Schmidt 1979[g, h]
			Choca et al. 1977	Volpicelli et al. 1990[b, d]
			Cox and Stainbrook 1977[g, h]	Vengeliene et al. 2003
			Ng Cheong Ton et al. 1983	Siegmund et al. 2005[f]
			Fidler and LoLordo 1996	Fullgrabe et al. 2007[f]
			Brunell and Spear 2005[f]	
	Mouse		Chester et al. 2008[d, f]	Racz et al. 2003[e]
			Matthews et al. 2008[e]	
RS	Rat	Abraham and Gogate 1989[h]	Ng Cheong Ton et al. 1983	Derr and Lindblad 1980[h]
		Krishnan et al. 1991	Nash and Maickel 1985[d]	Lynch et al. 1999[h]
		Sprague and Maickel 1994	Rockman et al. 1986[b, d]	Ploj et al. 2003
		Haleem 1996	Rockman et al. 1987[b, d]	Roman et al. 2004
		Chester et al. 2004[d]	Bowers et al. 1997	
			Roman et al. 2003	
			Bertholomey et al. 2011	
	Mouse		Chester et al. 2006[h]	
			Tambour et al. 2008	
			Yang et al. 2008[e]	
FST	Rat		Vengeliene et al. 2003[e]	Siegmund et al. 2005
			Sommer et al. 2008	Fullgrabe et al. 2007[f]
	Mouse	Boyce-Rustay et al. 2008[e]	Sillaber et al. 2002[d]	Cowen et al. 2003a
			Boyce-Rustay et al. 2007	Cowen et al. 2003b
			Lowery et al. 2008[d, e]	Sperling et al. 2010[e]
			Mutschler et al. 2010[e]	
SD	Rat	van Erp et al. 2001		
		van Erp and Miczek 2001[h]		
		Funk et al. 2005[h]		
	Mouse		Sillaber et al. 2002[d]	
			Croft et al. 2005[d]	

Table 1 (continued)

Stressor	Species	Decreased intake	No change	Increased intake
ISO	Rat	Weisinger et al. 1989	Nash and Maickel 1985[d]	Nunez et al. 1999
		Sprague and Maickel 1994		Nunez et al. 2002
		Doremus et al. 2005[f]		Mediratta et al. 2003
Other	Rat	Sandbak and Murison 2001	Rockman and Glavin 1986[b]	
			Adams 1995[c, e]	
			Turyabahika-Thyen and Wolffgramm 2006	
			Bertotto et al. 2010	
	Mouse		Little et al. 1999[b]	Sacharczuk et al. 2008[e]
			O'Callaghan et al. 2002[b]	
			Schroff et al. 2004[d, e]	

FS footshock, *SD* social defeat, *RS* restraint, *ISO* isolate housing, *FST* forced swim test

[a] Studies in which stressor exposure resulted in an increase in ethanol intake during the stressor phase are listed in the "Increased Intake" column of this table. However, if stress did not significantly alter ethanol intake during the stress phase (even if there was a subsequent increase in intake during the post-stress phase), reports of this nature were listed in the "No Change" column. Finally, if multiple strains and/or both sexes were examined, the article was placed in the column of direction of the effect that the majority of the stressed groups (or the wild-type strain) exhibited (e.g., in the Matthews et al. 2008 paper, two strains showed no change in intake, whereas only one strain showed an increase—therefore, this report was listed in the "No Change" column)

[b] Direction of stress effects on ethanol intake depended upon initial preference levels

[c] Sex-related differences in stress-induced changes in ethanol intake were observed (paper was placed in the column reflecting the direction of the influence of stress on ethanol consumption among males)

[d] Stress-induced increases in ethanol consumption were only apparent during a post-stress observation period

[e] Strain differences or differences among genetically manipulated lines were observed with respect to the influence of stress on ethanol consumption

[f] Study observed age-related differences in the interaction between stressor exposure and ethanol intake

[g] Properties of the shock stressor or the relationship between shock presentation/ethanol availability influenced the relationship between footshock exposure and ethanol drinking

[h] Intake was not measured in a continuous-access and/or choice situation

only observed for a short time immediately following stress exposure (there was no difference in overall 24-h intake). Although Vengeliene et al. (2003) also demonstrated that three consecutive days of 10-min exposure to footshock increased alcohol intake among several different strains/lines of rats (Wistar, HAD, P, and AA rats), these increases were only observed on one or maximally 2 days of shock exposure.

In contrast, there have been several studies that have utilized inescapable footshock and subsequently found stress-associated decreases in alcohol intake (Bond 1978; Champagne and Kirouac 1987; Darnaudery et al. 2007). For example, when footshock was administered for 6 days to male Sprague–Dawley rats, alcohol intake significantly decreased, returning to prestress levels after stress exposure was terminated (Bond 1978). While Volpicelli et al. (1990) showed that a short period of footshock increased alcohol intake in rats that initially exhibited low preference for alcohol, other findings indicate that rodents exhibiting a relatively high preference for alcohol prior to stress will exhibit footshock-induced decreases in alcohol consumption (Bond 1978; Volpicelli et al. 1990). Adding to these mixed results, there are instances in which no change in alcohol consumption following inescapable footshock treatment has been reported. For example, several studies examining the effects of footshock stress reported no appreciable change in alcohol consumption among adult male rats under a variety of circumstances (e.g., Brunell and Spear 2005; Fidler and LoLordo 1996; Myers and Holman 1967; Powell et al. 1966). Similarly, several strains of mice, including DBA/2 and A/J (Matthews et al. 2008), and the high alcohol preferring selectively bred HAP1 line (Chester et al. 2008) have failed to demonstrate footshock-related changes in alcohol intake.

When analyzing the possible variables that may have contributed to differences across studies in regards to the effect of footshock stress on alcohol consumption, there are virtually no clear patterns that would seemingly explain a reliable increase or decrease in consumption. In considering whether the footshock stressor is administered in a predictable vs. unpredictable manner, for example, in two different rat studies (Cicero et al. 1968; Kinney and Schmidt 1979) and one mouse study (Racz et al. 2003), a cued inescapable footshock elicited significant increases in ethanol consumption, whereas random unsignalled footshocks did not. It would be tempting to conclude, therefore, that presentation of a cued inescapable shock is more likely to result in increased alcohol intake. Yet, in most studies

that reported increased alcohol consumption following footshock (see Table 1), the shock was not signaled. The same could be said for the duration of footshock exposure: studies reporting footshock-induced increases in alcohol intake have used as few as one (Racz et al. 2003) or three repeated days of footshock exposure (e.g., Siegmund et al. 2005; Vengeliene et al. 2003), while others have reported increases in intake after as many as 27 (Kinney and Schmidt 1979) or even 35 (Myers and Cicero 1969) exposures to the stressor. When examining studies reporting no change in intake, both mouse (Matthews et al. 2008) and rat (Brunell and Spear 2005) studies have failed to observe footshock-related increases in intake with as few as 1 day of stress exposure or as many as 24–30 repeated footshock sessions (Cox and Stainbrook 1977; Ng Cheong Ton et al. 1983).

The amount of experience with alcohol consumption prior to stress presentation is another variable that differed greatly across these studies, yet seemed to have no predictive value for determining whether footshock would significantly alter alcohol intake. For instance, studies in which animals had little or no prior opportunity to drink alcohol have reported decreased (e.g., Bond 1978), increased (e.g., Anisman and Waller 1974), or unchanged (e.g., Brunell and Spear 2005; Myers and Holman 1967; Von Wright et al. 1971) alcohol intake following footshock experience. Likewise, studies in which animals were given at least 2 weeks access to alcohol prior to stress administration have reported decreased (Darnaudery et al. 2007), increased (Mills et al. 1977; Vengeliene et al. 2003), or unaltered (Fidler and LoLordo 1996; Ng Cheong Ton et al. 1983) alcohol consumption as a function of footshock exposure.

It is tempting to speculate that biological variables (sex, genotype) may play a significant role in determining the outcome of these studies. Unfortunately, when assessing the role that sex of the animal may have on whether or not footshock stress is likely to result in increases or decreases in intake, limited studies are available. While only a few studies included analysis of female subjects, results from those studies were similarly mixed. Specifically, footshock stress in females was reported to increase (Fullgrabe et al. 2007), decrease (Darnaudery et al. 2007), or not significantly alter (Chester et al. 2008; Cox and Stainbrook 1977; Powell et al. 1966) alcohol consumption.

When considering strain of rat, however, there is some evidence to suggest that certain strains may be more prone to demonstrate footshock stress-induced increases in intake. Specifically, the majority of studies reporting stress-related increases in ethanol intake were experiments that utilized Long–Evans (Mills et al. 1977; Mills and Bean 1978; Myers and Cicero 1969) or Wistar rats (Fullgrabe et al. 2007; Siegmund et al. 2005; Vengeliene et al. 2003). In contrast, with the exception of one case (Volpicelli et al. 1990), studies using Sprague–Dawley rats as subjects have most often found either no change in intake (Brunell and Spear 2005; Casey 1960; Cox and Stainbrook 1977; Fidler and LoLordo 1996) or decreased alcohol consumption (Champagne and Kirouac 1987; Darnaudery et al. 2007) during exposure to footshock stress. To our knowledge, the effects of footshock stress on alcohol consumption have not been directly compared among different outbred or inbred strains of rats. Future studies that directly compare some of these strains of rats will be necessary in order to more firmly establish whether a particular genotype confers greater or lesser susceptibility to footshock-induced changes in alcohol consumption. Unfortunately, since so few studies have assessed the effects of footshock stress on alcohol intake among mice, it is premature to draw conclusions as to genetic contributions to the outcome of such studies. Only one study directly compared three inbred mouse strains for the ability of footshock stress to alter drinking. Results from this study indicated that C57BL/6J mice increased alcohol intake in the 24 h following a single acute 15-min footshock exposure, while no change in intake was reported in DBA/2J and A/J mouse strains (Matthews et al. 2008). Given the extensive literature regarding genetic influences on alcohol consumption and stress response in mice (Crabbe 2008; Crabbe et al. 2006; Holmes 2008; Mozhui et al. 2010), systematic evaluation of the influence of footshock stress on alcohol consumption among different genetic mouse models is certainly warranted.

Restraint Another popularly explored stressor in rodent studies is restraint or immobilization stress. As with footshock stress, some studies employing restraint have reported this stressor to significantly increase alcohol consumption (Derr and Lindblad 1980; Lynch et al. 1999; Ploj et al. 2003; Roman et al. 2004). For example, Lynch et al. (1999) found male Wistar rats that experienced repeated immobilization stress increased alcohol intake compared to non-stressed controls. However, in this study, rats were exposed to several phases of forced access to alcohol, which may have impacted the effects of stress on "choice" drinking. Additionally, while 4 days of repeated restraint were shown to significantly increase alcohol intake in both adult male (Ploj et al. 2003) and female (Roman et al. 2004) Wistar rats, this effect was dependent upon whether the animals were earlier exposed to maternal separation stress, and the interaction of this variable on drinking outcome differed for males and females. There are, alternatively, numerous studies in the literature that have reported either restraint stress-induced decreases in alcohol intake (e.g., Chester et al. 2004; Ng Cheong Ton et al. 1983; Sprague and Maickel 1994) or no change in alcohol consumption following exposure to this type of stressor (e.g., Bertholomey et al. 2011; Bowers et al. 1997; Rockman et al. 1987; Roman et al. 2003).

Upon examination of the many variables that could potentially influence the manner in which restraint stress impacts alcohol drinking, there appears to be no clear factor that emerges as a primary determinant of the outcome of such studies. For example, if considering the influence of amount of restraint stress exposure, studies have shown increased (Ploj et al. 2003; Roman et al. 2004), decreased (Haleem 1996; Sprague and Maickel 1994), or no change (Roman et al. 2003; Tambour et al. 2008) in alcohol consumption with as few as 1–4 days of restraint treatment. Similarly, studies involving more extensive restraint stress exposure (2–8 weeks) have reported increased (Derr and Lindblad 1980; Lynch et al. 1999), decreased (Chester et al. 2004; Krishnan et al. 1991), or unaltered (Nash and Maickel 1985; Ng Cheong Ton et al. 1983) alcohol intake.

Another variable to consider is the duration of restraint during each stress session. For this variable, there is again no clear pattern that emerges as to whether duration/intensity of restraint relates to an increase or decrease in alcohol consumption. For example, relatively short exposures (~15–30 min restraint) have been shown to increase (Lynch et al. 1999) or have little effect (Ng Cheong Ton et al. 1983; Roman et al. 2003) on alcohol intake. Likewise, studies that employed relatively long durations of daily restraint (≥18 h) reported increased (Derr and Lindblad 1980) or decreased (Abraham and Gogate 1989) levels of alcohol consumption. Variable unpredictable restraint has been utilized as well, with several studies reporting decreased (Chester et al. 2004; Krishnan et al. 1991; Sprague and Maickel 1994) or unaltered (Nash and Maickel 1985; Rockman et al. 1987) alcohol intake.

As was the case for studies employing footshock stress, there is little indication that the amount of experience with alcohol prior to stress exposure predicts the manner in which restraint stress subsequently modifies drinking behavior. Specifically, studies in which animals were given a relatively short period of "baseline" drinking prior to stress (i.e., ≤1 week) have reported increased (Derr and Lindblad 1980) or no change (Nash and Maickel 1985) in alcohol intake subsequent to restraint exposure. Likewise, studies in which animals were provided access to alcohol for longer periods of time prior to stress exposure (≥2 weeks) report increased (Ploj et al. 2003; Roman et al. 2004), decreased (Abraham and Gogate 1989; Chester et al. 2004; Krishnan et al. 1991), or no change (Bertholomey et al. 2011; Roman et al. 2003; Tambour et al. 2008) in alcohol consumption once restraint stress was administered.

Examining the influence of sex on restraint stress-induced changes in alcohol drinking is difficult due to the fact that so few studies have included analysis of female subjects. To our knowledge, only three such studies have been conducted: one demonstrating restraint-induced increases (Roman et al. 2004) and two reporting unchanged alcohol consumption (Bertholomey et al. 2011; Tambour et al. 2008) after restraint stress. Finally, it is difficult to draw conclusions regarding the influence of genetics on the ability of restraint stress to modulate alcohol drinking. While it is the case that three of the four studies reporting restraint stress-induced increases in alcohol intake used Wistar rats (Lynch et al. 1999; Ploj et al. 2003; Roman et al. 2004), studies reporting unchanged or decreased intake were conducted across a variety of strains, including Wistar rats. Again, very few studies have systematically examined the effects of restraint stress on alcohol consumption in different strains/lines of mice.

Forced swim More recently, researchers have begun to explore the potential of other stressors such as forced swim to influence alcohol consumption. Generally, the forced swim test (FST) consists of inescapable exposure to a tank of room temperature water for a session ranging from 6 to 15 min in duration. Currently, there are a limited number of studies in which repeated exposure to the FST is reported to significantly elevate alcohol intake and, in most instances, the change in alcohol consumption was modest and transient in nature. This is true for studies conducted with rats (Fullgrabe et al. 2007; Siegmund et al. 2005) and mice (Cowen et al. 2003a, b; Sperling et al. 2010). On the other hand, there are several instances in which forced swim stress exposure either did not alter alcohol intake during the stress exposure phase in rats (Sommer et al. 2008; Vengeliene et al. 2003) and mice (Boyce-Rustay et al. 2007; Lowery et al. 2008) or even resulted in decreased alcohol intake (Boyce-Rustay et al. 2008). It is important to note that a few reports have observed significant FST-induced increases in alcohol intake long after the stress exposure ended, with these post-stress increases not emerging until at least 3 weeks later and only in certain mouse strains (e.g., BALB/cJ but not C57BL/6N, in Lowery et al. 2008) or genetic models (e.g., CRFR1 knockouts but not wild-type mice, in Sillaber et al. 2002).

Since duration of the swim test is relatively short, generally 5–10 min, and varies little across studies, this variable is unlikely to have contributed to the discordant results noted above. Additionally, it is difficult to conclude that the number of FST stress sessions relates to a particular outcome in these studies since alcohol drinking was typically assessed in the context of FST exposure being repeated over 2–5 days. For example, FST stress-induced increases in alcohol intake have been reported in both rats and mice following two (Cowen et al. 2003a, b) and three (Fullgrabe et al. 2007; Siegmund et al. 2005) days of repeated forced swim testing. Other studies, however, have indicated little change in alcohol consumption after a single acute FST session (Boyce-Rustay et al. 2007), or when FST testing was repeated for 3 days (Sillaber et al. 2002;

Sommer et al. 2008; Vengeliene et al. 2003) or five consecutive days (Lowery et al. 2008; Mutschler et al. 2010). Although one study that used a more protracted period of FST exposures (14 consecutive days) reported stress-related decreases in consumption, this reduction was strain dependent, being significant in DBA/2J and BALB/cByJ strains but not in C57BL/6J mice (Boyce-Rustay et al. 2008). Furthermore, in another study by the same group (Boyce-Rustay et al. 2007), the same 14-day regimen of repeated FST exposures did not alter alcohol consumption, suggesting that a longer period of stress presentations in and of itself will not necessarily lead to an observation of FST-induced decreased alcohol intake. Taken together, it is difficult to attribute a specific effect of this stressor on alcohol drinking to the amount of forced swim stress exposure.

Since all of the studies examining FST exposure in Table 1 have involved providing animals with access to alcohol for at least 2 weeks prior to accessing the effects of the stressor on alcohol drinking, it is unlikely that this variable can effectively sort out the discrepant outcomes reported in these studies. Further, as noted above for footshock and restraint stressors, it is difficult to gauge the role of sex in defining the effects of restraint stress on alcohol consumption because so few studies have examined such effects in female subjects. Despite the relatively small number of studies conducted with rats, Wistar rats were shown to exhibit slight increases in alcohol intake following FST exposure (Fullgrabe et al. 2007; Siegmund et al. 2005; Vengeliene et al. 2003). Interestingly, FST exposure did not significantly alter alcohol intake in several lines of rats selectively bred for high alcohol preference (P, HAD, AA lines) (Vengeliene et al. 2003). Therefore, as with sex of the animal, strain of rat used is a variable that has not yet been systematically examined in the literature.

For studies that have utilized different mouse strains/genotypes, again, it is difficult to directly ascertain whether particular lines are more or less susceptible to the effects of FST on alcohol intake since so few studies have been conducted to specifically address this issue. For instance, though results from a few studies would suggest that C57BL/6 mice may be relatively insensitive to the effects of FST exposure on alcohol drinking (e.g., Boyce-Rustay et al. 2007, 2008; Lowery et al. 2008), another study recently reported that FST exposure increased alcohol consumption in this same inbred mouse strain (Sperling et al. 2010). Clearly, more studies are needed that directly compare the effects of FST stress on alcohol drinking in several mouse genotypes.

It is noteworthy that a unique feature of the forced swim stressor is that, as opposed to other stressors such as footshock and restraint, the FST procedure enables assessment of behavioral responsiveness to the stressor during its application. This is attractive because it provides an opportunity to gain insight about how individual differences in coping strategies exhibited during FST exposure may relate to subsequent avidity for alcohol. Unfortunately, to our knowledge, none of the studies examining the effects of an FST stressor on alcohol intake have attempted to relate behavioral (coping) response exhibited during FST exposure with later levels of alcohol intake. In a few instances, behavioral response during FST exposure was recorded in studies involving different age groups (e.g., Fullgrabe et al. 2007) or genetically manipulated lines (e.g., Cowen et al. 2003a, b; Sperling et al. 2010; Vengeliene et al. 2003). However, in these few cases, group differences that were either present or absent in FST-related behavior failed to explain later group differences in alcohol consumption. It is important to note that in these studies, individual relationships between FST behavior and later drinking within a group were not analyzed. Using a different approach, Weiss and his colleagues have shown that rats selectively bred for stress-induced suppression of struggling behavior in the FST procedure (the "stress susceptible" or "SUS" line) demonstrated increased levels of alcohol intake under basal (unstressed) conditions compared to a stress-resistant line and non-selected control line of rats. Further, the increased alcohol consumption in SUS rats, measured in a two-bottle choice situation, approached levels of intake and preference exhibited by rats selectively bred for high alcohol consumption (Weiss et al. 2008; West and Weiss 2006). In a similar vein, another study involving outbred CD1 mice examined the relationship between stress response in a related procedure (tail suspension test; TST) and later alcohol drinking. After characterizing mice as exhibiting high vs. low immobility in the TST, it was shown that the more stress-responsive mice consumed more alcohol in a two-bottle choice situation compared to mice that displayed less immobility (more struggling) in the task (Pelloux et al. 2005). This effect was only observed in females. Nevertheless, these latter findings suggest that more rigorous examination of individual differences in behavioral (coping) response to stressors such as the FST might provide additional insight into the complex relationship between stress responsiveness and propensity to drink. Clearly, this is an area of research that warrants further investigation.

Social defeat This stressor is particularly ethologically relevant to rodents, containing both physical and psychological components (Miczek et al. 2008). Generally, experimental subjects are placed into the home cage of a "resident" (who has been shown to consistently display aggressive behavior towards intruders) for a short period of time, allowing for the resident to physically chase and attack the experimental subject. In some instances, a perforated divider is then placed in the cage to prevent the

animals from physically interacting with each other, yet allowing the intruder to still see, smell, and hear the aggressive resident for a certain period of time. Studies investigating the effects of social defeat stress on the intruder rodent have shown that this stressor reduces both home cage (van Erp and Miczek 2001; van Erp et al. 2001) and operant self-administration (Funk et al. 2005; van Erp and Miczek 2001) of alcohol in rats. A few experiments that have investigated the effects of social defeat stress in mice have generally found little change in alcohol consumption during the stressor phase of the study (Croft et al. 2005; Sillaber et al. 2002). Interestingly, in both of these mouse studies post-stress increases in intake were observed, but not until several weeks after the conclusion of the social defeat experience. Since such a limited number of studies using social defeat stress have been conducted, elucidating the variables responsible for discrepancies across studies is not possible at this time. While evidence from rat studies might suggest that more intense social defeat sessions result in an even greater reduction in ethanol intake (e.g., van Erp et al. 2001), future research would need to validate and expand on this relationship between stressor duration/intensity and ethanol consumption before more firm conclusions are drawn.

Social isolation Although the effects of individual housing on subsequent alcohol consumption have generally been examined following long-term periods of social isolation (see below), there have been a few instances in which shorter periods of isolation were investigated in rats. Not surprisingly, results regarding the effects of brief periods of social isolation have been mixed as well, with increased (Mediratta et al. 2003; Nunez et al. 2002, 1999), decreased (Doremus et al. 2005; Sprague and Maickel 1994), and unaltered alcohol intake (Nash and Maickel 1985) relative to non-stressed (group-housed) controls reported during the period of stressor exposure. It is important to note that in most of the studies in the literature that have examined the relationship between stress exposure and alcohol consumption, animals are individually housed in order to easily and more accurately assess alcohol intake of individual animals during the experiment. Since the few available studies that have examined the effects of social isolation for more brief periods after weaning have provided such conflicting results, future studies examining the influence of social isolation stress on alcohol consumption would be beneficial as they would help to inform researchers designing future studies regarding the potential influence that isolate housing may have on the results obtained.

Other stressors In addition to the types of stressors utilized as described above, there are several other stress procedures that researchers have used to examine the relationship between stress and alcohol consumption. For example, tail pinch (Adams 1995), fear-conditioned memories (Bertotto et al. 2010), food restriction (Schroff et al. 2004), shock probe exposure (Sandbak and Murison 2001), saline injections (Little et al. 1999), repeated cage changes (O'Callaghan et al. 2002), ultrasonic noise (O'Callaghan et al. 2002) and overcrowding (Weisinger et al. 1989) are all stressors which have been studied for their ability to influence alcohol consumption, with again, these stressors varying in the direction of their effects on intake (see Table 1 for details).

Post-stress increases in alcohol consumption When examining the literature concerning the effects of acute/sub-chronic stress exposure on alcohol intake, there have been several instances in which post-stress increases in intake have been observed (e.g., Casey 1960; Croft et al. 2005; Lynch et al. 1999; Nash and Maickel 1985; Volpicelli et al. 1986, 1990). In one study, the effect was reported to last for as many as 6 months after stress exposure (Sillaber et al. 2002). However, other groups have failed to observe delayed effects of stress on alcohol consumption (Boyce-Rustay et al. 2007; Fidler and LoLordo 1996; Tambour et al. 2008) or have found that post-stress elevations in intake are only observed under limited conditions—in certain genotypes and/or only one sex (e.g., Chester et al. 2006; Sillaber et al. 2002). Specifically, of the 78 individual citations listed in Table 1, 59 monitored ethanol intake for a period of time following the termination of stressor exposure. Of these 59 studies, only 41% (24 studies) reported a significant post-stress increase in intake, while the remaining 35 studies reported a decrease or no change in alcohol consumption. Therefore, a more general overview of the literature would indicate that increases in alcohol consumption during a period of time following termination of stress exposure are not observed in as many studies as is often thought.

Summary Over several decades, a large body of work has been conducted in animals examining the influence of acute/sub-chronic stress experience on alcohol consumption. Various stress procedures have been employed using numerous models and a wide variety of experimental conditions. Despite a general perception in the field that stress is associated with increased alcohol drinking, as shown in Table 1, an overview of this literature reveals equivocal findings, with studies indicating increased, decreased, or no change in alcohol consumption under a variety of stress conditions. There have been multiple proposed hypotheses as to why models of acute/sub-chronic stress exposure do not always increase alcohol intake, and many of these revolve around specific experimental parameters that are thought to favor a particular outcome. These include, but are not limited to, the context in which

the stressor is experienced in relation to drinking access (Caplan and Puglisi 1986; Volpicelli et al. 1982), controllability of the stressor (Volpicelli and Ulm 1990), and whether the stressor is signaled or unsignalled (Kinney and Schmidt 1979). While there may be general trends in the influence of these variables on stress-induced changes in alcohol consumption, there are exceptions in nearly every case, and these observations may no longer remain true when considering different species, strains, or stressors.

The factors contributing to stress-induced decreases in alcohol consumption are not entirely clear, although numerous explanations have been hypothesized. In some studies, it has been suggested that rats exhibiting a higher alcohol preference due to such factors as sweetening of the alcohol solution (Bond 1978), induction of drinking via forced consumption (Bond 1978), naturally occurring individual differences in consumption (Darnaudery et al. 2007), or genetic selection for high alcohol intake (Chester et al. 2004) are more likely to express stress-induced reductions in intake. However, this explanation may be too simplistic since there are other circumstances in which initial high alcohol preference was not associated with stress-related suppression of alcohol consumption (Boyce-Rustay et al. 2008; Fidler and LoLordo 1996; Powell et al. 1966). Finally, it should be noted that as indicated in Table 1, there are a substantial number of studies that report no change in alcohol consumption following acute/sub-chronic exposure to various stressors. No doubt, many factors including prior alcohol experience, predictability of the stressor, duration of stressor application, as well as the nature and intensity of the stressor contribute to these equivocal findings in the literature. In surveying this body of work, it is difficult to draw consensus about factors that contribute to a particular outcome (increased vs. decreased alcohol intake) because these variables do not seem to account for differences in results across studies in a systematic or reliable manner.

Chronic stress exposure before and/or during alcohol access

Several studies have centered on evaluation of chronic stress experience, especially during early development, as a risk factor for increased alcohol intake. These studies have mostly focused on consequences of long-term alterations in conditions of socialization, either through early maternal separation, housing manipulations (isolation vs. overcrowding), or evaluation of effects of social status on subsequent alcohol consumption. The main concept guiding these studies is that experience with chronic stress has long-lasting effects on stress- and anxiety-related behaviors which, in turn, play a role in modulating voluntary alcohol intake. These studies are summarized in Table 2.

Maternal separation Most of the studies that examined effects of early maternal separation in rodents reported decreased alcohol intake or no change in later drinking (for a review see Roman and Nylander 2005). This is especially the case when the duration of daily maternal separation was relatively short (<60 min; usually about 15 min). For example, except for one study (Lancaster 1998), daily separation of rat pups from their mothers for short time intervals during the first 3 weeks of life have generally resulted in decreased alcohol intake during adulthood (e.g., Ploj et al. 2003; Roman et al. 2005, 2003). In contrast, relatively long-term daily maternal separation (60–360 min per day) resulted in increased alcohol intake later in life (Huot et al. 2001; Ploj et al. 2003; Roman et al. 2005), although other studies reported no change in alcohol consumption (e.g., Jaworski et al. 2005; Marmendal et al. 2004). In these studies, maternal separation was repeated for several days, which varied across studies (7–20 days). However, it is the duration of each episode of maternal separation (short vs. long) that appears to determine the direction of the effect (increase vs. no change) rather than the number of days that maternal deprivation was experienced by the pups.

Maternal separation studies in rats have included use of several strains (e.g., Wistar, Long–Evans) as well as lines selectively bred for high alcohol intake (alcohol accepting; AA line). The only study that reported elevated alcohol intake following short duration maternal separation was conducted with Long–Evans rats (Lancaster 1998). The remaining studies cited in Table 2 that involved short-duration maternal separation reported either no change or decrease in alcohol intake, and none of these studies used Long–Evans rats. Thus, increased alcohol consumption following short-duration maternal separation may be unique to this particular strain of rats. In the case of long-duration maternal separation, increased alcohol consumption was observed across different strains of rats: Wistar (Ploj et al. 2003), Long–Evans (Huot et al. 2001), and AA (Roman et al. 2005). In most cases, the effect of maternal separation exposure on later alcohol consumption was similar in both male and female offspring. The one exception was an apparent sex-dependent increase in drinking observed only in male AA rats following long-duration maternal separation (Roman et al. 2005).

Studies examining the effects of maternal separation on alcohol self-administration in mice are more limited. In one study, repeated maternal separation prior to weaning did not alter subsequent alcohol intake in C57BL/6J mice, although increased alcohol consumption was reported in female offspring that experienced maternal separation and then

Table 2 Chronic stress exposure before and/or during alcohol access

Stressor	Species	Decreased intake	No change	Increased intake
MS (short)	Rat	Weinberg 1987	Huot et al. 2001	Lancaster 1998
		Hilakivi-Clarke et al. 1991	Roman et al. 2004	
		Ploj et al. 2003		
		Roman et al. 2003		
		Roman et al. 2005		
	Mouse		Advani et al. 2007	
MS (long)	Rat		Marmendal et al. 2004	Huot et al. 2001
			Roman et al. 2004	Ploj et al. 2003
			Gustafsson et al. 2005	Roman et al. 2005
			Jaworski et al. 2005	
			Gustafsson and Nylander 2006	
	Mouse			Cruz et al. 2008
	Nonhuman primates			Higley et al. 1991b
				Fahlke et al. 2000
				Barr et al. 2004
				Barr et al. 2009
ISO	Rat	Fahlke et al. 1997	Parker and Radow 1974	Deatherage 1972
		Pisu et al. 2011	Rockman et al. 1988	Rockman et al. 1987
			Adams and Oldham 1996	Schenk et al. 1990
			Lodge and Lawrence 2003a, b	Wolffgramm 1990
			Thorsell et al. 2005c	Wolffgramm and Heyne 1991
				Roske et al. 1994
				Hall et al. 1998
				Juarez and Vazquez-Cortes 2003
				Deehan et al. 2007
				Ehlers et al. 2007
				McCool and Chappell 2009
	Mouse			Yanai and Ginsburg 1976
				Advani et al. 2007
				Lopez et al. 2011
	Nonhuman primates			Kraemer and McKinney 1985
				McKenzie-Quirk and Miczek 2008
OC	Rat		Deatherage 1972	Hannon and Donlon-Bantz 1976
			Heminway and Furumoto 1972	Nagaraja and Jeganathan 2002
				Nagaraja and Jeganathan 2003
	Mouse		Rodgers and Thiessen 1964	
SS	Rat	Kulkosky et al. 1980	Ellison 1987	Blanchard et al. 1987
				Wolffgramm and Heyne 1991
				Pohorecky 2006
				Pohorecky 2008
				Pohorecky 2010
	Mouse			Kudryavtseva et al. 1991
				Hilakivi-Clarke and Lister 1992
				Kudryavtseva et al. 2006
	Nonhuman primates	Crowley and Andrews 1987		McKenzie-Quirk and Miczek 2008
		Crowley et al. 1990		
SCC	Rat	Goodwin et al. 1999		Gauvin et al. 1997
		Clark et al. 2007		
		Rosenwasser et al. 2010		

Table 2 (continued)

Stressor	Species	Decreased intake	No change	Increased intake
	Mouse	Millard and Dole 1983 Trujillo et al. 2011		
CVS	Mouse			Lopez et al. 2011

MS maternal separation, *OC* overcrowding, *ISO* isolate housing, *SS* social status, *SCC* shift in circadian cycle, *CVS* chronic variable stress

were housed in isolation prior to testing (Advani et al. 2007). In another study, daily maternal separation (180 min) in outbred CFW mice produced higher levels of drinking and operant self-administration in adulthood, but progressive ratio testing did not reveal an apparent alteration in the reinforcing efficacy of alcohol (Cruz et al. 2008). Taken together, although there is limited evidence from studies conducted with mice, a similar pattern emerges in that short-duration maternal deprivation produces little change in later alcohol intake (Advani et al. 2007), while more prolonged maternal deprivation favors an outcome of increased alcohol consumption (Cruz et al. 2008).

Studies conducted with nonhuman primates have shown that maternal deprivation has long-lasting effects on behavioral and biological indices of stress and anxiety (Higley et al. 1991b). For example, peer-reared rhesus monkeys show profound alterations in neuroendocrine stress response (chronic elevation of cortisol and ACTH levels) when compared to mother-reared controls. Peer-reared monkeys also showed elevated voluntary alcohol intake in daily 1-h sessions, with intake achieving significantly higher blood alcohol concentrations compared to mother-reared monkeys (Higley et al. 1991a). In another study conducted with rhesus monkeys, although peer-reared and mother-reared subjects did not differ in magnitude of the stress response to social isolation during adulthood, altered stress responsiveness was related to voluntary alcohol consumption. That is, monkeys exhibiting a higher cortisol response to social separation consumed significantly more alcohol in a limited access (1 h) drinking situation (Fahlke et al. 2000). More recently, female macaques that were peer-reared were reported to evidence elevated alcohol intake compared to mother-reared subjects, with the effect modulated by genetic variation in genes related to serotonin regulation of the HPA axis (Barr et al. 2009, 2004).

Chronic isolation Several studies have examined the effects of prolonged social isolation (typically accomplished by individual housing) on subsequent alcohol consumption. Although one study using rats reports decreased alcohol intake (Fahlke et al. 1997) and a few others report no effect of chronic isolation on later alcohol intake (e.g., Lodge and Lawrence 2003b; Rockman et al. 1988), the large preponderance of studies indicate that chronic isolation increases subsequent alcohol consumption in mouse, rat, and monkey species (see Table 2). For example, several studies conducted with different rat strains (e.g., Hall et al. 1998; Juarez and Vazquez-Cortes 2003) and rats selectively bred for high alcohol preference (Ehlers et al. 2007) have reported that chronic social isolation during adolescence leads to higher alcohol self-administration in adulthood. In a recent study, Long–Evans rats that were chronically isolated during adolescence were shown to exhibit higher levels of alcohol self-administration along with elevated behavioral measures of anxiety (McCool and Chappell 2009). Likewise, studies in mice have shown that chronic social isolation during adolescence results in increased alcohol consumption (Advani et al. 2007). In a recent study conducted in our laboratory, chronic social isolation during early development (14 days, starting at weaning) produced significantly higher voluntary alcohol consumption in male and female C57BL/6J mice compared to group-housed controls (Lopez et al. 2011). A common factor across all of these studies in rats and mice is that chronic social isolation during a critical period of development results in elevated alcohol intake later in adulthood. It is not clear whether chronic isolation during adulthood also affects alcohol intake. To our knowledge, only one study in rats (Schenk et al. 1990) and one study in mice (Lopez et al. 2011) have directly compared the effect of chronic social isolation exposure experience during adolescence vs. adulthood, and these results indicated that isolation housing for the same duration during adulthood did not alter subsequent alcohol intake. This suggests that the timing of chronic isolation stress experience is key, and that interactions with dynamic developmental changes (neural, endocrine) may underlie subsequent enhanced avidity for alcohol in rodents. Clearly, this issue deserves more experimental attention.

A couple of studies have evaluated the effects of chronic isolation on alcohol consumption in nonhuman primates. In one study, adult rhesus monkeys that were socially isolated intermittently (every other week) consumed more alcohol while isolated than during periods of group housing (Kraemer and McKinney 1985). Interestingly, monkeys that experienced intermittent (weekly) separations consumed more alcohol than those continuously isolated prior to and during alcohol access. Despite some methodological issues (alcohol intake when monkeys were together was

estimated based on the group consumption from a single bottle), this study showed that social isolation induced higher alcohol intake (Kraemer and McKinney 1985). Other studies conducted with adult male and female squirrel monkeys showed that while acute (20 min) social separation resulted in reduced alcohol intake (and reduced intake of a control fluid) along with anxiety-like behavior, extending social isolation for a week produced selective elevation of alcohol consumption in the male subjects (McKenzie-Quirk and Miczek 2008; Miczek et al. 2008). This increase in alcohol intake returned to baseline levels when monkeys returned to their social housing conditions (McKenzie-Quirk and Miczek 2008; Miczek et al. 2008). Collectively, results from these studies indicate that the timing and duration of social isolation are critical factors that influence impact on alcohol drinking in adult monkeys. To our knowledge, the effects of chronic social isolation during early developmental periods (adolescence) on subsequent alcohol self-administration have not been systematically studied in monkeys.

Overcrowding Several studies have evaluated the effect of overcrowding on voluntary alcohol intake in rodents. Results have been mixed and, unfortunately, in some cases methodological problems (e.g., using average group intake as dependent variable) have obscured study outcomes (Deatherage 1972; Heminway and Furumoto 1972). Studies in Wistar rats have shown that 7 or 14 days of overcrowding resulted in elevated alcohol intake when rats were subsequently individually housed for testing (Nagaraja and Jeganathan 2002, 2003). However, the overcrowding housing condition decreased food intake, leaving open the possibility that rats increased their alcohol consumption to compensate for reduced caloric intake (Nagaraja and Jeganathan 2002). Similar results were reported in another study conducted with Sprague–Dawley rats (Hannon and Donlon-Bantz 1976). In this study, overcrowding induced high alcohol intake in both male and female rats. Unlike the previously cited study (Nagaraja and Jeganathan 2002), overcrowding did not affect water or saccharin intake. However, the increase in alcohol intake was transient (5–7 days) and the authors speculate that once rats adapted to the housing situation, alcohol intake returned to baseline levels (Hannon and Donlon-Bantz 1976). Thus, while few studies have examined the effects of overcrowding on alcohol consumption, existing results do not suggest robust or durable effects in rodents.

Social status A number of studies have examined the influence of dynamic social interactions in group-housed animals on alcohol consumption. In one study, Long–Evans rats housed in a colonial and environmentally enriched housing condition consumed less alcohol than rats housed in groups or individually in standard cages (Kulkosky et al. 1980). Whether an enriched housing environment and/or its interaction with opportunities for social interaction contribute to this outcome was not (and has not been) directly examined. Other studies using Long–Evans rats found that despite similar overall amount of alcohol consumed, intake was much more variable in group-housed rats compared to those individually housed. Further analysis revealed that the greater heterogeneity in alcohol intake among group-housed rats was attributed to higher levels of alcohol consumption in subordinate subjects (Blanchard et al. 1987). These results are congruent with an earlier study showing reduced alcohol intake in dominant Wistar rats (Wolffgramm and Heyne 1991). More recent studies evaluating the effect of social rank on alcohol intake using triads of Long–Evans rats also showed reduced alcohol intake in dominant rats relative to intake in the sub-dominant and subordinate animals (Pohorecky 2006, 2008, 2010). Studies in mice have generally shown similar results. For example, in one study, Swiss mice were housed in groups to determine social rank based on aggressive behavior (mice that evidenced wounds were identified as subordinates). Mice were then individually housed for alcohol intake assessment and results indicated that mice presenting with wounds showed the highest level of alcohol intake (Hilakivi-Clarke and Lister 1992). Similar results were obtained with C57BL/6J mice that were either identified and categorized based on expression of aggressive or submissive behavior (Kudryavtseva et al. 1991) or C57BL/6J mice that were continuously tested for social aggressive interaction while alcohol intake was assessed (Kudryavtseva et al. 2006). In both cases, mice that exhibited more submissive behavior or were defeated in social interaction tests consumed more alcohol. It should be noted that the effect of pairing the aggressive and subordinate mice on intake was not immediate and was observed only during the second week of pair housing (Kudryavtseva et al. 1991). Also, this effect was observed in C57BL/6J mice but not in CBA/lac mice (Kudryavtseva et al. 1991).

Only a very limited number of studies have examined the relation between social dominance and alcohol intake in nonhuman primates, and results have been mixed. Some studies have reported higher alcohol consumption in dominant monkeys (Crowley and Andrews 1987; Crowley et al. 1990), while other studies reported elevated drinking in monkeys with a lower social rank (McKenzie-Quirk and Miczek 2008; Miczek et al. 2008). There are several factors that might explain the opposing results observed in this set of studies. For example, two different species of monkeys were used: male Japanese Snow monkeys (Crowley and Andrews 1987; Crowley et al. 1990) and both male and female squirrel monkeys (McKenzie-Quirk and Miczek 2008). However, perhaps the most influencing factor was

the procedure used to evaluate alcohol intake. In one case, monkeys had shared access to the alcohol bottle and, as might be predicted, dominant monkeys were able to gain more access to the alcohol bottles (Crowley and Andrews 1987; Crowley et al. 1990). However, when competition for alcohol access was relaxed and all monkeys had similar access to the drinking bottles, the differences in alcohol intake between dominant and subordinate monkeys disappeared (Crowley et al. 1990). Studies involving squirrel monkeys involved first determining social rank based on a dominance index and then the animals were individually given access to alcohol (McKenzie-Quirk and Miczek 2008).

Shifts in circadian cycle When rodents are given free 24 h access to alcohol, consumption follows the pattern of water and food intake, with higher levels of consumption during the dark phase of the circadian cycle (Hiller-Sturmhofel and Kulkosky 2001; Spanagel et al. 2005). The introduction of a shift in the normal light/dark cycle has been proven to be stressful in rodents, adversely affecting the overall health of the subjects (Kort and Weijma 1982; Penev et al. 1998; Tsai et al. 2005). Only a few studies have examined the influence of circadian shifts on alcohol consumption. In one study, adult male Sprague–Dawley rats that experienced a single 8-h shift in the light/dark schedule as well as repeated changes in the lights-on schedule showed a significant increase in voluntary alcohol intake (Gauvin et al. 1997). Other studies conducted with male and female Fisher and Lewis rats (Rosenwasser et al. 2010) or male and female HAD1 rats (Clark et al. 2007) showed a significant decrease in alcohol intake when the animals were subjected to 6-h shifts in the light/dark cycle. In another study, male Wistar rats kept constantly in the dark or with the lights on showed reduced alcohol intake as well (Goodwin et al. 1999). Similar results were obtained with C57BL/6J mice that were switched from a 12:12-h light/dark cycle to a 6:6-h light/dark cycle (Millard and Dole 1983). Additionally, C57BL/6J mice, and the selectively bred high alcohol-preferring (HAP2) and low alcohol-preferring (LAP2) mice that experienced significant changes in their light/dark cycle schedules showed reduced alcohol intake (Trujillo et al. 2011). Taken together, most studies examining the effect of shifts in circadian cycles on voluntary alcohol drinking in rats and mice have shown significant reductions in alcohol intake. An explanation for this general outcome remains to be determined.

Chronic variable stress Several studies that have shown that experience with chronic variable and unpredictable stress has long-lasting effects on HPA axis regulation and stress responsiveness (Flak et al. 2009; Jankord and Herman 2008; Ostrander et al. 2009; Zurita et al. 2000). There is also evidence from studies conducted with rats indicating that experience with chronic variable stress affects later responsiveness to drugs of abuse such as cocaine (Lepsch et al. 2005), morphine, (Molina et al. 1994) and amphetamine (Kabbaj et al. 2002; Lin et al. 2002). However, the effect of chronic variable stress on voluntary alcohol intake remains largely unexplored. In a recent study, exposure to variable and unpredictable mild stressors for 14 days during early development (starting at weaning) resulted in elevated alcohol intake in adult C57BL/6J mice using a two-bottle choice (alcohol vs. water) limited access (2 h/day) testing procedure (Lopez et al. 2011). Additional studies are needed to determine the generality of these effects, and whether similar findings are obtained if chronic variable stress is administered during adulthood.

Summary A large portion of the studies presented in this section demonstrate that chronic stress exposure, especially when experienced during early life, can subsequently produce increased propensity to self-administer alcohol later in adulthood. Evidence in support of such observations come from studies involving mice, rats, and nonhuman primates, and they are based on the general premise that stressful conditions during early development induce long-lasting epigenetic, physiological, and behavioral alterations that impact motivation to drink alcohol (Higley et al. 1991a; Holmes et al. 2005). A review of this literature indicates that a number of procedural variables have significant modulating effects on the outcome. For example, studies involving maternal separation manipulations suggest that effects on subsequent alcohol drinking are dependent on the duration of the maternal separation episode as well as sex of the test subjects (Ploj et al. 2003; Roman et al. 2005). Most of the studies that used long periods of maternal separation reported higher voluntary ethanol intake, and this effect was observed in rats, mice, and nonhuman primates (see Table 2). In some instances, the strain of rats (Lancaster 1998) or the combination of a particular strain and sex (Roman et al. 2005) appeared to modulate the effect of maternal separation. Additionally, in the case of social isolation, the timing of chronic stress exposure appears important, but may be dependent on the species studied. For example, chronic social isolation in rodents can induce higher alcohol intake when the stress is experienced during early (but not later) development (Lopez et al. 2011; Schenk et al. 1990). However, in nonhuman primates, chronic isolation during adulthood also produced increases in voluntary alcohol intake (McKenzie-Quirk and Miczek 2008; Miczek et al. 2008). When considering the social status of rodents housed in groups, most studies have indicated either reduced intake in social dominant subjects (e.g., Pohorecky 2010; Wolffgramm and Heyne 1991) and/or elevated intake in subordinates (e.g., Hilakivi-Clarke and Lister 1992; Kudryavtseva et al.

2006). These results in rodent studies suggest there may be an inverse relationship between social rank and alcohol intake. However, studies conducted with nonhuman primates do not entirely support such a relationship. Specifically, some studies in monkeys have shown that dominant subjects drink more (Crowley and Andrews 1987; Crowley et al. 1990) while other studies indicate subordinate subjects drink more (McKenzie-Quirk and Miczek 2008; Miczek et al. 2008). Differences in monkey species and methods for assessing alcohol consumption may contribute to the mixed results. However, since so few studies have been conducted with nonhuman primates, it is difficult to discern which factors may contribute to higher or lower drinking in dominant subjects. Another issue to be considered relates to the persistence of effects on alcohol drinking. In some cases, the effects of maternal separation and chronic social isolation on later alcohol drinking were transient (Advani et al. 2007; Lancaster 1998; Lopez et al. 2011), while in other cases, the effects were more durable (Ehlers et al. 2007; Roman et al. 2005). At present, it is not known whether it is the characteristics of the stress experience, intervening variables, or an interaction of these factors that play a role in determining not only the direction, but also the persistence of changes in alcohol drinking. As a growing body of evidence suggests that various chronic stress procedures, especially when administered early in development, result in later increased alcohol drinking, more studies focused on examining (epi)genetic, physiological, and neural mechanisms underlying the phenomena are certainly warranted.

Chronic intermittent alcohol exposure as a stressor

As previously noted, it is well known that alcohol activates the HPA axis, and both clinical and experimental studies have documented profound disturbances in HPA axis function following chronic alcohol exposure and withdrawal. For example, in humans and rodents, chronic alcohol consumption results in a general elevation in blood corticosteroid levels, flattening of normal circadian fluctuations, and dampened HPA response to subsequent stress challenge (Errico et al. 1993; Kakihana and Moore 1976; Lee et al. 2000; Rasmussen et al. 2000; Tabakoff et al. 1978; Wand and Dobs 1991). While heightened HPA axis activation associated with withdrawal usually resolves within a few days (Adinoff et al. 1991; Tabakoff et al. 1978; Willenbring et al. 1984), blunted HPA axis responsiveness along with reduced basal levels of circulating corticosteroids appear to persist for a protracted period of time (Adinoff et al. 1990; Costa et al. 1996; Lovallo et al. 2000; Marchesi et al. 1997; Rasmussen et al. 2000; Zorrilla et al. 2001).

In addition to these HPA axis-related effects, alcohol alters CRF activity independent from the HPA axis (Heilig and Koob 2007; Koob and Zorrilla 2010; Uhart and Wand 2009). Increased CRF activity in several brain structures following chronic alcohol exposure represents an important neuroadaptive change that is thought to be key in the emergence of withdrawal-related anxiety and dysphoria, components of the alcohol withdrawal syndrome that are suggested to be intimately tied to alcohol drinking and relapse (Becker 1999, 2009; Heilig and Koob 2007; Koob and Kreek 2007; Koob 2003; Koob and Le Moal 2008). Thus, chronic alcohol exposure and withdrawal experience can be viewed as a potent stressor that disrupts the functional integrity of the HPA axis along with recruiting extrahypothalamic CRF systems, and this perturbation in brain/neuroendocrine stress axes may have significant implications regarding motivation for ethanol self-administration behavior.

Indeed, alcohol dependence has long been postulated to play a significant role in driving and maintaining excessive drinking. As shown in Table 3, numerous studies involving mice and rats have demonstrated escalated alcohol consumption using home cage free choice models and operant-conditioning procedures. In most cases, dependence has been induced by delivering alcohol vapor via inhalation chambers. For example, we have established a mouse model of dependence and relapse drinking that demonstrate repeated cycles of chronic alcohol exposure delivered by inhalation results in an escalation of voluntary alcohol drinking (Becker and Lopez 2004; Lopez and Becker 2005). More detailed analysis of the pattern of alcohol consumption revealed that dependent mice not only consumed a greater overall amount of alcohol compared to non-dependent mice, but also the rate of consumption was faster and progressively increased over successive withdrawal test periods (Griffin et al. 2009b). This enhanced alcohol consumption in dependent mice produced significantly higher and more sustained blood and brain alcohol levels compared to that achieved by more modest (stable) intake in non-dependent mice (Griffin et al. 2009b). Additionally, an increased number of cycles of chronic intermittent alcohol exposure resulted in greater and longer lasting enhancement of voluntary alcohol drinking (Griffin et al. 2009a; Lopez and Becker 2005). The mice are not food or water deprived and, importantly, the effect appears specific to alcohol because repeated cycles of chronic intermittent alcohol exposure did not produce alterations in water or sucrose intake (Becker and Lopez 2004). Others have reported similar results using inhalation procedures in mice (Dhaher et al. 2008; Finn et al. 2007) and in rats (Rimondini et al. 2002, Rimondini et al. 2003; Sommer et al. 2008). Likewise, studies using operant procedures have demonstrated increased alcohol self-administration in mice

Table 3 Chronic intermittent alcohol exposure effects on alcohol drinking

Procedure	Species	Increased intake
Home cage Drinking	Mouse	Becker and Lopez 2004
		Lopez and Becker 2005
		Finn et al. 2007
		Dhaher et al. 2008
		Griffin et al. 2009a
		Griffin et al. 2009b
	Rat	Rimondini et al. 2002[a]
		Rimondini et al. 2008[a]
		Sommer et al. 2008[a]
Operant Self-administration	Mouse	Chu et al. 2007
		Lopez et al. 2006
		Lopez et al. 2008
	Rat	Roberts et al. 1996
		Brown et al. 1998[b]
		Roberts et al. 2000
		Liu and Weiss 2002
		O'Dell et al. 2004
		Thorsell et al. 2005a
		Thorsell et al. 2005b
		Funk et al. 2006
		Funk and Koob 2007
		Gehlert et al. 2007
		Gilpin et al. 2008a, b, c
		Richardson et al. 2008
		Gilpin et al. 2009

[a] No drinking before inhalation

[b] Liquid diet

(Chu et al. 2007; Lopez et al. 2006) and rats (Gilpin et al. 2008b, 2009; O'Dell et al. 2004; Roberts et al. 1996, 2000) with a history of repeated chronic intermittent alcohol exposure, with evidence indicating that the reinforcing efficacy of ethanol is enhanced (Brown et al. 1998; Lopez et al. 2008). Further, studies in mice and rats have demonstrated that significant escalation of alcohol self-administration is facilitated when dependence is induced by delivery of chronic alcohol vapor exposure in an intermittent rather than continuous fashion (Lopez and Becker 2005; O'Dell et al. 2004). These latter findings suggest that repeated experience with alcohol withdrawal plays an important role in favoring excessive alcohol consumption associated with these models of dependence. Hence, it is reasonable to suggest that stress associated with chronic alcohol exposure and, in particular, repeated experience with withdrawal contributes to enhanced motivation to consume alcohol.

Indeed, work in our laboratory and others have demonstrated that these models involving chronic intermittent alcohol exposure constitute potent stressors, as evidenced by initial HPA axis activation and then dysregulation of HPA axis activity (Lopez et al. 2010; Richardson et al. 2008). Additionally, several studies have shown that a history of dependence not only engenders elevated drinking, but also alters stress responsiveness as measured by several behavioral procedures (Breese et al. 2005; Gehlert et al. 2007; Sommer et al. 2008). This latter effect may be critical in rendering subjects more vulnerable to relapse and return to uncontrolled, harmful levels of alcohol consumption. Further, several studies have shown these models to engage various stress-related neuropeptides and modulators within brain stress–reward pathways that are postulated to contribute to drive/mediate excessive levels of alcohol drinking. For example, CRF (extrahypothalamic) (Finn et al. 2007; Gilpin et al. 2008a; Roberto et al. 2010; Sommer et al. 2008; Thorsell et al. 2005a), NPY (Gilpin et al. 2008c, 2011; Thorsell et al. 2005a, b), and opioid (Gilpin et al. 2008a; Walker and Koob 2008; Walker et al. 2011) systems have been implicated in excessive drinking that follows chronic intermittent alcohol exposure. Recent work in our laboratory indicates that with increased cycles of chronic intermittent alcohol exposure there is an apparent blunting of HPA axis activation, as measured by reduced levels of plasma corticosterone, while at the same time an accentuation of changes in CRF mRNA/peptide expression and release capacity in extrahypothalamic brain regions that are implicated in motivational effects of alcohol (Lopez et al. 2010; Griffin et al. 2011). These changes also have been accompanied by altered expression of the neuroactive steroid allopregnanolone in brain (Morrow et al. 2009). Brain-derived neurotrophic factor (BDNF) has been implicated in stress and addiction processes (Briand and Blendy 2010; Chourbaji et al. 2011; Davis 2008), and there is recent evidence indicating that brain regional changes in BDNF expression/activity following chronic alcohol exposure play a role in mediating withdrawal-related anxiety and regulation of alcohol consumption (Logrip et al. 2009; Pandey et al. 1999, 2006). Other stress-responsive systems (e.g., adrenergic, substance P, and orexin/hypocretin) have been shown to influence alcohol consumption (Ciccocioppo et al. 2009; Heilig et al. 2010; Sinha et al. 2011), but their role in mediating excessive drinking associated with dependence has not been specifically examined. Most of this work has focused on elucidating the role of these neurotransmitters and modulators within corticolimbic circuitry. Recently, basal ganglia circuitry, particularly the striatum, has been implicated in the transition to habit-like, inflexible patterns of behavior that result from chronic stress and chronic alcohol exposure, including excessive levels of drinking associated with dependence (Chen et al. 2011; Dias-Ferreira et al. 2009). Clearly, identifying neuroadaptive changes within relevant motivational and stress

pathways associated with dependence that promote/mediate excessive drinking is key to better understand the complex reciprocal relationship between stress and alcohol and conditions in which stress modulates drinking in the context of dependence.

Future directions: toward developing better animal models

As reviewed above, despite an extensive amount of research using animal models aimed at examining the effects of stress on alcohol drinking, results from this large body of work have been generally equivocal. Thus, while it is frequently argued that stress plays an important role in triggering relapse and maintaining harmful levels of drinking in the "real" world, this scenario has been difficult to reliably model in preclinical studies. Stress appraisal and response, as well as alcohol drinking are very complex and multifaceted behavioral phenotypes themselves. The biological underpinnings and behavioral processes regulating these phenomena are equally complex and dynamic. Nonetheless, in reviewing this relatively large body of literature, several general principles emerge that not only offer explanation for the diversity of outcomes reported, but also provide insight and guidance for future work that will be valuable in designing better animal models for studying interactions of stress and alcohol consumption.

Several genetic and biological variables play a clear role in modulating stress–alcohol interactions. In humans, an interplay between individual differences in stress appraisal and ability to mount effective coping strategies and individual differences in response to alcohol intoxication are likely to contribute to unique stress–alcohol interactions (Childs et al. 2011; Claessens et al. 2011; Williams et al. 2009). While the use of subhuman primates has several advantages as models of the human condition (e.g., genetic, endocrine, and cognitive), these studies have been relatively limited. Most of this work has been conducted using rodent models. However, there are important species-specific differences in response to stress and rarely has this issue been considered in evaluating the effects of a particular stressor on alcohol drinking in mice vs. rats. It is possible (and quite likely) that a distinct set of experimental conditions for studying stress effects on alcohol drinking may be optimal for one species but not for the other. In this vein, consideration of the ethological relevance of stimuli/events may be critical in formulating models to study stress effects on alcohol drinking in a given species. Additionally, there are known differences in stress responsiveness among different strains within a species, such as rats (Giorgi et al. 2003; Walker et al. 2009) and mice (Belzung and Griebel 2001; Millstein and Holmes 2007; Tannenbaum and Anisman 2003). This indicates that genetic factors play an important role in defining responses to stress and, presumably, impact on drinking. Physiological and/or behavioral measures of stress response should be incorporated in study designs to enable addressing this general issue as well as facilitate more informed comparisons across studies and different models.

In a variety of circumstances and testing conditions, genetic-defined differences in alcohol preference (either through comparison of inbred genotypes or selective breeding) have been shown to influence stress–alcohol drinking interactions. Unfortunately, there is no general consensus on whether propensity (high or low) to consume alcohol confers a unique response to the modulatory effects of stress on drinking. It is interesting that studies have not focused on genetic models that demonstrate differences in stress responsiveness (vulnerability or resiliency) as it relates to the capacity of stress to alter alcohol consumption. This may be a fruitful and complimentary avenue to pursue in examining genetic factors that shape stress–alcohol interactions. Sex/gender is a variable that has frequently been included in animal studies, yet a clear picture regarding the influence of this factor has not emerged from the extant literature. While age of the subjects has not been systematically examined, it is clear that stress experience early in life (especially during critical windows of development) can have long-lasting effects on both stress responsiveness and alcohol drinking. Such models appear useful in approximating the impact of early life trauma on propensity to later drink. Studies designed to identify underlying biological mediators of this effect will be important in developing interventions that most effectively prevent later vulnerability to excessive drinking.

As described in this review, a wide array of stress procedures has been employed to study the effects of stress on alcohol drinking in animals. It is now appreciated that not all stressors produce the same biological and behavioral response (Koolhaas et al. 2011). The ethological relevance and qualitative nature of a stressor (i.e., where it lies along a physical vs. psychogenic spectrum), along with physiological and behavioral responses evoked are important aspects of a stressor that undoubtedly contribute to its impact on alcohol consumption. Hence, it is not surprising that study outcomes related to alcohol drinking vary as a function of the stressor used. There is a clear need for systematic comparison of physiological (and when appropriate, behavioral) responses to different stress procedures, and how such effects impact the capacity of different stressors to exert unique modulatory effects on alcohol consumption. Aside from qualitative differences in stress (i.e., the nature of the stressor), there are also significant quantitative differences that are important to consider as well. Intensity, chronicity, and intermittency dimensions of stress have all been addressed in the literature. However, systematic evaluation of these characteristics using

an experimental paradigm in which other factors are held constant is needed to help tease apart specific conditions and aspects of a given stressor that engender reliable changes in alcohol drinking. Likewise, predictability and controllability of stress has not been systematically examined in the context of animal models studying stress effects on alcohol self-administration. This represents another important opportunity for future efforts in addressing the role of cognitive aspects of stress that heretofore have not been adequately examined with regard to impact on motivation to drink in animal models. Clearly, the capacity of an organism to mount effective and appropriate coping mechanisms is critical for not only handling a stressful challenge at hand, but it is also likely to bear on motivation to engage in behaviors such as alcohol drinking that may be perceived, at least to some extent, as part of a coping response. Related to this issue is a key role for learning in stress–alcohol interactions. In general, there is a paucity of studies that focus on the role of associative factors in examining stress effects on alcohol drinking. Conditioned responses to alcohol and stress-related stimuli/events are critical for guiding future behavior, yet few studies have examined the relevance of this behavioral plasticity in relation to alcohol drinking. This includes analyses of the role of conditioning (learning) in both stress-modulating effects of alcohol and alcohol-modulatory effects on stress perception and response.

Alcohol drinking history is another important factor that influences the outcome of studies examining stress–alcohol interactions. Surprisingly, this variable has not been systematically examined. Although duration of prestress alcohol experience has typically not been examined, correlation analyses have attempted to relate prestress drinking levels with subsequent changes in drinking following stress exposure. The limited data available do not indicate a clear relationship. In contrast, a history of substantial alcohol experience has been shown to not only constitute a potent stressor itself, but also reliably engender elevated alcohol drinking. These studies have predominantly involved the use of inhalation to induce dependence and various self-administration models to assess subsequent effects on drinking in mice and rats. A general guiding principle that has emerged from these studies postulates that stress associated with chronic alcohol exposure and withdrawal experience continually challenges the physiological integrity of the organism through progressive dysregulation of peripheral and brain stress and reward systems beyond normal homeostatic limits. This, in turn, results in an allostatic state, which refers to a situation in which the organism attempts to maintain physiological stability in the face of continual perturbation (McEwen 2000). In this case, the allostatic state that arises as a result of chronic intoxication is characterized by neuroadaptive changes in brain reward and stress pathways that drive/promote escalation of drinking as well as alter stress responsiveness. In this vein, alcohol dependence may be viewed as a persistent allostatic state, with the organism rendered ill equipped to exert appropriate behavioral control over alcohol consumption, as well as appropriately respond to other (additional) stressful events that may provoke return to excessive drinking. Studies aimed at elucidating underlying neurobiological mechanisms in these models will be critical for advancing our understanding of how stress associated with prolonged alcohol exposure (i.e., dependence) influences motivation to drink, impacts physiological and behavioral response to stress, and influences the ability of stress to modulate alcohol drinking in the context of dependence.

There still remains the question as to why stress effects on alcohol drinking in animal models have produced such equivocal outcomes, but it has proven to be a very effective provocateur of relapse behavior in operant reinstatement paradigms. The latter findings involving reinstatement models have been reviewed elsewhere (Shaham et al. 2003; Shalev et al. 2002, 2010). As previously noted, an important component of operant reinstatement procedures is that stress-induced activation of responding for alcohol (and other drugs) is tested under extinction conditions. Thus, the use of such models does not afford the opportunity to examine stress effects on alcohol consumption per se. While operant self-administration procedures can effectively separate alcohol "seeking" and "taking" (consumption) components, few studies have applied this approach to study stress effects on alcohol self-administration behavior. Further, as advances have been made in identifying neural pathways involved in various aspects of alcohol/drug addiction and relapse, it will be valuable for future efforts to focus on elucidating overlapping vs. distinct neural circuitries that underlie alcohol "seeking" and drinking behaviors. This, in turn, may reveal unique mechanisms by which stress modulates motivational processes involved in procuring alcohol compared to those underlying cognitive and regulatory processes that govern control over alcohol consumption.

Finally, a number of methodological issues deserve attention. Most of the studies reviewed in this paper do not report whether a particular stress procedure employed was, in fact, an effective stressful challenge to the organism. Since inferences are made that exposure to stress produces change in alcohol consumption, it behooves investigators to demonstrate the effectiveness of the stress challenge using physiological and/or behavioral indices. This is especially relevant for studies examining chronic stress effects on alcohol drinking since animals may habituate to certain stressors when repeatedly exposed. Such outcomes may point to potential dissociation between physiological responses to a stressor and its ability to modify alcohol drinking. Thus, while measures of HPA axis activity (plasma corticosteroid levels) may habituate with repeated stress exposure, adaptive changes in other brain stress

pathways may become of greater significance with regard to influences on motivation to consume alcohol. Another important consideration is the manner in which alcohol intake is assessed, as it relates to the extent of stress-induced changes in alcohol consumption. In many cases, stress is reported to produce a statistically significant change in alcohol intake but the alteration in consumption may be of minimal or marginal biological relevance. Relatively small, albeit statistically significant changes in alcohol intake over long access periods (e.g., 24 h) may be of questionable relevance if it cannot be demonstrated that a large proportion of the change occurs within a specific time frame, thereby producing a significant elevation in blood alcohol concentrations. Thus, it is critical for such studies to incorporate measures of blood alcohol levels associated with alcohol intake so that the magnitude of stress-modulated drinking can be gauged in proper context. Another issue concerns the temporal relationship between stress exposure and access to alcohol. Many studies examine effects of stress on alcohol drinking where the stress experience occurs concurrent with alcohol access. In other cases, alcohol consumption is assessed during a period after stress exposure is terminated. These scenarios provide valuable information regarding the acute vs. protracted effects of stress on alcohol consumption. Also, timing alcohol access to occur either before or after stress exposure enables analysis of whether changes in drinking manifest as a "coping" strategy (i.e., drinking in anticipation of stress vs. drinking as a consequence of stress). Systematic analysis of this issue with inclusion of appropriate control conditions deserves more experimental attention in animal models. Finally, some studies have reported changes in drinking after long delays since stress experience. Such outcomes suggest underlying long-lasting adaptations that eventually become expressed through altered alcohol consumption. Identifying the nature of these changes will be critical for understanding factors that mediate and influence stress–alcohol interactions. This, in turn, will help guide more refined models that better approximate the complex reciprocal relationship between stress and alcohol drinking in clinical settings.

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