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# Ethanol and Circadian Rhythms in the Syrian Hamster: Effects on Entrained Phase, Reentrainment Rate, and Period

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MISTLBERGER, R. E. AND J. NADEAU. *Ethanol and circadian rhythms in the Syrian hamster: Effects on entrained phase, reentrainment rate, and period.* PHARMACOL BIOCHEM BEHAV 43(1) 159–165, 1992. – Wheel-running rhythms were examined in male hamsters with access to 28% ethanol in lieu of water. One group was recorded in a light–dark (LD) cycle that was phase advanced by 8 h on three occasions separated by 23–27 days. On two of the three occasions, hamsters were subjected to a 2- to 3-h cage change procedure designed to stimulate wheel running, which accelerates the rate of reentrainment to 8-h advances. Ethanol and control hamsters showed no group differences in rhythm amplitude, entrained phase, or reentrainment rate. Both groups showed faster reentrainment in the cage change condition. A second group of hamsters recorded in constant dim showed a small but significant lengthening of the free-running period of their wheel-running rhythm when provided with a 28% ethanol solution. Wheel running decreased during ethanol access in this group. Voluntary ethanol consumption evidently can slow the circadian pacemaker regulating activity rhythms in hamsters but has no measurable effect on photic entrainment or pacemaker response to LD shifts or nonphotic manipulations (stimulated activity). Period lengthening may be secondary to decreased activity, but other period–activity correlations obtained did not reveal a strong association between these two variables.

Circadian rhythms  Entrainment  Wheel running  Nonphotic zeitgebers  Ethanol  Syrian hamster

DAILY rhythms in mammals are regulated by a system of internal circadian (approximately 24 h) clocks (pacemakers, oscillators) that can be synchronized (entrained) by periodic photic and nonphotic stimuli (zeitgebers) (35,41). Disorder within this circadian timekeeping system has been implicated in the pathogenesis of depression and insomnia (8,49), and misalignment between internal clocks and external zeitgebers (primarily the day–night cycle) is experienced by travelers and shift workers as "jet lag," with attendant difficulties in sleep, arousal, and digestive processes (18,36).

Current approaches to mitigating circadian disorders include identifying natural zeitgebers and drugs that can be used to rapidly shift the phase of circadian rhythms. The primary zeitgeber for most species is the daily light–dark (LD) cycle, but a number of nonphotic zeitgebers, including daily cycles of temperature, social cues, restricted food availability, and exercise (33,35,37,41), can also phase shift or entrain daily rhythms in various species. Chemical agents that can alter rhythm phase or period ($\tau$) include cholinergic (10) and GABAergic agonists (21,44,46–48), excitatory amino acids (31), neuropeptides (1), and several less specific psychoactive agents (5,12,20,26,40).

If drugs and natural zeitgebers are to be incorporated into schedules for regulating circadian rhythms, the nature of interactions among these agents and other commonly used drugs will need to be specified. This study is concerned with one of the most commonly used drugs, ethanol. Despite its wide use, the data base on ethanol and mammalian circadian rhythms is surprisingly limited. Nonetheless, a range of observations suggest that ethanol may alter circadian rhythms. First, acute or chronic application of ethanol can shift the phase or alter $\tau$ of circadian rhythms in several invertebrate organisms (6,13,19,25,45). Second, in vertebrates ethanol interacts with the GABA–benzodiazepine (BDZ) receptor complex (9), which in hamsters mediates the circadian phase-shifting effects of BDZs (48) and muscimol (44). Ethanol also interacts with NMDA receptors (9), which may mediate the effects of light on circadian rhythms (7). Third, ethanol alters membrane permeability to $K^+$ (9), and other treatments that alter $K^+$ gradients have been shown to alter circadian rhythms in several species (6,19,26,28).

Circadian studies of ethanol ingestion in mammals have focused primarily on the daily distribution of ethanol intake and metabolism in mice and rats. Voluntary ethanol consump-

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tion in these rodents is nocturnal (14,15,16,42); ethanol thus clearly does not preclude the expression of circadian rhythms of fluid ingestion. However, other studies have reported a flattening of the daily rhythms of corticosterone (24), food intake, and activity (4), and at least one study observed a delay of the entrained phase of feeding and drinking rhythms in mice (17), although inspection of raw data from a similar study did not confirm this result (32). One study of human alcoholics reported a significant delay of the daily cortisol rhythm during abstinence (22), but another study of abstaining alcoholics reported an advance of the core body temperature rhythm, although this was confounded with depression in at least some of the subjects (27). Only two studies have assessed the effects of ethanol on $\tau$ of circadian rhythms in a mammalian species (23,51). Both studies, reported in preliminary form, found that voluntary consumption of 20–25% ethanol in hamsters was associated with a lengthening of $\tau$ of the free-running activity rhythm recorded in constant dark (DD). One of the studies further showed that the phase-shifting effect of the benzodiazepine triazolam was attenuated by chronic ethanol consumption (23).

These studies suggest that ethanol does effect the mammalian circadian system, possibly altering the amplitude, phase, or $\tau$ of circadian rhythms, depending upon the procedures and species used and the specific rhythms monitored. However, the effects appear modest and in some cases inconsistent or lacking quantification. Moreover, a comprehensive examination of these effects in a single species is lacking. This study used several procedures and analytic methods designed to assess the effect of ethanol on the entrained phase, amplitude, and free-running $\tau$ of the circadian activity rhythm in the Syrian hamster, a species notable for a robust wheel-running rhythm and an avidity for ethanol in concentrations up to 40% (2,29). In addition, the effects of ethanol on the rate of reentrainment to a shifted LD cycle were examined both in undisturbed hamsters and in hamsters subjected to a 2- to 3-h "exercise" procedure (wheel running induced by cage changing) that has been shown to greatly accelerate the reentrainment process (38).

## METHOD

### *Animals and Apparatus*

Fifty adult, male Syrian hamsters were used (120–160 g; Charles River, Montreal). Animals were housed individually in plastic, wire-bottomed cages (47 × 26 × 20 cm) equipped with running wheels (17 cm diameter). Wheel revolutions were detected by mechanical microswitches or interruption of an infrared photobeam and were monitored continuously by an AppleIIe computer. Activity counts were summed and saved to disc at 10-min intervals.

### *Procedure*

*Experiment 1.* Twenty hamsters were recorded under an LD cycle (14 h at 70–270 lux fluorescent light, 10 h at $<1$ lux dim red incandescent light) for 40 days with free access to food (Purina rodent chow) and water. Ten hamsters then received a 28% ethanol solution in place of water for the remainder of the study. Fluid intake in the ethanol and water groups was measured every other day at various times early in the dark period. Ethanol was topped up at that time and was completely replaced once per week. Ethanol concentrations varied by less than 1% between replacements.

After 26 days, all 20 hamsters were subjected to an 8-h advance of the LD cycle, starting with an advance of the dark period. In half the animals (five ethanol and five water), this advance was combined with a cage change procedure whereby animals were manually transferred into the wheel of a clean Wahmann activity cage for 2 h beginning at dark onset on the first day of the phase advance. This procedure was intended to stimulate wheel running for that 2-h period. The other animals were left undisturbed.

Twenty-three days were permitted for reentrainment to the new LD cycle. A second 8-h advance of the LD cycle then occurred, again combined with a cage change procedure using the same 10 animals as in the first shift. This cage change procedure differed in two ways. First, it lasted 3 h. Second, animals were transferred into the vacant cage of a neighboring hamster and confined to the running wheel area using a wire mesh barrier. Quiescent animals were gently prodded to encourage wheel running. These changes were designed to increase the amount of wheel running during the cage change, which was minimal during the first cage change test. Again, the other 10 hamsters were left undisturbed.

A third 8-h advance occurred 27 days later. This was again combined with the 3-h cage change procedure but using the 10 previously undisturbed hamsters. After 26 days, the LD cycle was replaced by constant dim (DD, $<1$ lux red) for 1 month.

*Experiment 2.* Thirty hamsters were recorded in the plastic, wire-bottomed cages for 7 days in LD 14 : 10, then for 70 days in DD. During the first 27 days in DD, 11 hamsters (EW group) received 28% ethanol in place of water. During the next 22 days, these hamsters were returned to water and the other 19 hamsters (WE group) were switched to 28% ethanol. During the last 22 days, all hamsters received only water.

### *Data Analysis*

Activity data were periodically downloaded from the AppleIIe to a MacIntosh FX for statistical and graphical analyses using Circadia (Behavioral Cybernetics, Cambridge, MA) and Systat (Systat, Inc., Evanston, IL). Activity data were plotted as standard actograms. The phase of entrainment to the LD schedule was quantified in two ways: first, as the time at which the daily wheel-running period began and, second, as the acrophase of a cosine function fit by linear least squares to the average waveform of a set of consecutive days. Wheel-running onset was defined as the first 10-min bin during which running exceeded 100 counts after a 240-min interval during which it did not exceed this level. The rate of reentrainment to the 8-h LD phase shifts was quantified as the number of days required for activity onset to begin within the range of onset times, expressed as differences from dark onset time, observed over the last 7 days prior to the LD shift. The period of free-running rhythms in DD was determined by the slope of a line fit by linear least-squares regression to computer-detected activity onsets over 10–14 consecutive days during the second and third weeks of the ethanol and water conditions. This was supplemented by a cosine spectrum analysis that measured periodicities by linear least-squares cosine fitting in those animals whose activity rhythms lacked precise activity onsets.

Statistical comparisons between ethanol and water groups were made using two-tailed $t$-tests for independent means. Comparisons within groups (ethanol vs. water conditions) were made using paired $t$-tests. Significant levels were set using the Bonferroni adjustment for multiple tests where applicable. Pearson correlation coefficients were calculated to assess associations between $\tau$ and wheel-running levels.

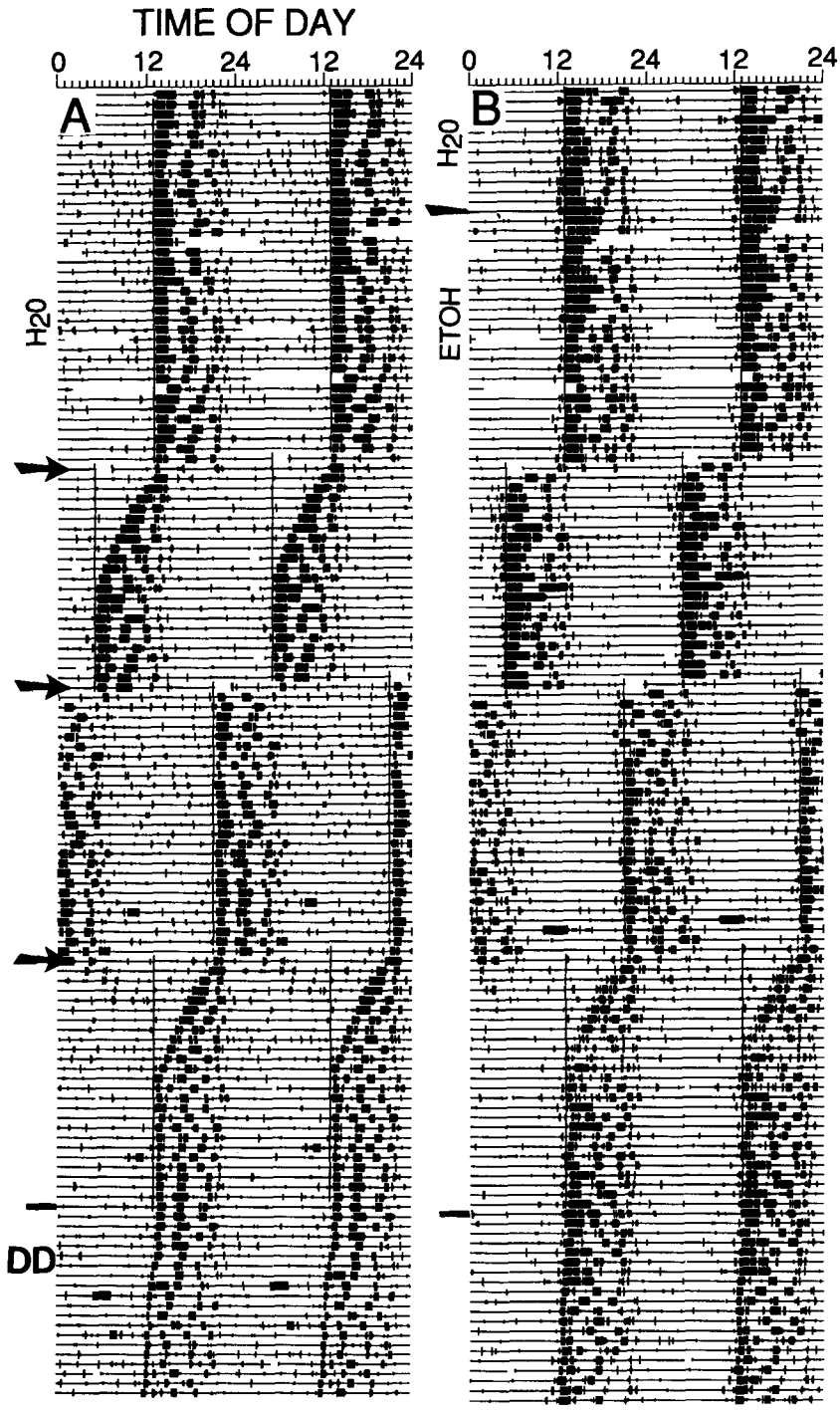


FIG. 1. Wheel-running activity charts of two hamsters from Experiment 1. Each line represents 2 consecutive days plotted in 10-min bins from left to right. Consecutive days are also aligned vertically. Bins during which activity counts were registered are indicated by vertical deflections from the zero activity line for each day. Lights-off time is indicated by the vertical lines. Both animals were subjected to three 8-h advances of the lights-off period occurring on the days indicated by the arrows on the left. (A) A control hamster receiving water throughout the study. During the first 8-h advance, the hamster was removed from its cage and placed in a Wahmann wheel for the first 2 h of dark on day 1. The animal did not run in the wheel. Reentrainment to the shifted LD cycle took 11 days. During the second 8-h advance, the hamster was transferred into another hamster's home cage for the first 3 h of dark on day 1. The animal did run in the wheel and reentrained within 2 days. During the last 8-h advance, the hamster was left undisturbed and took 11 days to reentrain. (B) A hamster with access to 28% ethanol beginning on the day indicated by the arrow. Procedures were the same as for animal A. This was the only hamster to reentrain within 2 days to both the first and second 8-h advances. When left undisturbed after the third 8-h advance, reentrainment took 9 days. Both hamsters were maintained in DD for the last 21 days.

TABLE 1

GROUP MEANS (± SD) FOR ACTIVITY ONSET, ACROPHASE, AND AMPLITUDE IN LD AND PERIOD AND WHEEL-RUNNING COUNTS IN DD

| Group | LD Activity Onset | LD Acrophase | LD Amplitude | $\tau$ DD | Wheel Counts/10 min DD |
|---|---|---|---|---|---|
| $H_20$ | 21:10 (16) | 17.66 (64) | 274 (78) | 23.95 (0.06) | 47 (23) |
| | :02 (13)* | −0.02 (0.19)* | 54 (112)* | | |
| EtOH | 21:12 (17) | 17.67 (72) | 258 (90) | 24.03 (0.12) | 65 (31) |
| | :05 (16)* | −0.01 (0.82)* | 69 (131)* | | |

*Group mean ± SD difference from baseline set of days; not significant ($p > 0.1$).

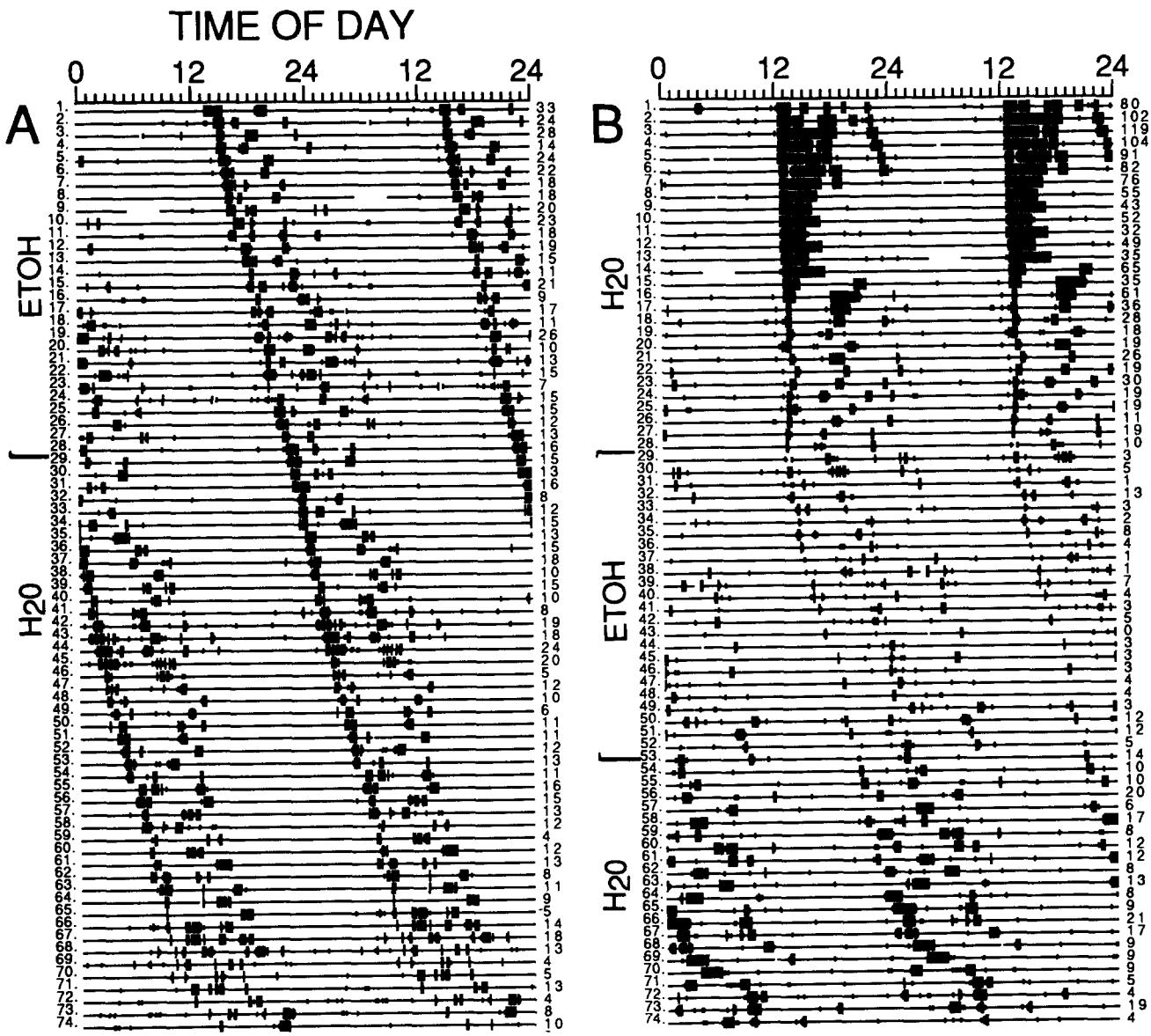


FIG. 2. Activity charts from two hamsters maintained in DD in Experiment 2. (A) A hamster from the EW group. Ethanol was provided for the first 28 days. This animal showed a stable $\tau$ of 24.23 h during both ethanol and water conditions. (B) A hamster from the WE group. This hamster showed a stable $\tau$ of 24.00 h until switched to ethanol, at which time $\tau$ lengthened to 24.30 h. This animal's rhythm became less precise during the last 3 weeks, when only water was available. See Fig. 1 for plotting conventions.

## RESULTS

### *Experiment 1*

*Ethanol intake and activity levels.* Ethanol intake increased over the first 1-2 weeks to reach a stable level of 12.9 ± 0.9 g/day across animals. This corresponds to a daily ethanol intake of 24 g/kg, based upon an average hamster weight of 150 g, and is comparable to other studies that used similar ethanol concentrations (29,30).

Compared to control hamsters, ethanol-consuming hamsters responded more aggressively to handling during the dark yet appeared more difficult to arouse in the light. They were often observed to fall over when attempting to drink from the water spouts. Wheel running, however, was not affected by ethanol ingestion, although wheel-running counts did tend to decrease over time in both groups.

*Phase of entrainment to LD.* Activity charts from representative hamsters are presented in Fig. 1. Two animals showed a delay of activity onset (i.e., later onset) in LD during ethanol access and one animal showed an advance (i.e., earlier onset), but these effects were small and did not approach the Bonferroni adjusted significance level. Ethanol ingestion did not alter the group mean onset time of nocturnal wheel-running activity in LD nor did it significantly affect the group mean acrophase of the cosine functions that best fit the individual entrained wheel-running rhythms (Table 1). There was also no significant difference in mean activity onset time or acrophase between ethanol and water groups. The amplitude of the best-fitting cosine functions tended to decrease in most hamsters during ethanol treatment, but the group mean change did not approach significance.

Since LD cycles can mask the true phase of the underlying circadian pacemaker, the time of activity onset was also obtained for the first day in DD and compared to the mean activity onset for the last 7 days of LD. Both ethanol and water groups showed a tendency for earlier activity onsets on that day, but in neither case did this approach significance, and there was no significant difference between groups.

*Rate of reentrainment.*

*Without cage change.* Ethanol and water groups reentrained to an 8-h phase advance of the LD cycle in 9.6 ± 3.5 days and 8.1 ± 3.4 days, respectively (Figs. 1A and 1B). This difference was not significant.

*With cage change.* During the first 8-h advance, only one hamster showed wheel running when transferred to the Wahmann running wheel. These data were thus not used for reentrainment rate comparisons. During the second and third 8-h advances, the revised cage change procedure elicited high levels of wheel running through much of the 3-h session. Following these shifts, there was no significant difference between the ethanol and water groups either in the mean shift rate (7.2 ± 4.4 and 4.4 ± 3.4 days, respectively) or in the percentage of animals reentraining immediately (i.e., within 2 days following the LD shift; 4 of 10 and 5 of 10, respectively). However, there was a significant effect of cage change; for all 20 hamsters combined (water and ethanol groups), reentrainment was faster in the revised-cage change condition (5.8 ± 3.7 days) compared to the no-cage change condition (8.9 ± 3.4 days; $t = -2.83, p = 0.011$).

*$\tau$ in constant dim.* During subsequent recording in DD, ethanol-treated hamsters showed a longer group mean $\tau$ than water hamsters, but this difference was not statistically significant (Table 1). The amplitude of the best-fitting cosine function was significantly reduced in both groups during exposure to DD (ethanol, $t = 5.01, p = 0.001$; water, $t = 4.74, p = 0.001$), but there was no significant difference between groups.

### *Experiment 2*

*$\tau$ in constant dim.* Activity charts of representative animals are presented in Fig. 2. During the first 27 days in DD, $\tau$ did not differ between EW and WE groups (Table 2). When the ethanol and water conditions were reversed, $\tau$ lengthened in 17 of 19 hamsters in the WE group, now receiving ethanol, by 10 ± 8 min ($t = -5.32, p < 0.0001$), but did not change in any consistent direction in EW hamsters, now receiving water (Table 2). The two groups differed significantly at this time ($t = 2.68, p = 0.012$). By the final 3 weeks of recording, when the WE group was returned to water, the amplitude and precision of free-running rhythms in several hamsters was poor and precluded reliable assessment of $\tau$. Of those animals in which $\tau$ could be measured, six appeared to show a shortening of $\tau$, three showed a lengthening, and three showed no apparent change.

*$\tau$ and activity.* Prior to reversal, the EW group showed significantly lower wheel-running levels than the WE group ($t = -3.52, p = 0.002$; Table 2). When the conditions were reversed, the EW group, now receiving water, did not show a change in activity levels but the WE group, now receiving ethanol, did show a significant drop in wheel running ($t = 3.57, p = 0.002$). Overall, the EW group showed a significant correlation between activity levels and $\tau$ ($r = -0.35, p = 0.029$). However, within groups for a given condition there were no significant correlations.

## DISCUSSION

Consistent with earlier reports (29,30), hamsters in this study readily consumed a 28% ethanol solution as their sole drinking fluid for long durations (up to 143 days) without

TABLE 2

GROUP-MEAN ± SD FOR FREE-RUNNING PERIOD (HOURS) AND WHEEL-RUNNING COUNTS (PER 10 min) IN EXPERIMENT 2

| | Water Condition | | Ethanol Condition | |
|---|---|---|---|---|
| Group | $\tau$ DD | activity DD | $\tau$ DD | activity DD |
| EW | 24.09 ± 0.18 | 23 ± 19 | 24.08 ± 23 | 26 ± 20 |
| WE | 24.07 ± 0.12 | 61 ± 35 | 24.24 ± 0.11* | 29 ± 27 |

*Significantly different from water condition and from EW group, $p = 0.011$.

apparent ill effects. However, the effects on circadian activity rhythms were also minimal. Ethanol-consuming hamsters showed no consistent changes in the phase of entrainment to LD, measured either as the onset time of daily wheel running during a set of LD days or on the first day of DD or as the acrophase of the best-fitting cosine function during LD. There was also no significant effect on the amplitude of the cosine functions in either LD or DD. In addition, ethanol consumption had no effect on the rate of reentrainment to an 8-h phase advance of the LD cycle with or without exposure to the "exercise" procedure on the first night of the shift.

The only significant effect observed was a lengthening of $\tau$ in the WE hamsters that were switched to ethanol after 4 weeks of stable free running in DD. This lengthening, however, was small and amounted to only about 10 min across animals. This may account for the lack of significant group differences noted in Experiment 1, which used only 10 animals per group, compared to the 19 within-group comparisons in Experiment 2. The magnitude of the $\tau$ change was, nonetheless, comparable to that observed in a previous study (23).

A shortening of $\tau$ after removal of ethanol was rarely observed. Similar results have been noted previously (51). This may reflect an aftereffect of exposure to ethanol. Alternatively, "permanent" $\tau$ lengthening may be an acute response to ethanol that is limited to initial exposure to the drug.

The mechanism by which ethanol alters $\tau$ is unknown. Ethanol may directly effect period-regulating processes within a master circadian pacemaker or alter phase relations among a population of oscillators that together determine $\tau$. Alternatively, ethanol may alter $\tau$ by its effect on overt activity. The WE group that showed a significant lengthening of $\tau$ also showed a significant reduction in wheel running during ethanol access. Several recent studies indicate that wheel-running activity can feedback to alter the phase or period of circadian rhythms in several species, including rats (34,50), mice (11), and hamsters (37,38). One study of blind rats reported a significant negative correlation between the daily amount of wheel running and $\tau$ (43). However, whether free-running $\tau$ is influenced by the level of spontaneous wheel running in hamsters has yet to be established. In fact, in this study no significant correlations between $\tau$ and activity level were observed within groups for a given treatment condition (ethanol or water access). Also, an older study by Aschoff et al. (3) suggested that decreased wheel running should shorten, not lengthen, $\tau$, because in that study access to a wheel (i.e., increased wheel running) was associated with $\tau$ lengthening in hamsters. The changes in $\tau$ noted in the WE hamsters may have been independent from, or possibly even antagonized by, concurrent changes in activity. Measurements of $\tau$ in ethanol-consuming hamsters that do not have access to running wheels may help resolve this issue.

Recent studies have established that single injections of the BDZ triazolam can shift the phase of hamster circadian rhythms free running in DD (46–48). This phase-shifting effect appears to be mediated, at least in part, by an acute stimulation of wheel running in response to the injections because procedures that prevent wheel running also prevent the phase-shifting effect (37,47). Joy and Turek (23) reported that chronic ethanol consumption attenuates the phase-shifting effect of triazolam. This could be due to either attenuation of wheel running in response to the drug or attenuation of the effect of wheel running on the circadian clock. Approximately 50% of the hamsters in our study showed immediate reentrainment to a LD shift when the shift was combined with a procedure to acutely stimulate wheel running at dark onset. This effect was not attenuated by chronic ethanol consumption. This suggests that ethanol may attenuate triazolam-induced phase shifts by reducing the activity-stimulating effects of the triazolam injections.

Although this study utilized several procedures designed to gain a comprehensive view of ethanol and circadian rhythms in the hamster, its limitations are worth noting. First, the effects of ethanol on reentrainment in response to LD shifts alone and in combination with stimulated activity were assessed at only one circadian phase. Second, and perhaps more important, the species utilized, although a standard model for circadian research and, conveniently, an avid consumer of ethanol, may be less likely than most other mammals to exhibit altered circadian rhythms in response to chronic, voluntary ethanol ingestion. In all mammals, ethanol is continuously metabolized so maintaining consistently high levels of blood-brain ethanol is problematic. This is particularly true in hamsters because they metabolize ethanol rapidly, which may underlie their ability to ingest copious quantities of the drug without exhibiting physical dependence (30). At ethanol concentrations above about 20%, hamsters reduce their daily fluid intake to maintain a constant daily dose of ethanol. Repeated bolus injections of amounts above those voluntarily ingested may thus be necessary to establish more significant effects on circadian parameters in this species.

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