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Alcohol and lithium have opposing effects on the period and phase of the behavioral free-running activity rhythm

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ABSTRACT

Bipolar patients have a high prevalence of comorbid alcohol use and abuse disorders, while chronic alcohol drinking may increase the presence and severity of certain symptoms of bipolar disorder. As such, there may be many individuals that are prescribed lithium to alleviate the manic symptoms of bipolar disorder, but also drink alcohol concurrently. In addition, both alcoholics and individuals with bipolar disorder often exhibit disruptions to their sleep-wake cycles and other circadian rhythms. Interestingly, both ethanol and lithium are known to alter both the period and the phase of free-running rhythms in mammals. While lithium is known to lengthen the period, ethanol seems to shorten the period and attenuate the responses to acute light pulses. Therefore, the present study aimed to determine whether ethanol and lithium have opposing effects on the circadian pacemaker when administered together. C57BL/6J mice were provided drinking solutions containing lithium, alcohol, or both, and their free-running rhythms along with their response to photic phase shifts were investigated. Mice treated with lithium displayed period lengthening, which was almost completely negated when ethanol was added. Moreover, ethanol significantly attenuated light-induced phase delays while the addition of lithium partially restored this response. These results indicate that alcohol and lithium have opposing effects on behavioral circadian rhythms. Individuals with bipolar disorder who are prescribed lithium and who drink alcohol might be inadvertently altering their sleep and circadian cycles, which may exacerbate their symptoms.

Introduction

Bipolar disorder has an approximate 33–50% comorbidity with substance abuse disorders, including alcoholism (Chengappa, Levine, Gershon, & Kupfer, 2000; Salloum et al., 2005). This alcohol comorbidity is associated with increased risk of suicide (Oquendo et al., 2010), decreased persistence (the ability to overcome frustration and fatigue) (Nery et al., 2008), increased impulsivity (Holmes et al., 2009), and increased depression (Cardoso et al., 2008). Interestingly, alcohol drinking may produce an earlier onset of manic episodes associated with bipolar disorder (Winokur et al., 1998), and an increase in the number of alcohol drinking days increases the likelihood of an individual experiencing a depressive episode (Jaffee et al., 2009).

Lithium is a commonly prescribed drug that can treat bipolar disorder. Historically, lithium was also used to reduce alcohol drinking in human alcoholics (Kline, Wren, Cooper, Varga, & Canal, 1974), which was corroborated by animal studies reporting that lithium reduces drinking in rodents (Ho, Tsai, & Kissin, 1975). However, lithium treatment does not seem to reduce alcohol intake in individuals who suffer from bipolar disorder (Dorus et al., 1989). Lithium is no longer used to treat alcoholics, as safer pharmaceuticals have been developed, such as naltrexone. Naltrexone treatment appears to be a useful treatment for individuals with bipolar disorder and comorbid alcoholism, as it produces decreases in alcohol drinking days, alcohol craving, manic episodes, and depressive symptoms (Brown, Beard, Dobbs, & Rush, 2006; Brown et al., 2009). Regarding drugs that are used to treat bipolar disorder, some have also been shown to be efficacious in treating alcohol dependence, while others have not. Valproate (an anticonvulsant) can reduce the frequency of heavy drinking days and can prolong time to relapse in alcohol-dependent bipolar patients (Brady, Sonne, Anton, & Ballenger, 1995). Carbamazepine, an anticonvulsant that potentiates GABA-A receptors, is effective in reducing relapse drinking and treating withdrawal in alcoholics with comorbid bipolar disorder (Malcolm et al., 2002). On the other hand,

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findings from several studies have shown that quetiapine (an antipsychotic, and a dopamine and serotonin antagonist) does not reduce alcohol consumption in patients with bipolar disorder and alcohol dependence (Guardia et al., 2011; Litten et al., 2012; Stedman et al., 2010). While both antipsychotics and anticonvulsants are both efficacious in treating bipolar disorder, it appears that GABA-A drugs are effective in treating both bipolar disorder and excessive alcohol drinking.

Many bipolar patients exhibit alterations in both their sleep cycles and biological clock, most commonly in the form of abnormally fast circadian rhythms (shortened period). It has been posited that part of the therapeutic effects of lithium may be through its ability to slow down the "fast clock" in those with bipolar disorder (Kripke, Mullaney, Atkinson, & Wolf, 1978) by lengthening the period of the circadian rhythm (Engelmann, 1972). However, not all bipolar patients respond to lithium treatment. Alterations to genes that regulate the circadian clock, such as *period2* (*per2*), *cryptochrome2*, and *reverb-α*, are associated with both bipolar disorder and lithium responsiveness (McCarthy, Nievergelt, Kelsoe, & Welsh, 2012; McCarthy et al., 2011). Additionally, lithium-induced increases in *per2* mRNA and protein levels, rather than changes in protein degradation or turnover rate, may be involved in the lengthening properties of lithium (Li, Lu, Beesley, Loudon, & Meng, 2012). Lithium treatment can also enhance the robustness of the clock by enhancing and resynchronizing a dampened rhythm, which may be present without the addition of a fast clock (McCarthy et al., 2013). Interestingly, both valproate (Johansson, Brask, Owe-Larsson, Hetta, & Lundkvist, 2011) and quetiapine (Moriya et al., 2014) can also lead to increases in *per2* levels without lengthening the circadian period, potentially indicating a common mechanism for therapeutic action. Together, these results implicate an increase in *period* protein expression, which is independent of the period lengthening properties of these compounds, and may be involved in their ability to improve circadian function and sleep in bipolar patients.

Alcoholics also show alterations in their sleep cycles, including decreased sleep time, shortened REM rhythms, and increased REM latency (Brower, 2001), as well as their circadian rhythms (Hasler, Smith, Cousins, & Bootzin, 2012). Abstinent alcoholics with insomnia are more likely to relapse than alcoholics without sleep problems (Brower & Perron, 2010). Sleep disturbances are a predictor of admission into an alcoholism treatment program (Wallen et al., 2014), and sleep problems during childhood can be a predictor of early alcohol drinking (Wong, Brower, & Zucker, 2009). Alcohol drinking also affects the biological clock. Alcoholics display reduced circadian gene expression in peripheral leukocytes (Huang et al., 2010), and alterations in their temperature (Danel, Libersa, & Touitou, 2001) and melatonin rhythms (Danel, Cottencin, Tisserand, & Touitou, 2009). Moreover, some human genetics studies (Dong et al., 2011; Spanagel et al., 2005; Wang et al., 2012) have shown that mutations in the *period* genes are associated with increased alcohol drinking.

In animal models, alcohol consumption produces alterations to the behavioral free-running activity rhythm under constant lighting conditions (i.e., constant darkness), although some of these effects seem to be species- and organism-dependent. For example, mice provided access to an ethanol-containing drinking solution display a significantly shortened circadian period (Seggio, Fixaris, Reed, Logan, & Rosenwasser, 2009), whereas the lengthening is often observed in hamsters under similar experimental conditions (Mistlberger & Nadeau, 1992). Wistar rats given access to ethanol in their drinking fluid exhibit period shortening (Dwyer & Rosenwasser, 1998), while Long-Evans rats can exhibit either period lengthening or shortening, depending upon their baseline circadian period (Rosenwasser, Fecteau, & Logan, 2005). Similarly, wild-type *Canton-S Drosophila melanogaster* have shorter free-running periods (Seggio, Possidente, & Ahmad, 2012), while *period* short flies (fruit flies with a mutation in the *period* gene which produces a severely short circadian cycle) show period lengthening, and *period* long mutants exhibit period shortening (Ahmad, Steinmetz, Bussey, Possidente, & Seggio, 2013) after larval alcohol exposure. There also appears to be genetic selection for both alcohol drinking and circadian rhythm phenotypes – rodents selectively bred for high-alcohol drinking exhibit alterations of circadian function compared to their low-drinking counterparts (Hofstetter, Grahame, & Mayeda, 2003; Rosenwasser, Fecteau, Logan, Reed, et al., 2005). In addition, P and HAD rats (lines that were selectively bred for increased alcohol consumption and preference) also exhibit shortening of their free-running period when exposed to an ethanol solution (Rosenwasser, McCulley, & Fecteau, 2014). These studies show a clear bidirectional relationship between alcohol drinking and circadian function, because alcohol drinking can modify circadian function, and alcohol-drinking phenotypes are associated with differences in circadian behavior compared to animals not selected for alcohol drinking.

Both chronic and acute alcohol treatment can alter the phase and timing of the rhythm by blunting the responsiveness of the pacemaker to photic input. While ethanol is known to produce reductions of light-induced phase responses consistently across all species, the specific phase that ethanol affects of this aspect of the biological clock *in vivo* is different among different species. Acute ethanol exposure through IP injections or chronic ethanol through a drinking solution blocks photic phase advances, but not delays in rats (Rosenwasser, Logan, & Fecteau, 2005) and hamsters (Ruby, Brager, DePaul, Prosser, & Glass, 2009; Ruby, Prosser, DePaul, Roberts, & Glass, 2009; Seggio, Logan, & Rosenwasser, 2007), while alcohol treatment blocks phase delays and not advances in mice (Brager, Ruby, Prosser, & Glass, 2010; Seggio et al., 2009). Because ethanol is a glutamate antagonist, one way ethanol affects the phase of the circadian clock is through modulating glutamatergic signaling from the retina to the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract (RHT). Indeed, the application of ethanol to mouse SCN slices held *in vitro* completely blocks glutamatergic phase advances and delays (Prosser, Mangrum, & Glass, 2008), providing insight on the mechanism of how ethanol manipulates the phase of the biological clock. While the reason why alcohol blocks both phase advances and delays *in vitro*, while blocking only delays or advances *in vivo*, is relatively unknown, these differences may be due to the organisms' behavioral free-running circadian period. Organisms, such as rats and hamsters, with average circadian periods longer than 24 h show larger phase advances, while mice, which exhibit periods shorter than 24 h, show larger phase delays (Daan & Pittendrigh, 1976). Ethanol selectively attenuates the larger phase responses in these animal species. Parameters that modify the period or the phase of the circadian rhythm are said to be affecting the underlying circadian pacemaker itself, rather than some secondary effector mechanism (Rosenwasser, 2001; Turek, 1987).

Individuals with bipolar disorder and co-morbid alcohol use were more likely to be morning-type (Hätönen, Forsblom, Kieseppä, Lönnqvist, & Partonen, 2008), while individuals with only a bipolar diagnosis are more likely to be evening-types (Giglio et al., 2010; Wood et al., 2009). These results suggest that chronic alcohol intake leads to more morning-type preference, which fits with the hypothesis that chronic alcohol drinking alone most likely produces a shortening of the circadian period in humans (Danel et al., 2009) and in many animal studies (see above). This trend might further exacerbate the poor sleep (reduced REM, total sleep time) already associated with mania (Krystal, Thakur, & Roth, 2008). Although quetiapine is not useful in treating alcohol drinking in