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Short communication

Initial ethanol exposure results in decreased heart rate variability in ethanol-naive rhesus monkeys

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Abstract

Ethanol's effects on heart rate variability may contribute to the increased cardiac disease and mortality observed in alcoholics. We assessed cardiac response to ethanol in seven previously ethanol-naive monkeys given a standard dose of ethanol, or saline. Ethanol exposure reduced cardiac signal complexity [mean ± S.D. (ethanol: Hurst parameter = 0.39 ± 0.02; saline: Hurst parameter = 0.32 ± 0.06)] and increased the spectral exponent (ethanol: $\beta = 1.36 \pm 0.35$; saline: $\beta = 1.12 \pm 0.35$) when compared to saline, while heart rate itself was unaffected (saline: interbeat interval = 303.57 ± 24.57; ethanol: interbeat interval = 308.14 ± 20.45). Taken together with data that show autonomic disregulation in alcoholics, these findings provide further evidence of deleterious ethanol effects on cardiac signal dynamics. © 2001 Published by Elsevier Science B.V.

Keywords: Ethanol; Heart rate; Dynamics, nonlinear

1. Introduction

Human studies rarely address the effects of initial ethanol exposure by measuring response to the drug in ethanol-naive subjects. As a result, it is often difficult to dissociate either the premorbid factors that influence the pathogenesis of alcoholism, or the cumulative and interactive effects of continued ethanol exposure, from its initial effects. Uncovering both the mechanisms for ethanol effects, as well as individual differences in vulnerability (or resilience), requires characterization of the result of first ethanol exposure. Controlling for differences in experiential histories with ethanol, as well as the ethical issues inherent in giving naive humans their first ethanol exposure as part of an experimental protocol, provide a compelling rationale for using monkeys to study initial response to ethanol administration. Old World monkeys show a close behavioral, physiological, and genetic similarity to humans that extends to their responses to ethanol, as well as to risk factors for excessive ethanol consumption (Juarez et al., 1993; Kraemer and McKinney, 1985; Higley et al., 1991, 1996a,b; Higley and Bennett, 1999).

In humans, acute ethanol administration consistently results in decreased heart rate variability (Koskinen et al., 1994; Rossinen et al., 1997; Sehesterd et al., 1998). After chronic excessive ethanol use, heart rate variability is decreased (DePetrillo et al., 1999b), suggesting that the increased cardiac disease and mortality observed in alcoholics (Miralles et al., 1995; Murata et al., 1994) may result from altered cardiac rhythm regulation. Inasmuch as the duration of the pharmacodynamic effects of ethanol on cardiac signal dynamics is unknown, the results of these previous studies may be confounded by their measurement of the acute effects of ethanol in human subjects who, although not alcoholic, were not ethanol-naive.

In the study reported here, we used ethanol-naive, adolescent rhesus monkeys to assess acute initial cardiac response to ethanol. To accomplish this, we administered a standard dose of ethanol or an equivalent volume of saline

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under restraint conditions. A single, high-dose of ethanol was used in an initial attempt to determine the effect of a clinically relevant ethanol exposure on cardiac function. Cardiac signal dynamics were measured by calculating the Hurst parameter of the electrocardiographically derived interbeat interval time-series (see DePetrillo et al., 1999a) as a measure of the magnitude of statistical autocorrelation. Previous studies in human (DePetrillo et al., 1999b) and nonhuman primates (DePetrillo et al., 2000) demonstrate that the Hurst parameter provides a more sensitive index of drug effects than does heart rate alone.

2. Methods

2.1. Subjects

Seven ethanol-naive rhesus monkeys (*Macaca mulatta*, four male and three female) between 35 and 42 months of age (mean ± S.D. = 40.2 ± 2.41) at the onset of testing served as subjects. Subjects were socially housed with age-mate peers in indoor:outdoor runs at the time of testing. All animal procedures were approved by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Animal Care and Use Committee (protocol #LCS 75). The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.2. Experimental procedure

To begin testing, each subject was caught and briefly restrained for intravenous infusion of saline or ethanol. No fewer than 8 days lapsed between the two test sessions. After 5 min of restraint, either drug (16.8% ethanol/saline solution, 2.1 g/kg for males, or 2.0 g/kg for females) or saline (equivalent volume) infusion began and continued at a constant rate over 15 min. Saphenous blood samples obtained 5 min after the infusion were assayed for blood ethanol concentrations. Electrocardiographic (ECG) interbeat interval data was collected during restraint and infusion. The procedure for data collection is described elsewhere (DePetrillo et al., 2000); briefly, gel ECG electrodes were placed on its limbs and/or sides, were connected to a MM Polar XR (Mini-Mitter, SunRiver, OR) transmitter with a Mini-Logger Series 2000 receiver (Mini-Mitter) which was used to collect the interbeat interval data.

2.3. Data analysis

Interbeat interval data, in milliseconds, were retrieved from the Mini-Logger receiver and were filtered using linear interpolation if any single interbeat interval was more than twice the magnitude of the previous interbeat interval. The maximum number of data points requiring adjustment for any interbeat interval time series examined was 7.6% of the total number of interbeat interval data points. Data were analyzed using an algorithm described elsewhere (DePetrillo et al., 1999a) which extracts the Hurst exponent of the time-series. Interbeat interval time series were also analyzed in the frequency domain using a Fast Fourier Transform and spectral analysis by means of TSAS Version 3.01.01b. (Yamamoto and Hughson, 1991). The relative contribution of the high-frequency components of each interbeat interval time series was determined by calculating the spectral exponent, β (Yamamoto and Hughson, 1993). This is simply the negative slope of the least-mean square fit of the linear portion of the relationship:

$$\log\ (\text{Power Spectral Density}) = -\beta \log(f) + c$$

where f is frequency in Hz, power is in ms^2/Hz and c is a constant.

The acute effect of ethanol was assessed by repeated-measures analysis of variance for the Hurst parameter, spectral exponent, and interbeat interval.

3. Results

Ethanol exposure significantly reduced cardiac signal complexity (mean ± S.D. = 0.39 ± 0.02) when compared to saline values (0.32 ± 0.06), $F(1, 6) = 9.51$, $P = 0.02$ (Figs. 1 and 2A). A similar increase was evident in the spectral exponent for ethanol (1.36 ± 0.35) compared to saline (1.12 ± 0.35) $F(1, 6) = 8.39$, $P = 0.03$ (Fig. 2B). By contrast, heart rate was unaffected by intravenous ethanol infusion, (saline: 308.14 ± 20.45; ethanol: 303.57 ± 24.57), $F(1, 6) = 0.41$, P = 0.54 (Fig. 2C). The ethanol infusion produced mean blood ethanol concentrations of 0.28 mg/dl (S.D. = 0.04, range 0.22–0.34). Blood ethanol concentration was not

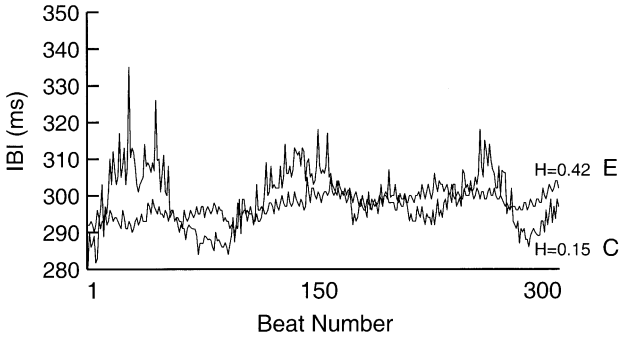

Fig. 1. The interbeat interval time-series and corresponding Hurst parameter values from one monkey undergoing saline (A) and ethanol infusion (B) are shown to illustrate the effect of ethanol on cardiac measures. The *y*-axis shows the magnitude of each interbeat interval and value of the Hurst parameter X 1000. The arrows point to the beat number at which ethanol or saline infusion began.

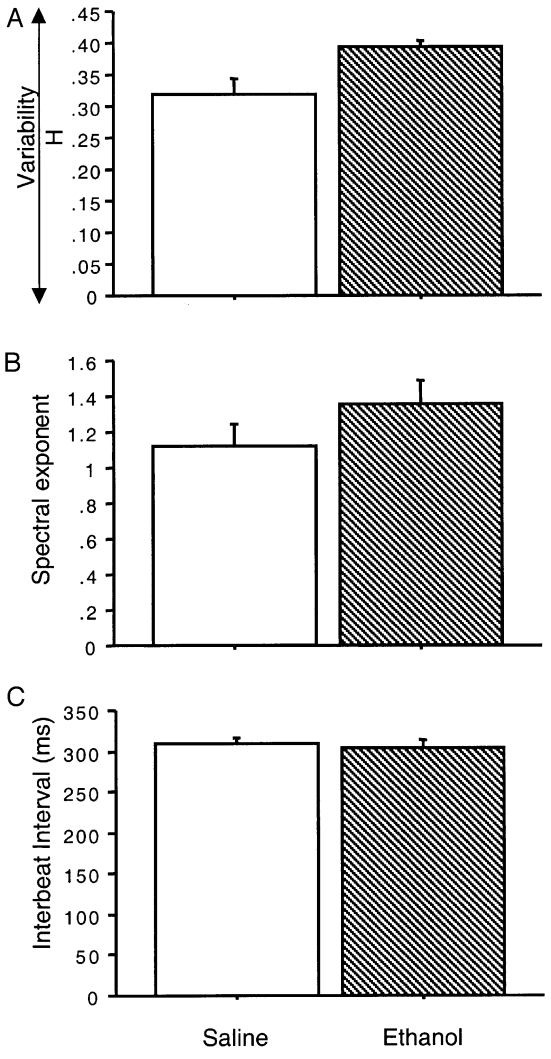

Fig. 2. (A) Mean Hurst parameter after intravenous saline (open bar) and ethanol infusions (striped bar). Ethanol administration resulted in significant increases in the Hurst parameter, $F(1, 6) = 1.82$, $P = 0.005$. (B) Mean spectral exponent after intravenous saline (open bar) and ethanol infusions (striped bar). Spectral exponent was significantly increased after ethanol administration, $F(1, 6) = 1.82$, $P = 0.005$. (C) Mean interbeat interval after intravenous saline (open bar) and ethanol infusions (striped bar). Interbeat interval was not significantly influenced by ethanol administration relative to saline control, $F(1, 6) = 0.41$, $P = 0.54$.

correlated with either measure of cardiac response to ethanol, $P > 0.10$.

4. Discussion

The data reported here are the first to show a decrease in heart rate variability in ethanol-naive animals following an initial administration of ethanol. Heart rate variability as measured by both the Hurst parameter and the spectral exponent, β, was significantly decreased by an initial dose of ethanol that produced blood ethanol concentrations within the range reported for binge drinking, particularly in adolescents and young adults. Multiple measures derived from ECG interbeat interval data have been used to index cardiovascular health and to assess potential deleterious drug effects. We found that both the Hurst parameter, a measure of cardiac signal complexity estimated as the Hurst parameter of the interbeat interval time series, and the spectral exponent β resulted in better measures of ethanol's effect on cardiac rhythm, while heart rate alone failed to differentiate the drug effect. Although heart rate did not appear to provide a sensitive measure of the drug effect, it is also possible that the small sample size may have resulted in Type II error and hence, a failure to detect a difference for this measure. Our results, however, are consistent with the previous finding that human alcoholics, tested while ethanol-free, showed an increased Hurst parameter, but no difference in heart rate, when compared to nonalcoholic controls.

In humans, parasympatholysis with atropine administration has been shown to increase β and increase in H, a result of vagal blockade (Yamamoto et al., 1995). Although peripheral nervous system (PNS) blockade decreases measures of heart rate variability, alterations of heart rate variability as a function of decreased PNS activity do not occur in the absence of central nervous system (CNS) input and modulation (Bailey et al., 1996; Setty et al., 1998). The increase in spectral exponent β seen in this study can be attributed to a relative decrease in the high-frequency components of the interbeat interval time series. These data suggest that acute ethanol administration is likely associated with a decrease in parasympathetic outflow, but this should be interpreted carefully, as it does not exclude the possibility that the feedback between the peripheral and central nervous system components that determine heart rate variability was also altered by ethanol. It has previously been shown in a denervated dog model that direct stimulation of vagal efferents resulted in predictable increases in heart rate and high-frequency components of the interbeat interval time series, but in the absence of central modulation, there was no effect of vagal stimulation on measures of heart rate variability (Bailey et al., 1996), even while interbeat interval magnitude increased. Thus, while decreases in heart rate variability resulting from acute ethanol exposure may be due to a decrease in PNS activity, the possibility exists that an alteration in feedback between central and peripheral determinants of heart rate might also have been present.

Taken together with human data that show autonomic disregulation in alcoholics, these findings provide further evidence of the disruptive effects of ethanol on autonomic function and suggest that such toxicity may not require an extended period of repetitive ethanol administration or be due to other factors associated with excessive consumption in humans. These findings underscore the importance of studying ethanol-naive individuals in order to understand the mechanism that produce physiological risk factors for vulnerability to ethanol abuse and alcoholism. Emerging epidemiologic evidence supports the hypothesis that binge drinking is strongly associated with sudden death (Britton and McKee, 2000). After myocardial infraction, decreased

heart rate variability is known to be risk factor for sudden death (Hohnloser et al., 1999). Along with the current results, this suggest that binge ethanol exposure may predispose the myocardium to electrical instability, which may be expressed as decreased heart rate variability after acute ethanol consumption. While alcoholics have decreased measures of heart rate variability as determined by the Hurst parameter measured 48 h after the last episode of ethanol consumption in the absence of symptoms consistent with ethanol withdrawal syndrome, the longevity of ethanol effects on heart rate variability remains undetermined (DePetrillo et al., 1999b). Similarly, the dose–response relationship for ethanol's effect on cardiac function and possible individual determinants influencing its potential cardiac toxicity, including identification of the threshold for alteration of heart rate, remains for future study.

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