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The Importance of Glucocorticoids in Alcohol Dependence and Neurotoxicity

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Abstract

Alterations in hypothalamo-pituitary adrenal (HPA) function have been described in alcoholics and in rodents after chronic alcohol consumption but the role of glucocorticoids in alcohol consumption, and the mechanisms involved, have received little attention until recently. Both alcohol consumption and withdrawal from chronic alcohol intake raise circulating glucocorticoid levels and prolonged high concentrations of glucocorticoids are known to have detrimental effects on neuronal function and cognition. This minireview covers the ways in which glucocorticoids may be involved in drinking behavior, from social drinking to dependence, and the negative consequences of alcohol consumption seen during withdrawal which may have a detrimental effect on treatment outcome. Research shows increases in brain glucocorticoid concentrations and decreased glucocorticoid receptor occupancy during prolonged abstinence after withdrawal from chronic alcohol treatments. Evidence suggests that increased glucocorticoid levels in the brain after chronic alcohol treatment are associated with the cognitive deficits seen during abstinence which impact on treatment efficacy and quality of life. Studies on organotypic cultures also demonstrate the importance of glucocorticoids in the neuropathological consequences of alcohol dependence.

Keywords

Alcohol; glucocorticoids; cortisol

Introduction

Glucocorticoids (cortisol in humans, corticosterone in rodents) may be involved in both the consequences of long term alcohol drinking and in the causes of alcohol dependence. Many alcohol dependent individuals have a history of affective disorders and altered HPA axis function (Akil 1993), raising the possibility that HPA axis dysfunction may contribute to the development of alcohol dependence. Clinical studies have shown a higher incidence of stressful major life events in alcohol dependence (Gorman et al., 1990) and greater relapse

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rates in abstinent alcoholics after severe psychosocial stress (Brown et al., 1995). Changes in the HPA system are known to occur during and after chronic alcohol intake. Plasma glucocorticoids are raised during acute and chronic alcohol consumption and the initial phase of the alcohol withdrawal period (Adinoff et al., 1991; 1998; 2003) The glucocorticoid responses to various forms of stress are considerably reduced following cessation of excessive drinking (Ehrenreich et al., 1997; Vescovi et al., 1997). Rivier and colleagues have shown that ethanol-associated HPA axis activation requires activation of the hypothalamic paraventricular nucleus, CRF release and adrenocorticotropic hormone (ACTH) release (Lee et al. 2003; Rivest and Rivier 1994; Rivier et al. 1984).

This minireview[1] describes particular aspects of the interactions between alcohol and glucocorticoids, specifically the involvement of glucocorticoids in motivation for alcohol drinking and in the adverse effects of chronic alcohol consumption and withdrawal. Evidence relating to the potential role of glucocorticoids in alcohol priming, stress and cue responsivity, the effects of alcohol on brain glucocorticoid concentrations and the involvement of glucocorticoids in cognitive deficits and neuronal damage caused by alcohol withdrawal are described.

Glucocorticoids themselves have been shown to possess reinforcing effects; rats will self-administer corticosterone to achieve the plasma concentrations of this hormone in the range (1 - 1.5 μM) that occurs during stressful experiences (Piazza et al., 1993). Corticosterone administration increased voluntary alcohol drinking in rats and the corticosterone synthesis inhibitor, metyrapone, or adrenalectomy, decreased ethanol intake (Fahlke et al., 1994a; 1994b; 1995; Fahlke and Hanson, 1999). The Type II glucocorticoid receptor antagonist mifepristone blocks operant responding for ethanol, but not water, in rats (Koenig and Olive, 2004). Although some laboratory reports find that acute stress has short term effects in decreasing alcohol consumption (e.g. van Erp et al., 2001), stressful experiences have been shown to have more prolonged effects in increasing voluntary alcohol drinking, especially in low alcohol preference animals (Little et al., 1999; Rockman et al., 1987; Volpicelli et al., 1986). In addition, stress can activate the reward circuits of the brain and this effect could sensitize the rewarding effects of drinking, again making consumption more likely (positive reinforcement) (Cho and Little, 1999; Piazza and Le Moal, 1997).

Human studies suggest motivation for drinking can involve both positive and negative feelings, both of which can activate the HPA. The positive reinforcing effects of initial alcohol consumption can act as a prime and facilitate further drinking. In addition, it has been argued that negative feelings highlight the mood enhancing and anxiolytic effects of alcohol, motivating some individuals to drink in order to alleviate the negative affect (negative reinforcement) (Birch et al., 2004: Sher and Levenson, 1982).

Chronic excess alcohol consumption is well established to cause cognitive deficits in human alcoholics and in animal models. These take the form of difficulties in learning new information and retention over long delay intervals, increased sensitivity to interference from distracting activities, and deficits in information encoding and information processing (Brandt et al., 1983; Parsons, 1998; Riege et al., 1981; Zhang et al., 1997). Many clinical studies showing neuroanatomical damage have included patients with Korsakoff's syndrome, an organic brain disorder attributed to the thiamine deficiency frequent in alcoholics. The causes of cognitive deficits and neuroanatomical damage after chronic alcohol intake, however, are not understood. Here we present evidence that chronic alcohol consumption may alter brain concentrations of glucocorticoids independently of the plasma levels and of the involvement of glucocorticoids in the genesis of the cognitive deficits

[1]The majority of the studies described in this minireview were presented in a symposium at RSA in 2008

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following alcohol cessation. Prolonged ethanol dependence in humans is associated with the development of neurological abnormalities and reduced volume of many brain structures (Eckardt and Martin, 1986; Fama et al., 2006; Hulse et al., 2005; Schweinsburg et al., 2001). Such changes are likely the result of multiple biological actions of ethanol, including the function of ethanol-sensitive NMDA-type glutamate receptors in particular and, more specifically, NR2 subunit function. Studies supporting the involvement of this subunit in the neuronal damage caused by alcohol will be described.

The Role of Cortisol in Motivation to Drink

Understanding the motivation to drink is essential in determining how alcohol use disorders develop and should contribute to policies and interventions aimed at reducing drinking levels. Both dependent and non-dependent drinkers are motivated to drink by certain cues (Shaham et al., 2003; Weiss et al., 2001): an initial dose, or 'prime', of a drug (de Wit, 1996; Rose and Duka, 2006; Rose & Grunsell, 2008), environmental cues (Weitzman et al., 2003), and negative mood - particularly stress (de Wit et al., 2003; Nesic and Duka, 2006). Although a number of pharmacological systems, such as dopamine (Hutchison et al., 2001), have been implicated in underlying some of the effects of these cues, recent work has also highlighted a potential role for cortisol.

Alcohol dependent individuals wishing to control their intake, but not seeking total abstinence, reported increased alcohol craving after experience of an alcohol cue and alcohol priming relative to control cues (Hammarberg et al., 2009). In comparison with the controls, plasma cortisol levels increased marginally after the alcohol cue and significantly after alcohol priming. Acamprosate is a drug used in alcohol dependence that affects glutamate and GABA neurotransmission and neuronal calcium channels, although its precise mechanism of action is not certain. A 21 day treatment regime of acamprosate blocked the alcohol priming effect and reduced the cortisol levels associated with priming. No such relationships were found with regard to cue reactivity (Hammarberg et al., 2009).

A blunted cortisol response was found in heavy, relative to light, social drinkers in response to a moderate (0.8 g/kg) priming dose of alcohol (King et al., 2006). As these participants were non-dependent drinkers, it is possible that tolerance to neuroendocrine responses develops before dependence. Rats with low (non-dependent, <0.2 g/kg/session) levels of alcohol consumption showed greater cortisol response to an alcohol challenge (1 g/kg) relative to animals with moderate (non-dependent, ~0.3-0.4 g/kg/session) and high (dependent, ~1 g/kg/session) levels of alcohol consumption, suggesting neuroendocrine tolerance preceded dependence (Richardson et al., 2008). Alcohol withdrawal results in anxiety-related behavior in animal models (Rassnick et al., 1993). If hyporeactive cortisol responses underlie some of the negative characteristics of dependence and withdrawal, e.g. anxiety and dysphoria, this identifies a pathway of negative reinforcement by which cortisol function may be involved in motivation to drink and relapse (Richardson et al., 2008).

Alternatively, it is possible that hyporeactive cortisol function is a risk marker for abuse propensity. Males with a positive familial risk of alcohol dependence showed lower basal plasma levels of ACTH and β-endorphin, but not cortisol, than males without a familial risk (Gianoulakis et al., 2005). The low risk males reported more anxiety which positively correlated with cortisol levels, a finding absent in the high risk males. Research is needed which captures people before heavy drinking develops to determine whether cortisol dysfunction is a risk factor for alcohol use disorders. King et al's (2006) work did not include measures of alcohol craving and, although alcohol priming is known to be an important motivator for drinking behavior in social drinkers, there has not been, to our

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knowledge, any work which specifically investigates cortisol function with respect to alcohol priming in non-dependent populations.

Environmental cues are also known to trigger alcohol-related behavior in social and dependent drinkers (Grusser al., 2004; Kuo et al., 2003). Salivary cortisol levels increased in reaction to alcohol, but not stress, imagery scripts in a population of abstinent alcoholics (Fox et al., 2007). Sinha et al (2009) found something similar; guided stress and alcohol imagery techniques resulted in increased alcohol craving and anxiety in 28 day abstinent alcoholics, compared with controls. Salivary cortisol levels were greatest in the dependent drinkers only during exposure to the alcohol cues. This contrasted with the control participants, who displayed an increase in salivary cortisol only during exposure to the stress condition. In both studies, the stress and alcohol scripts elicited anxiety and, therefore, an increase in cortisol would have been expected in all conditions. The lack of any cortisol effect fits with the finding that, although acute alcohol consumption stimulates cortisol release, alcohol dependence results in a blunted cortisol response to a range of psychological and physical stressors (Lovallo, 2006). As acute alcohol consumption triggers cortisol release, it is possible that conditioning results in an appetitive response to cues which also includes cortisol release and which may be involved in motivation to drink. However, depressed cortisol plasma levels at baseline, throughout alcohol cue exposure and during consumption of alcohol have also been observed in inpatient alcoholics relative to controls (Dolinsky et al., 1987). The mixed findings from research investigating the relationship between cortisol function and alcohol cues, suggests a dysfunctional HPA system rather than specific cortisol hyporesponsivity.

The HPA axis is key in behavioral and physiological stress responses and stress reactivity has been associated with hazardous drinking and risk of alcohol use disorders (Helig and Koob, 2007; Koob 2006). The change in cortisol response between a stress (Paced Auditory Serial Addition Test) and a control condition has been found to negatively correlate with the difference in alcohol consumption levels between the two conditions in non-treatment-seeking alcoholics (Pratt and Davidson, 2009). These findings suggest that alcohol-related behaviors triggered by stress may be an attempt to compensate for blunted cortisol processes.

Far less research has been conducted which looks specifically at stress, cortisol function and motivation to drink alcohol in non-dependent human populations, even though it is apparent that identifying risk factors in sub-clinical populations is important. Stress (the Trier Social Stress test) can maintain raised cortisol levels in social drinkers, but this effect can reduce alcohol consumption in women (Nesic and Duka, 2006), suggesting that men may be more vulnerable to the motivating effects of stress on alcohol consumption. Personality characteristics may also influence the role of stress in alcohol motivation. Individuals high in hostility ratings demonstrate greater cortisol reactivity to stressful manipulations as well as greater increases in alcohol desire (Nesic and Duka, 2008).

Animal and human research has highlighted a role for cortisol in the motivating power of cues known to be important in hazardous drinking and relapse but research is still needed which identifies the specific mechanisms by which cortisol has its effect.

Brain Glucocorticoid Levels and Alcohol

As described in the Introduction, alcohol has considerable influence on the release of glucocorticoids. Ellis reported many years ago (1966) that ethanol increases corticosterone secretion in rodents. Some studies report basal circulating glucocorticoid levels in alcoholics are similar to controls, others that there are increases (Farren et al., 1995), but this may depend on the time of sampling as the circadian rhythm of plasma glucocorticoid

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concentrations is disturbed (Adinoff et al., 1990; 2003; Marchesi et al., 1997). Acute and chronic intake of ethanol, as well as withdrawal, in both humans and rodents markedly increases plasma glucocorticoid levels and, with chronic use, produces a pattern of HPA axis dysfunction similar to that observed in depressed patients (Adinoff et al., 2003; Esel et al., 2001; Rasmussen et al., 2000; Tabakoff et al., 1978).

Until recently, studies assumed that brain concentrations of glucocorticoid simply followed the plasma levels, and that the adrenals were the sole source of glucocorticoids. However, there was little evidence to support such an assumption, as there were very few published reports demonstrating measurements of brain glucocortioids. The great majority of such publications date back to the 1970s, with only minimal examination of central levels since then. These early studies, however, showed that despite the less sophisticated methodology, compared with current research, dissociations were seen between central and plasma glucocorticoid levels (Diez et al., 1976; Lengavari and Liposits, 1977). During our studies on the effects of corticosterone on dopamine neurons in the VTA, described above (Cho and Little, 1999), we had cause to consider what the physiological levels of this hormone actually were in the brain as it was important to know whether or not the concentrations that showed effects in vitro on responses to excitatory amino acids were relevant to the situation in vivo. In order to provide a definitive answer to this, we therefore measured corticosterone concentrations in various brain regions. These experiments showed that brain levels in control mouse brains ranged between 10 and 500 nM, when direct extrapolation was made from corticosterone measured as mg per gram of wet brain tissue, assuming equal distribution throughout the tissue. These levels were close to those that we found to affect the excitatory responses of VTA neurons in vitro, where the threshold corticosterone levels were around 100 nM (Cho and Little, 1999).

We then hypothesized that long term alcohol consumption might have differential effects on brain and plasma corticosterone concentrations. We measured the effects of chronic alcohol treatment on brain corticosterone levels, using a range of well-established experimental protocols, to demonstrate any potential influences of mode and duration of alcohol administration, and species and strain of animal, on any changes observed (Little et al., 2008). The corticosterone levels were measured using a standard radioimmunoassay after alcohol extraction from brain regions. The identity of the corticosterone immunoreactivity was validated by high performance liquid chromatography, gas chromatography and mass spectroscopy. We found that withdrawal from chronic alcohol treatment caused considerable increases in corticosterone concentrations in specific brain areas, in both rats and mice. The increases were seen not only during the acute phase of withdrawal, when raised central corticosterone concentrations would be expected in view of the raised plasma levels, but also at more extended times after alcohol withdrawal, even as long as two months. In contrast, plasma corticosterone was raised only during the acute phase of alcohol withdrawal then returned to control levels within 24 hours. The regions in which the highest levels of corticosterone were seen following withdrawal from chronic alcohol treatment were the prefrontal cortex and hippocampus. In prefrontal cortex the concentrations were equivalent to as high as 1 μM. Further verification of these changes, and that the corticosterone was in an active form, was shown by radioligand binding studies. Available Type II glucocorticoid receptor binding in prefrontal cortex was found to be decreased during the abstinence phase after chronic alcohol treatment in vivo. This change could have been due either to increases in the local concentrations of hormone, or to reduction in the binding protein. Western blot analysis, however, showed increased receptor protein in the nuclear fraction. After binding to glucocorticoid, the Type II receptor is translocated to the neuronal nucleus, so this pattern of Western blot data is consistent with raised local concentrations of ligand.

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Glucocorticoids and Cognitive Deficits Caused by Chronic Alcohol Intake

Neuronal hyperexcitability during the alcohol withdrawal syndrome is thought to contribute to both neuronal degeneration and cognitive deficits, although some neuronal damage can occur without withdrawal (Hunt, 1993). Greater neuronal degeneration was reported after cessation of chronic alcohol intake than during its consumption (Cadete-Leite, 1990; Phillips and Cragg, 1984). Evidence implicating the acute withdrawal syndrome in the genesis of cognitive deficits also comes from animal studies that showed that memory deficits in rats were seen after withdrawal from chronic alcohol consumption but not during alcohol intake (Farr et al., 2005; Lukoyanov et al., 1999).

Surprisingly little information is available about the cause of the neuronal damage caused by long term alcohol intake but increased glutamate activity, increased calcium flux and glucocorticoids have been implicated. Upregulation of N-methyl-D-aspartate (NMDA) receptors (Grant et al., 1990) and increased NMDA-receptor mediated activity (Whittington et al., 1995) are known to occur during the acute phase of alcohol withdrawal. Increased calcium flux into neurons is also a factor and an upregulation of dihydropyridine sensitive L-type calcium channels occurs during the acute withdrawal phase (Dolin et al., 1987). Neurotrophic factors may also be involved in the neurotoxicity caused by chronic alcohol consumption and withdrawal (Crews et al., 1999; Davidson et al., 1993; 1995). Changes in neuronal functions involved in memory including in long term potentiation (LTP), have been demonstrated experimentally during the abstinence phase (Durand and Carlen, 1984; Roberto et al., 2002). More severe cognitive deficits were found in those alcoholics who had higher cortisol levels during withdrawal (Errico et al., 2002; Keedwell et al., 2001). It is well established that prolonged high glucocorticoid concentrations cause neuronal changes, in particular neurotoxicity (Erickson et al., 2003; Sapolsky et al., 2000). The neurotoxic effects are particularly pronounced following activation of neurons by glutamate and when intracellular calcium concentrations are increased (Sapolsky, 1996b). During the acute phase of alcohol withdrawal, therefore, the conditions are precisely those that would be predicted to result in neuronal damage.

This raised the possibility of protecting against the neuronal damage by blocking either the action of the glucocorticoid or the entry of calcium into the neurons. In these studies, we measured the effects of drugs given only during the acute phase of alcohol withdrawal on the cognitive deficits measured later during the abstinence period. A single injection of the Type II glucocorticoid receptor antagonist, mifepristone (RU38486), given just as the alcohol was withdrawn at the end of several weeks chronic alcohol treatment, reduced the memory deficits seen in mice 1-2 weeks later (Jacquot et al., 2008). Although mifepristone has effects on progesterone receptors, as well as glucocorticoid receptors, a similar pattern was seen with another Type II glucocorticoid receptor antagonist that is selective for these receptors so it is highly likely that the effect was due to antagonism of the Type II receptors. Similar studies were carried out with dihydropyridine calcium channel antagonist, nimodipine. Either a single injection of this drug, given during the acute phase of alcohol withdrawal, or two weeks injections prior to alcohol withdrawal, prevented the loss of memory function measured in rats one month later during the abstinence phase (Brooks et al., 2008).

Our results show that it is possible to protect against the memory loss caused by prolonged alcohol intake and withdrawal by giving drugs selective for either the Type II glucocorticoid receptor or dihydropyridine-sensitive calcium channels, just during the acute phase of alcohol withdrawal. The alcohol treatment schedules used in our studies involved only a single withdrawal phase. The majority of alcoholics undergo frequent cycles of cessation and resumption of alcohol drinking and repeated withdrawal episodes are known to be

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associated both with greater cognitive deficits (Duka et al., 2003) and with increased risk of relapse drinking (Duka et al., 2004). It is possible that different results from those described above would be obtained if repeated withdrawal episodes were studied. However it is also possible that the use of drugs selective for glucocorticoid receptors or calcium channels during periods of cessation of alcohol drinking could have substantial benefits for alcoholics.

Central Nervous System Damage

CNS injury is one of the most widely studied consequences of alcohol abuse and dependence. As described above, alcohol dependence is associated with disruption of the HPA axis, in a manner that is clearly relevant to function of ethanol-sensitive NMDA-type glutamate receptors in particular and, more specifically, NR2 subunit function. It is clear that exposure to high concentrations of glucocorticoids may directly produce neurotoxicity or potentiate subsequent insults, including those characterized as excitotoxic, such as ethanol withdrawal (Mulholland et al., 2005). In these studies, organotypic hippocampal slice cultures were exposed to 50 mM ethanol and stress-relevant corticosterone concentrations for the duration of ethanol exposure and 24 hr of withdrawal. These and similar toxic effects of corticosteroid exposure are related, in part, to activation of glucocorticoid receptors (Abraham et al., 2001; Goodman et al., 1996; Mulholland et al., 2005) and corticosteroid-induced increases in the number or function of NMDA receptors or specific NR polypeptide subunits of NMDA receptors, even in the absence of concomitant ethanol exposure (Meyer et al. 2004; Takahashi et al. 2002; Weiland et al. 1997). Further, glucocorticoid exposure increases extracellular concentrations of glutamate (Abraham et al., 2001), suggesting a dual role for elevated HPA axis activation in promoting neuronal injury both in the presence and absence of ethanol exposure: increased expression of NMDA receptor subunits and increases release of the endogenous ligand glutamate.

Recent studies examined effects of binge-like ethanol exposure in vivo, employing a modified Majchrowicz (1975) model designed to produce peak blood ethanol levels of less than 200 mg/dl (described in Self et al., 2009). These studies demonstrate that thrice daily (every 8 hrs) gavage administration of ethanol with mean doses of approximately 8.5 g/kg/day to adult male rodents produce both metabolic tolerance, as evidenced by reduced peak blood ethanol levels following two days of ethanol administration, and physical dependence, as evidenced by significant ethanol withdrawal-associated behavioral abnormalities including seizure and tremor (Self et al., 2009). Significantly, more than a three-fold increase in plasma corticosterone levels was observed 60 min following ethanol administration on Day 2 of the 4-day administration regimen, as compared to control animals. Ethanol exposed rats obtained peak levels of approximately 150 ng/ml while control animals demonstrated peak levels of approximately 30 ng/ml. Marked tolerance to the HPA axis-activating effects of ethanol was observed (with administration of similar ethanol doses) by Day 4 of the regimen in that peak plasma corticosterone levels were approximately 50 ng/ml (vs 150 ng/ml on Day 2) in ethanol-exposed rats. In contrast, 12 hrs after the final ethanol administration, at the point of peak ethanol withdrawal-associated behavioral abnormalities, plasma corticosterone levels were elevated to nearly 200 ng/ml. Perhaps most interestingly, preliminary data were presented demonstrating that a single administration (s.c.) of the glucocorticoid receptor antagonist mifepristone (20 mg/kg) on the morning of each day of the 4 day ethanol exposure regimen significantly reduced the ethanol withdrawal-associated behavioral signs observed (data unpublished). Similar results were obtained by Jacquot et al. (2008) who used a longer period of alcohol administration.

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Conclusions

Research suggests that cortisol function is involved in motivation to drink, both within positive and negative reinforcement pathways. However, much of this research comes from animal models. The results from human research have been equivocal in establishing a clear understanding of cortisol and how it is involved in motivation triggered by stress, alcohol-related cues and alcohol priming. It is important to realize that when comparing data, many of the studies have used different participant populations, for example, dependent individuals wanting to abstain or those who wish to develop controlled drinking, and social drinkers with and without risk factors for alcohol dependence. The preceding discussion highlights the complexity of the potential role cortisol plays, both as a potential antecedent and consequence of hazardous drinking and as a key risk factor in the maintenance of excessive drinking and relapse. Human research is now needed which systematically looks at cortisol and motivation to drink alcohol while taking in to account factors such as drinking habits, personality characteristics and genetics. Such research could inform the development of multidisciplinary interventions and treatments for alcohol use disorders. For instance, initial work highlights that acamprosate might have some of its efficacy via its effect on cortisol function and its ability to reduce the alcohol priming effect.

The raised brain levels of glucocorticoid after withdrawal from chronic alcohol consumption have implications in several aspects of alcohol dependence. In view of the established neurotoxic effects of glucocorticoids (McEwen, 2000; Newcomer et al., 1999; Sapolsky, 1986; 1993; 1996a,b; 2000), it is likely that they play a major role in the cognitive deficits, as discussed below. In addition, high local concentrations of hormone could account at least in part for the reduced glucocorticoid release in response to stress during the abstinence phase, since there is feedback on the release of ACTH from the pituitary, which controls the adrenal glucocorticoid release. High brain concentrations of glucocorticoid may also influence alcohol consumption, in view of the experimental effects demonstrated in both voluntary drinking and operant studies. These results also demonstrate the importance of considering the whole system when studying HPA changes, including the potential for alterations in the CNS that do not originate from the periphery. Other examples of the value of comprehensive studies in this area are also described in this minireview, for example the changes in circadian rhythm for cortisol in alcoholics (Marchesi et al., 1977) and the delayed alterations in alcohol consumption after stress in rodent models (Little et al., 1999; Rockman et al., 1987; Volpicelli et al., 1986).

The prevention of the alcohol withdrawal-induced cognitive deficits by mifepristone and nimodipine show that the acute withdrawal phase could provide a window of opportunity for pharmacological treatments that would have prolonged effects. At present benzodiazepines or other anticonvulsant drugs are used to treat alcohol withdrawal symptoms. These are effective in protecting against the potentially lethal consequences of withdrawal seizures, but do not confer any benefit with respect to either alcohol consumption or cognitive deficits. Examination of the effects of other types of drugs could provide new approach to the treatment of alcohol dependence. It is intriguing to suggest that volumetric abnormalities associated with long-term dependence may reflect corticosteroid-associated elevations in glutamatergic activity during periods of repeated ethanol withdrawal. These findings suggest that glucocorticoid receptor antagonism is a pharmacological strategy that deserves examination as it relates to both detoxification from alcohol dependence and in the possible amelioration of alcoholism-associated brain injury.

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