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Locus coeruleus neuronal activity determines proclivity to consume alcohol in a selectively-bred line of rats that readily consumes alcohol

Charles H.K. West [a], Katherine A. Boss-Williams [a], James C. Ritchie [b], Jay M. Weiss [a,*]

[a] Department of Psychiatry and Behavioral Sciences, Emory University, School of Medicine, Woodruff Memorial Research Building (WMB), 4th Floor, 101 Woodruff Circle, Atlanta, GA 30322, USA
[b] Department of Pathology, Emory University, School of Medicine, Woodruff Memorial Research Building (WMB), 4th Floor, 101 Woodruff Circle, Atlanta, GA 30322, USA

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ABSTRACT

Sprague–Dawley rats selectively-bred for susceptibility to stress in our laboratory (Susceptible, or SUS rats) voluntarily consume large amounts of alcohol, and amounts that have, as shown here, pharmacological effects, which normal rats will not do. In this paper, we explore neural events in the brain that underlie this propensity to readily consume alcohol. Activity of locus coeruleus neurons (LC), the major noradrenergic cell body concentration in the brain, influences firing of ventral tegmentum dopaminergic cell bodies of the mesocorticolimbic system (VTA-DA neurons), which mediate rewarding aspects of alcohol. We tested the hypothesis that in SUS rats alcohol potently suppresses LC activity to markedly diminish LC-mediated inhibition of VTA-DA neurons, which permits alcohol to greatly increase VTA-DA activity and rewarding aspects of alcohol. Electrophysiological single-unit recording of LC and VTA-DA activity showed that in SUS rats alcohol decreased LC burst firing much more than in normal rats and as a result markedly increased VTA-DA activity in SUS rats while having no such effect in normal rats. Consistent with this, in a behavioral test for reward using conditioned place preference (CPP), SUS rats showed alcohol, given by intraperitoneal (i.p.) injection, to be rewarding. Next, manipulation of LC activity by microinfusion of drugs into the LC region of SUS rats showed that (a) decreasing LC activity increased alcohol intake and increasing LC activity decreased alcohol intake in accord with the formulation described above, and (b) increasing LC activity blocked both the rewarding effect of alcohol in the CPP test and the usual alcohol-induced increase in VTA-DA single-unit activity seen in SUS rats. An important ancillary finding in the CPP test was that an increase in LC activity was rewarding by itself, while a decrease in LC activity was aversive; consequently, effects of LC manipulations on alcohol-related reward in the CPP test were perhaps even larger than evident in the test. Finally, when increased LC activity was associated with (i.e., conditioned to) i.p. alcohol, subsequent alcohol consumption by SUS rats was markedly reduced, indicating that SUS rats consume large amounts of alcohol because of rewarding physiological consequences requiring increased VTA-DA activity. The findings reported here are consistent with the view that the influence of alcohol on LC activity leading to changes in VTA-DA activity strongly affects alcohol-mediated reward, and may well be the basis of the proclivity of SUS rats to avidly consume alcohol.

Introduction

In our laboratory, we have selectively bred albino Sprague–Dawley rats for being differentially susceptible to stress. We selectively bred rats for showing susceptibility to having their motor activity in a swim test reduced after they had been exposed to a stressful event (which we called “Swim-test Susceptible” or “SUS” rats), and also, in parallel, selectively bred rats for showing resistance to having their activity in a swim test reduced by stress (called “Swim-test Resistant” or “RES” rats) (Scott, Cierpial, Kilts, & Weiss, 1996; West & Weiss, 2005). The SUS and RES lines of rats, now maintained for over 50 generations since their inception, show, respectively, less swim-test activity after exposure to a

* Corresponding author. Emory University, School of Medicine, Department of Psychiatry and Behavioral Sciences, Woodruff Memorial Research Building (WMB), Suite 4103, 101 Woodruff Circle, Atlanta, GA 30322, USA. Tel.: +1 404 712 9772.
E-mail address: jweis01@emory.edu (J.M. Weiss).

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stressor than do randomly-bred (normal) rats, and more swim-test activity after exposure to a stressor than do randomly-bred (normal) rats. After the lines had been in existence for several years, we discovered (19th generation) that SUS rats voluntarily consume large amounts of alcohol. In over 30+ subsequent generations, we have observed SUS rats to consume large amounts of alcohol, in fact consuming similar amounts of alcohol to rat lines that have been specifically bred for the proclivity to consume alcohol (see discussion in West & Weiss, 2006). SUS rats do this even though consumption of alcohol had not played any part in the selective breeding development of the SUS rat. In comparison, normal Sprague–Dawley rats (and also RES rats) show notable resistance to consuming any alcohol voluntarily.

This paper describes studies that investigated possible neural events underlying the proclivity of SUS rats to avidly consume alcohol. The mesocorticolimbic dopaminergic system, originating from dopaminergic neurons in the ventral tegmentum (VTA-DA neurons), which project to prefrontal cortex and nucleus accumbens (NAC), has long been associated with the reinforcing actions of drugs of abuse. We first considered this system. Alcohol stimulates activity of VTA-DA neurons (Brodie, Pesold, & Appel, 1999; Brodie, Shefner, & Dunwiddie, 1990; Doyon et al., 2003; Imperato & Di Chiara, 1986; Melis, Diana, Enrico, Marinelli, & Brodie, 2009; Xiao et al., 2009), and activation of VTA-DA neurons has been associated with ethanol-induced reward (Gessa, Muntoni, Collu, Vargiu, & Mereu, 1985; McBride et al., 1991; Nowak, McBride, Lumeng, Li, & Murphy, 2000; Rodd et al., 2005). VTA-DA neuronal activity is higher in rats that drink significant amounts of alcohol compared to rats that do not drink alcohol; such studies have assessed VTA-DA activity in high responders to novelty vs. low responders (Marinelli & White, 2000), Lewis vs. Fischer 344 rats (Minabe, Emori, & Ashby, 1995), P vs. NP rats (Morzorati, 1998; Morzorati & Marunde, 2006), and Sardinian alcohol-preferring vs. non-preferring rats (Melis, Diana, et al., 2009; Melis, Pillolla, et al., 2009). High alcohol-seeking behavior is also associated with lower content of dopamine (DA) in the NAC (McBride, Bodart, Lumeng, & Li, 1995; McBride et al., 1991; Murphy, McBride, Lumeng, & Li, 1987; Murphy et al., 2002; reviewed in McBride & Li, 1998), which will induce higher activity in VTA-DA neurons of alcohol-preferring animals insofar as low DA levels in NAC will not exert normal "end-product negative feedback" and thus will lead to elevated VTA-DA activity. Interestingly, we have found that SUS rats, like some other alcohol-preferring lines, also have notably lower DA content in NAC than do normal and RES rats (Weiss et al., 2008). Therefore, evidence points to VTA-DA activity as mediating the reward produced by alcohol.

A brain region that plays an important role in regulating activity of VTA-DA neurons is the locus coeruleus (LC), site of the major concentration of noradrenergic cell bodies in the brain. Via axonal projections to the ventral tegmentum, LC neurons can both stimulate and inhibit VTA-DA neurons. Low, steady levels of LC activity stimulate VTA-DA neurons by norepinephrine release (NE) onto alpha-1 receptors (Andén & Grabowska, 1976; Donaldson, Dolphin, Jenner, Marsden, & Pycock, 1976; Grenhoff, Nisell, Ferré, Aston-Jones, & Svensson, 1993; Grenhoff & Svensson, 1993), while high rates of LC activity, particularly burst firing of LC, dramatically inhibit VTA-DA firing by causing release of the hyperpolarizing peptide galanin (GAL) from LC terminals in the VTA (Grenhoff et al., 1993). The latter condition may play a significant role in causing depression: we have proposed that elevated LC activity, which is seen in stressed animals and in human depression, brings about many of the behavioral changes in depression through inhibition of VTA-DA neuronal activity as a result of GAL being released from LC terminals in VTA due to excessive LC burst firing (Weiss, Bonsall, Demetrikopoulos, Emery, & West, 1998; Weiss et al., 2005; Weiss, Demetrikopoulos, West, & Bonsall, 1996). This LC-to-VTA-DA neuronal circuit also could be highly relevant to alcohol consumption. Studies have found that ethanol inhibits LC activity (Pohorecky & Brick, 1977; Strahlendorf & Strahlendorf, 1983), and Aston-Jones, Foote, and Bloom (1982) showed that ethanol predominantly inhibits sensory-evoked burst firing of LC neurons. Consistent with this, c-Fos activation of LC neurons was less in alcohol-preferring lines of rats (P, AA) than in non-preferring lines (NP, ANA) in response to high doses of ethanol (Thiele, van Dijk, & Bernstein, 1997), this difference in alcohol-induced LC activation being the one consistent effect these investigators found that distinguished both alcohol-preferring lines they studied from both non-preferring lines. Thus, the propensity of alcohol to reduce LC activity could be important in determining alcohol-mediated reward, through reduction of LC-mediated inhibition of VTA-DA activity.

Based on the foregoing, we tested the following: insofar as high rates of LC activity will inhibit VTA-DA neuronal activity and low rates of LC activity stimulate VTA-DA neurons, reducing LC activity should facilitate alcohol reward and consumption by disinhibiting and/or stimulating VTA-DA neuronal activity to enhance alcohol-derived reward, and increasing LC activity, particularly burst firing, should have the opposite effect on alcohol reward. First, we measured the effect of alcohol, given by i.p. injection, on single-unit electrophysiological activity of LC and then on VTA-DA neurons. After finding that alcohol markedly decreased LC activity and also increased VTA-DA activity in SUS rats, we manipulated LC activity by microinfusion of drugs into LC to determine whether this would affect voluntary alcohol consumption by SUS rats. We then tested whether one could demonstrate that alcohol was rewarding for SUS rats in the conditioned place preference (CPP) test. We note that it has been quite difficult to demonstrate that any rat, even lines of alcohol-preferring rats, experience a rewarding effect of alcohol in the CPP test (Busse, Lawrence, & Riley, 2005; Ciccocioppo, Panocka, Froldi, Quitadamo, & Massi, 1999; Matsuzawa, Suzuki, & Misawa, 1998; Quertemont & De Witte, 2001; Stewart, Murphy, McBride, Lumeng, & Li, 1996); thus, a positive finding in SUS rats would be noteworthy. Lastly, we again manipulated LC activity by microinfusion of drugs into LC to determine if this would alter reward that SUS rats experienced in the CPP test, and also to determine what effects the conditioning experience that rats underwent during the CPP procedure would have on their subsequent voluntary alcohol consumption.

Materials and methods

Animals

Rats were male, albino Sprague–Dawley rats, 3–6 months of age at the time of procedures and testing, and weighing 350–600 g. Rats were bred and housed in our rat colony on the Briarcliff Campus of Emory University. Rats were from the Swim-test Susceptible (SUS) rat line developed in our laboratory and also from randomly-bred (non-selected, normally-bred) rats that have been maintained in our colony under the same conditions. Details of the selective breeding procedure for the SUS line and also for the Swim-test Resistant (RES) line have been given previously (Scott et al., 1996; West & Weiss, 2005). Briefly, rats were selected for breeding based on the amount of activity (specifically, duration of "struggling" behavior) observed in a swim test immediately after the animals were exposed to an acute stressor. Struggling behavior is vigorous escape-directed behavior in which all four limbs are in motion with the front limbs breaking the surface of the water. SUS rats were chosen for breeding based on their showing a large decrease in struggling after exposure to the stressor compared to nonstressed littermates. The parallel line of RES rats were chosen