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Cross-Generalization of an EtOH "Hangover" Cue to Endogenously and Exogenously Induced Stimuli

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GAUVIN, D. V., R. J. BRISCOE, T. J. BAIRD, M. VALLETT, K. L. CARL AND F. A. HOLLOWAY. *Cross-generalization of an EtOH "hangover" cue to endogenously- and exogenously-induced stimuli.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 199–206, 1997.—Twenty male Sprague–Dawley rats were trained in a two-choice food-reinforced drug discrimination task (10 min sessions) using the state-dependent interoceptive stimulus attributes of ethanol's (EtOH) delayed or rebound effects (EDE) versus "normal" basal homeostasis. Cross-generalization tests were conducted with 0.18 mg/kg naloxone injected after three days of three injections per day of either SAL or 10 mg/kg morphine. Naloxone failed to generalize to the EDE-state after chronic saline; however, the precipitated morphine withdrawal state produced complete generalization to the EDE training cue. Daily tests were conducted after 8 h photoperiod phase-shifts. An 8 h phase-advance, equivalent to a west-to-east intercontinental night-time flight in humans, produced a biphasic, graded, increase in EDE-appropriate responding, which peaked on the second day after the phase-advance and recovered by the fourth day. The 8 h phase-delays failed to engender significant EDE-appropriate responding. These data provide evidence for the subjective similarity between EtOH hangover, opiate withdrawal states, and the physiological disruption induced by circadian phase-advances. © 1997 Elsevier Science Inc.

EtOH Ethanol Hangover Opiate withdrawal Circadian effects Phase-shifts Drug discrimination

WE have examined the subjective effects of acute ethanol (EtOH) withdrawal in rats using the drug discrimination procedure. We initially used a two-choice Drug 1-Drug 2 discrimination task, with 3.0 mg/kg chlordiazepoxide (CDP) and 20 mg/kg pentylenetetrazole (PTZ) as stimuli. In that study, we demonstrated a shift from CDP-appropriate to PTZ-appropriate responding during saline tests conducted at specific time points after acute high doses of EtOH (3 g/kg and 4 g/kg) were administered (18). At the time, we suggested that the high dose EtOH pretreatments challenged the rats homeostatic and affective systems to induce a delayed rebound (PTZ-like responding) that was qualitatively opposite to that of the initial EtOH effect (CDP-like responding). Using a more typical PTZ versus saline discrimination task, we subsequently demonstrated that high acute doses of 2, 3, and 4 g/kg of EtOH, administered at various time points prior to saline test sessions, engendered responding on the PTZ-appropriate lever in a quantitative and qualitative fashion, that was both dose- and time-dependent (22). More recently, we used the state-dependent interoceptive stimulus attributes of EtOH's delayed or rebound effects versus the "normal" basal homeostasis to train rats to differentially respond for food delivery (17). 4 g/kg of EtOH and equivalent volumes of saline administered 18 h before the training sessions served as training stimuli in this state-dependent discrimination task. Gas chromatographic analyses of tail blood samples demonstrated that the blood aliquots were void of any detectable levels of EtOH or any of its behaviorally-active metabolites by 14 h after administration of the highest tested dose of EtOH (4 g/kg). However, the behavioral or discriminative control test sessions conducted at various time points after EtOH injections demonstrated that the time-dependent, cyclic return from the experimental "hangover" state to the normal state, did not fully occur until 48 h after the injection of 4 g/kg of EtOH. While low doses of both EtOH and CDP blocked the hangover state, we discovered an enhanced sensitivity to the discriminative

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stimulus properties of PTZ, evident by the complete cross-generalization to the hangover state by a low dose of 5.6 mg/kg PTZ and the induction of clonic seizures at a low dose of 18 mg/kg PTZ.

There have been a number of reports demonstrating that the rebound or delayed effects from high acute dose pretreatment's of EtOH are associated with hyperexcitability in humans and animals (10,11,13,32,45,55,56). Similarly, withdrawal from both high acute pretreatments and chronic administration of EtOH in animals are characterized by increases in physiological arousal (13), circulating cortisol and catecholamine levels (9,41,42,46). Such evidence has led a number of researchers to suggest that the acute EtOH withdrawal syndrome, or hangover, and the manifestations occurring after withdrawal from chronic drug exposure may differ only on an intensity dimension (10,11,23–25,31,37).

Since the identification of the tetrahydroisoquinolines, numerous studies have linked EtOH and opiate dependency to common neurobiological mechanisms (6–8,30,52,53). Withdrawal from both EtOH and opiates are usually self-regulating states, which most often are restored without any pharmacological treatment (52). Many of the changes in animals observed during the first two days of experimentally-induced withdrawal from chronic alcohol (34,48,50) and chronic morphine (1,35,39) are similar, including behavioral activation, changes in open-field exploration, stereotyped behavior, jumping, and startle responses, and both are characterized by long-term sleep disturbances (52). As an animal analogue of human anxiety states, the PTZ-SAL drug discrimination procedure has demonstrated PTZ-like responding in tests conducted during periods of withdrawal from acute EtOH (22), chronic EtOH (4), and chronic morphine (12) exposure.

Rebound phenomena are natural events and are found: 1) after the decline of serum blood levels after acute drug administration; 2) after withdrawal from chronic exposure to any active drug; and 3) as a physiological compensatory mechanism of the central nervous system, without drugs (36). One of the most widely recognized, non-pharmacological, rebound-effects, characterized by many pathophysiological changes in locomotor and exploratory activity, behavioral activation, serum cortisol, and stereotyped behaviors in animals, relates to abrupt environmental phase shifts (44). Similar disturbances may occur in man either because of a change of work shift or because of a rapid flight across multiple time zones. Wiley Post (49) was the first to report the phenomenon of flight-induced phase-shifting and, later, it became a significant area of research for the National Aeronautics and Space Administration, with regards to space exploration (44). In a recent 50 year literature review on alcohol hangover, we concluded that many of the disruptive effects of EtOH and its associated hangover phenomena appear to occur in systems which vary cyclically each day (16). We noted that daily rhythms in the biological activity vary in length and appear to be related to environmental cues such as the light-dark cycle, or monthly and seasonal changes (exogenous rhythms), while others may vary in the absence of an environmental zeitgeber (endogenous rhythm). Newly acquired data from this laboratory presented in the review led us to conclude that large acute doses of alcohol disrupts the normal circadian rhythm in a number of systems (i.e., sleep architecture, temperature, urinary-potassium output, and activity). We, and others, have suggested that the hangover effects may be caused by some homeostatic rebound in response to either the direct acute effects of EtOH or secondary to the shifts in the normal circadian rhythmicity of multiple physiological systems which are modified by the acute injection of EtOH (14,16).

The purpose of the present study was three-fold: 1) In our previous state-dependent hangover discrimination task, we reported an enhanced sensitivity to the behavioral effects of PTZ. We further investigated the sensitivity factor by conducting dose-response tests with a full range of EtOH pretreatments; 2) With the numerous reports relating common neurobiological mechanisms shared by both EtOH and morphine withdrawal, we were interested in assessing the cross-generalization of the subjective effects of EtOH hangover to naloxone-precipitated morphine-withdrawal syndrome; and finally, 3) We were interested in examining the cross-generalization between the hangover training stimulus and an exogenously-induced pathophysiological state induced by photoperiod phase-shifts similar to those inducing the maximal and minimal "jet-lag" phenomena in humans (8 h phase-advance vs. phase-delay).

METHODS

Subjects

Twenty-four male Sprague–Dawley rats weighing 300–325 g were purchased from Sasco Laboratories, Inc. (Omaha, NE) and singly housed in stainless-steel suspended cages. Each rat was, initially, given ad libitum access to both food and water. The animal care and maintenance of the colony room were maintained by an AAALAC-accredited team of technicians and veterinarians from the Department of Animal Resources of the University of Oklahoma Health Sciences Center. Each rat was acclimated to the new environment for one week before the beginning of the drug discrimination training. Rats were placed on a food-deprivation schedule to reduce their body weights to 85% of their free-feeding weights. The body weights were initially maintained by restricted access to food, supplemental to that earned in the experimental sessions. Rats were allowed to gain 10 g/month to allow for normal growth and development. The animal colony room was maintained on a 12 h light/dark cycle (lights on 0530), 20–22°C, and relative humidity of 60%.

State-Dependent Discrimination Training

Subjects were trained to the location and operation of the pellet dispenser and to operate both levers by the method of successive approximations. The illumination of the stimulus and house lamps signalled the beginning of the experimental sessions. Initially, each response on either lever was reinforced (one 45 mg food pellet, P. J. Noyes, Inc., Lancaster, NH). Once each rat was trained to press the lever for food reinforcers, they received 4 g/kg EtOH or saline (SAL; ml equivalent to 4 g/kg EtOH injections) intraperitoneally 18 h before the session. The large volume injections (4 mls/100g body weight) were given in two separate slow-infusion injections, on opposite sides of the abdomen, approximately 5 min apart. An additional 1 ml/kg SAL injection was administered intraperitoneally 15 min before the sessions. The appropriate lever to obtain food was determined by the injection administered 18 h before the experimental sessions. The 18 h pretreatment of 4 g/kg of EtOH was hypothesized to correlate with the acute withdrawal state associated with high acute pretreatments of EtOH and hereafter referred to as a state associated with EtOH's rebound or delayed effects (EDE). This state is in contrast to that associated with the acute or immediate effects of EtOH.

The specific pretreatment interval was selected from previously published reports from this laboratory (17,18,22).

Training sessions ended after 100 food deliveries or 10 min, whichever occurred first. The number of responses required for reinforcement was gradually increased across successive sessions until 10 consecutive responses (FR10) were required. Once the contingencies for reinforcement were raised above FR-1, responses on the injection-inappropriate lever reset the ratio requirement on the injection-appropriate lever. Training sessions were conducted 5–7 days/week. Discrimination training continued until each rat met the criteria of emitting $>$ 90% of the total session responses on the injection-appropriate lever for four consecutive days. Each rat was then required to meet these criteria for four consecutive sessions in a double alternation sequence (i.e., SAL, SAL, EDE, EDE). EDE training sessions were always followed by a "day off." SAL training sessions were conducted between 36–96 h after an EDE training session. The 18 h pretreatment injections were administered in groups of four in 15 min intervals starting at 1045 h on the day before the experimental sessions. The additional small injections of SAL (1 ml/kg) were injected in 15 min intervals starting at 0430 h, and the experimental sessions conducted in 15 min intervals starting at 0445 h. All rats were fed supplemental rat chow at 0900 h. Our initial attempts, conducted with other rats, were to train the discrimination using an oral reinforcer (0.1% w/v sodium saccharin) which has minimal nutritive value. However, we have discovered that hangover is associated with a marked adipsogenic state (15), and after repeated failures to acquire stimulus control using saccharin, we shifted back to food reinforcement in a new group of rats.

Test Sessions

When discriminative control was established test sessions were conducted. Test sessions were identical to training sessions except (1) a novel EtOH dose, drug dose, or experimental condition was administered, and (2) 10 consecutive responses on either lever produced food. If a rat did not meet the criteria for stimulus control during a training session, further testing was postponed until one successful EDE and SAL training day was achieved. Test sessions were conducted once per week.

Naloxone-Precipitated Morphine Withdrawal

Accurate discriminative control could be maintained up to 5 days without continued training, therefore we imposed a short period of chronic, 3 injections/day administration (0000, 0800, 1600 h) of either saline or morphine (10 mg/kg/injection; 30 mg/kg/day) for three consecutive days. A single low dose of naloxone (0.18 mg/kg) was administered on the morning after both chronic saline and morphine administrations (starting at 0430 h) and 15 min before the discrimination test session, to assess the generalizability between these two conditions and the EDE state. The 0.18 mg/kg naloxone injection was selected because it was believed to be potent enough to exacerbate interoceptive cues of withdrawal, allow for sufficient response rates, and still provide a measure of weight loss as a second measure of opiate withdrawal (59).

Photoperiod Phase-Shifting

Time-zone shifts do not result from north to south flights. The disruptions in "normal" physiology are maximal in response to a phase-advance equivalent to an 8 h night-time flight from west-to-east (California to Europe) and minimal, and easily recoverable, from a phase-delay equivalent to up to an 8 h flight from east-to-west (44). Rats were run during a normal training session up to the day prior to photoperiod phase-shifts. Soon after the training sessions were completed the automated timing circuit on the colony room lights was manually adjusted to either turn the lights on 8 h earlier than normal (phase-advance) or to delay the onset of lights on by 8 h (phase delay). Subgroups of 10 rats were tested on Days 1, 2, 3 and 4 after the phase advance and on Days 1 and 2 after the phase delay. The differential testing resulted from the demonstration of SAL-appropriate responding on both days of phase-delays. A total of two phase advances and only one phase delay were required to complete this portion of the study. The study took approximately 12 months to complete to allow for appropriate recovery periods to be superimposed between phase shifts.

Drugs

Morphine sulfate and naloxone hydrochloride were purchased from Sigma Chemical Company (St. Louis, MO) and dissolved in 0.9% saline. Ethyl alcohol USP (190 proof, U.S. Industrial Chemicals Company, Houston, TX) was diluted to 10% w/v normal (0.9%) sterile saline.

Data Analysis

The data are presented as the percentage of the total sessions responses emitted on the EDE-appropriate lever. We have previously suggested that partial generalization to a training drug stimulus effects reflects an accurate assessment of the degree of quantitative and/or qualitative similarity between the test drug/drug condition and the training stimulus (20,28). A test drug or drug condition was considered to produce "complete generalization," that is discriminative effects similar to those of the hangover state, if at least 80% of the total session responses were emitted on the EDE-appropriate lever. The average response rates during the test session are expressed in responses/s. Such response rates provide a second measure of behavioral effects of the drug or drug-associated state that appears to be independent of the distribution of response choice on the two levers. All data were analyzed using a mixed factor (subject $\times$ treatment, repeated measures) ANOVA with *a posteriori* tests for individual treatment conditions with Duncan's new multiple range test.

RESULTS

Twenty out of the initial 24 rats met criterion performance for stimulus control in an average of 48 training sessions ($\pm$ 1.29 SE; range of 40–58 sessions); four rats were dropped from the study. Figure 1 shows the discriminative generalization (top panel) and response rate functions for the hangover state. Each EtOH dose was tested in a subgroup of 10 randomly selected rats from the 20 successfully trained rats. Various doses of EtOH were administered at the 18 h pretreatment interval. Significant dose-related effects were found for discriminative stimulus control ($F[5,45] = 26.1$, $p = 10^{-6}$), however relatively stable response-rates were engendered across the tested dose range ($F[5,45] = 1.61$, $p = 0.175$, n.s.). Surprisingly, the discriminative stimulus generalization function demonstrated remarkable sensitivity to EtOH, comparable to that found in a previously reported group of rats trained to discriminate the acute effects of EtOH (15 min pretreatments; [19]).

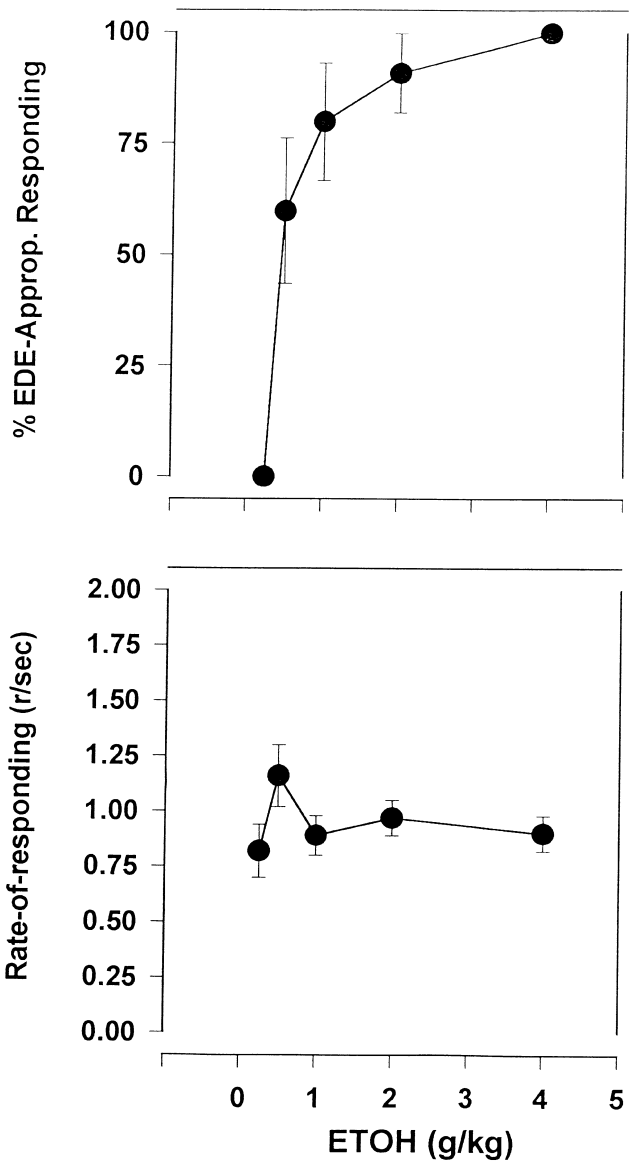

FIG. 1. Ethanol generalization function—The group mean percentage of total test session responses emitted on the EDE-appropriate lever (top panel) and the group mean rates-of-responding (bottom panel) are plotted as a function of EtOH test dose administered 18 h prior to the test session. The experimentally-induced 'hangover' demonstrated a dose-related increase in the percentage of responses emitted on the EDE-appropriate lever and relatively stable response rates. Each point represents the mean of 10 rats randomly selected from the 20 trained rats.

Figure 2 shows a bar chart of the results from tests conducted with SAL, EDE, and 0.18 mg/kg naloxone administered after three days of chronic administration of either SAL or morphine. Each test was conducted in 11 trained rats. The bar chart clearly shows the significant Main treatment effects ($F[3,30] = 9502.0, p < 10^{-6}$) resulting from these tests. Individual treatment comparisons (Duncan's test) demonstrated differences, as follows: SAL vs EDE: $p < 10^{-6}$: SAL vs naloxone + chronic SAL: $p = 0.97$, n.s.; SAL vs naloxone + chronic morphine: $p < 10^{-6}$; EDE vs naloxone + chronic SAL: $p < 10^{-6}$; EDE vs naloxone + chronic morphine: $p = 0.35$, n.s. There were no Main treatment effects found with the response-rate data. Rats were weighed preceding the injections and immediately following these test sessions; weight loss is a characteristic sign of opiate withdrawal. The 0.18 mg/kg naloxone injection induced a 0.0 g body weight loss in the chronic saline treated rats, but a 6.2 g (± 0.1 SE) body weight loss during precipitated morphine withdrawal.

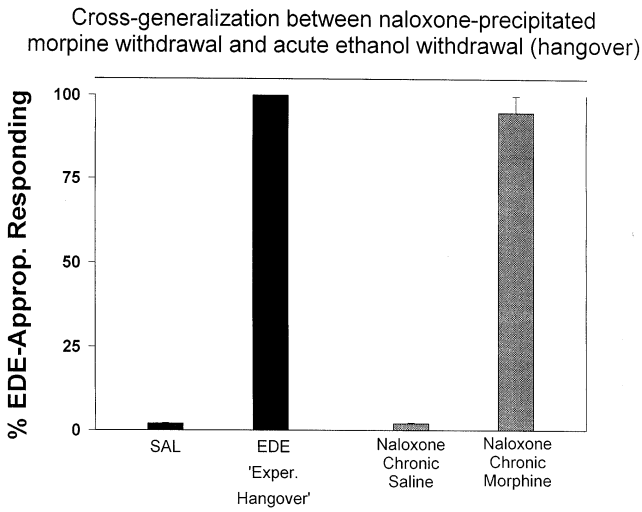

FIG. 2. Bar chart of group mean percentage (± SE) of responses emitted on the EDE-appropriate lever during test sessions conducted with the two state-dependent training stimuli and 0.18 mg/kg naloxone, administered 15 min prior to a single test session, in 11 rats exposed to 3 days of chronic three-daily injections of either saline or morphine (10 mg/kg/injection; 30 mg/kg/day). Rates-of-responding during tests conducted after chronic saline and morphine were 0.98 (± 0.02) and 0.88 (± 0.1) resp./s, respectively.

Figure 3 is a bar chart showing the temporal changes in the percentage of total test session responses emitted on the EDE-appropriate lever during SAL test sessions conducted on the four consecutive days following an 8 h photoperiod phase advance, equivalent to a west to east nightime intercontinental flight. A significant phase-shift effect was demonstrated ($F[5,45] = 20.1, p < 10^{-6}$). Individual day comparisons between the two training stimuli (SAL and EDE) demonstrated the following significant results: Day 1 vs SAL: $p = 002$; Day 1 vs EDE: $p = 003$; Day 2 vs SAL: $p = 0.003$; Day 2 vs EDE: $p = 0.46$,n.s.; Day 3 vs SAL: $p = 0.001$; Day 3 vs EDE: $p = 0.007$; Day 4 vs SAL: $p = 0.99$,n.s.; Day 4 vs EDE: $p = 0.0007$.

Figure 4 shows a similar bar chart showing the temporal changes in the percentage of total test session responses emitted on the EDE-appropriate lever during SAL test sessions conducted on two consecutive days following an 8 h photoperiod phase delay, equivalent to an east to west (Europe to America) flight. When compared to the "normal" photoperiod entrained SAL test data, the phase-delay failed to significantly shift responding to the "hangover"-like state on either day. Each individual time comparison was similar to the SAL state (both p's > 0.2), and significantly different from the EDE state (both p's > 0.0001). No significant rate-altering effects were demonstrated by photoperiod phase-advance nor phase-delay treatment conditions (Table 1).

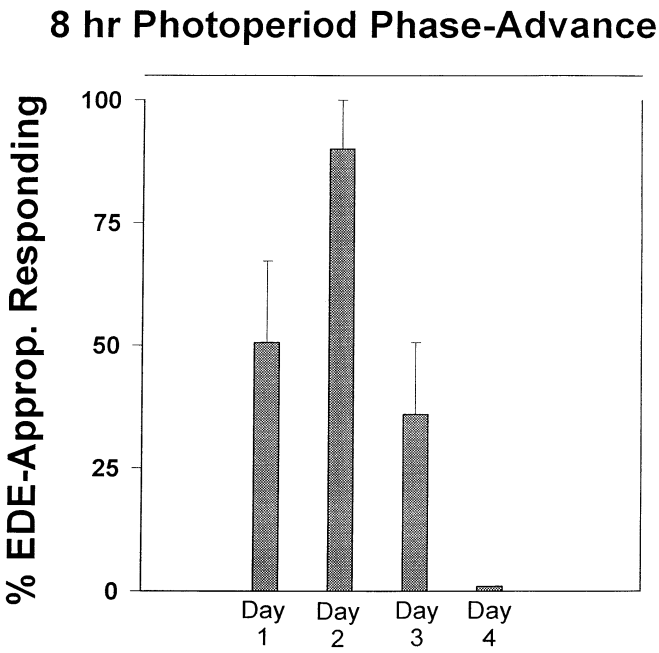

FIG. 3. Bar chart of the temporal changes in the group mean percentage (±SE) of responses emitted on the EDE-appropriate lever during daily test sessions conducted for four consecutive days after an 8 h photoperiod phase-advance in 10 trained rats.

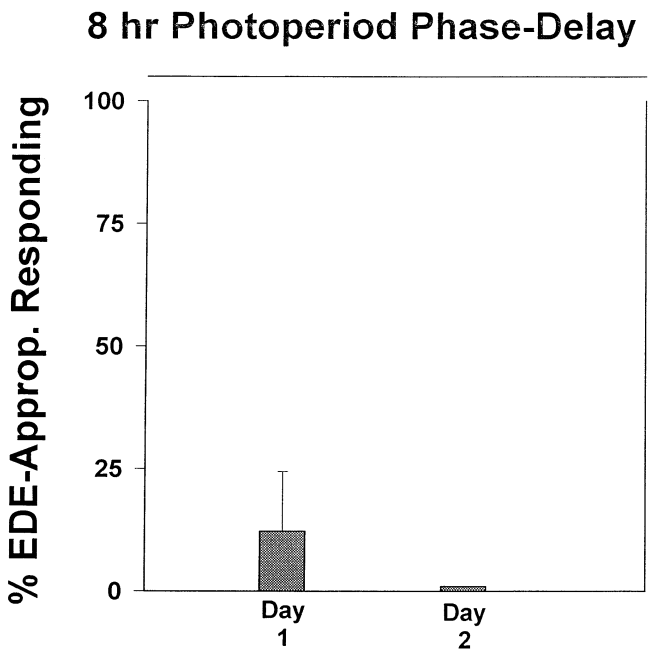

FIG. 4. Bar chart of the temporal changes in the group mean percentage (± SE) of responses emitted on the EDE-appropriate lever during daily test sessions conducted for the two consecutive days after an 8 h photoperiod phase-delay in 10 trained rats.

DISCUSSION

The present study demonstrates two important features of the EDE state: (a) a subjective similarity exists between an experimentally-induced acute EtOH withdrawal (hangover) state and a naloxone-precipitated morphine withdrawal state in rats, and (b) the slow development and sustained presence of subjectively potent interoceptive state in rats produced by an 8 h photoperiod phase-advance is also similar to that produced by the acute EtOH withdrawal state training cue. The latter phase shift is similar to that following a west-to-east intercontinental airflight (44).

For many years researchers have been suggesting similar underlying neurobiological mechanisms initiating, maintaining, and controlling the expression of both EtOH and morphine withdrawal syndromes (6–8,30,53). Blum, Hamilton and Wallace (8) have concluded that the severity of the EtOH withdrawal syndrome is directly related to norepinephrine and inversely related to dopamine release. That is, norepinephrine exacerbates withdrawal while dopamine ameliorates it. These authors further suggest that long lasting depletion of the brain's catecholamines by chronic EtOH administration is compensated for by induction of neuronal supersensitivity for both norepinephrine and dopamine. As cited by Blum, Hamilton and Wallace (8) other authors have similarly proposed that neuronal supersensitivity for catecholamines is an important factor in considering the mechanisms involved in the expression of the morphine abstinence syndrome (5,26,38, 58). The common mechanisms underlying both EtOH and morphine withdrawal symptomatology may also underlie similarities in their reinforcing attributes as well. Some reports have shown substitution of opiates for EtOH (54) and EtOH has been reported to substitute for opiate self-administration (57). And it has long been demonstrated that the opiate antagonist, naloxone, alters selfadministration of EtOH (2,19,27, 29,51). The "link" proposal of Blum (6) has been an interesting working hypothesis which has served to generate much controversy and research over the years. However, Rydberg (52) has more recently identified only a limited similarity between the two withdrawal syndromes with regards to time course, development, and detailed analysis of specific behavioral patterns expressed. Rydberg (52) concluded that sleep disturbances were the only real common behavior between the two. None of these studies, though, have examined the subjective or perceived internal milieu of the experimental subjects. Using the PTZ vs SAL drug discrimination task, both EtOH (4,22) and morphine (12) withdrawal states have engendered PTZ-appropriate responding. We have previously reported that rats trained to discriminate between the interoceptive

TABLE 1

RESPONSE RATES DURING PHOTOPERIOD PHASE SHIFT TESTS

Test Condition	Group Mean (± SE) Response Rates (r/sec)
8 h Phase-Advance	
Day 1	0.92 ± 0.07
Day 2	0.83 ± 0.08
Day 3	0.85 ± 0.10
Day 4	0.87 ± 0.08
8 h Phase-Delay	
Day 1	1.02 ± 0.09
Day 2	1.07 ± 0.06
SAL	1.02 ± 0.09
EDE	0.90 ± 0.07

stimulus attributes of the EtOH hangover state and their normal homeostatic state also demonstrated cross-generalization to PTZ. Therefore, it is not surprising that both opiate and EtOH withdrawal syndromes in rats share, at least in part, some stimulus characteristics in common. The data from the present study is the first clear demonstration of cross-generalization, or subjective similarity between EtOH and morphine withdrawal states.

The free-running period of circadian rhythms in a consistent environment can be influenced for 100 days or more by environmental changes such as photoperiod phase shifts (44). These physiological effects were termed "after-effects" by Pittendrigh (47). The typical symptoms occurring after travel across multiple time zones are sleep disturbances, gastrointestinal disturbances, decreased vigilance and attention span, and a general feeling of malaise (44). These same symptoms have been reported in humans experiencing opiate and EtOH withdrawal (6,52). It has been reported that westward travel, which phase-delays the circadian system, is followed by weak after-effects and a more rapid adjustment (33) when compared to eastward flights. Data from Klein and Wegmann (33) and those of Mill, Minors and Waterhouse (43) suggest that an eastward flight across 8–9 time zones shifts body temperature cycle with an 8–9 h phase advance or a 15 h phase delay and that not all rhythms will necessarily shift in the same direction. The greatest "jet-lag" effect appears to occur in those individuals travelling from west-to-east at night. The photoperiod phase advance used in the present study mimics this condition. Aschoff (3), Klein and Wegmann (33) and Mills, Minors and Waterhouse (43) have demonstrated that the full expression of "jet-lag" or phase-shift after-effects may not occur until the second or third day after the destination arrival. In the present study, the development of the interoceptive stimuli engendering EDE-appropriate responding was greatest for a photoperiod phase-advance and the amplitude of the effects was graded in nature and strongest on the second day after the photoperiod phase-shift. Minimal changes in the response choice measure were induced by photoperiod phase-delays.

These data strongly parallel the changes in the internal milieu of humans travelling and crossing multiple time-zones, and suggest a similar pattern of internal milieu changes may occur by both endogenously (drug) and exogenously (phase shifts) presented stimuli.

In conclusion, the present study pragmatically used the drug discrimination task to establish the perceived similarities between EtOH hangover, precipitated morphine withdrawal, and experimentally-induced phase-shifts typical of "jet-lag." The drug discrimination task has been used in a number of laboratories to implicate similar underlying neurobiological mechanisms which engender similar subjective responses. We have demonstrated data that supports the view that the homeostatic rebound from high EtOH dose pretreatments induces a potent interoceptive state in rats, referred here as "hangover." This time- and dose-dependent drug rebound state has demonstrated crossgeneralization to: A) the direct or acute effects of both naloxone, in chronic morphine-treated rats, and PTZ (17), and, B) to the delayed response to a single photoperiod phase-advance. Whether or not the subjective similarity between these stimulus events are associated with or linked to some common underlying neurobiological mechanisms would be speculative, at best, at this time.

Within a Pavlovian theoretical perspective, we suggest that the discriminative stimulus properties of EtOH's delayed effects reflect an *unconditioned response* to the effects (the UCS) of high dose EtOH pretreatments; the initial drug effect is not an unconditioned response to the drug, but an unconditioned stimulus. The cross-generalization induced by the acute administration of PTZ, produces a state similar to the rebound state induced by high acute pretreatments of chlordiazepoxide. While EtOH and chlordiazepoxide have demonstrated subjectively similar states, the CDP- and EtOH-rebound both engendered significant PTZ-appropriate responding in our previous PTZ vs SAL discrimination studies (17,18,22). In this sense, the state associated with acute PTZ effects is similar to the unconditioned response to high dose CDP and EtOH pretreatments. In the case of the naloxone precipitated morphine withdrawal state engendering EDE-appropriate responses, it has been previously demonstrated that both acute and chronic EtOH and opiate withdrawal engenders PTZ-appropriate responding. The naloxone injection precipitates a withdrawal state generally indistinguishable from that produced during the opiate withdrawal state occurring from the cessation of chronic administration. In this sense the naloxone precipitated withdrawal state is homologous to an unconditioned response to the behavioral effects of chronic morphine. The acute physiological effects or unconditioned stimulus effects of a phase-advance is also a compensatory unconditioned response of either a 15 h circadian delay or an 8 h circadian advance. Similar to the hangover stimulus, the EDE-appropriate responding engendered on the second day after the photoperiod phase-advance (the UCS) represents the unconditioned response to the initial stimulus effects of the phase-advance. Therefore, the response-choice data from the present study reflect a cross-generalization between *unconditioned responses*. The unconditioned stimuli of EtOH's acute effects, high dose pretreatments of CDP, chronic morphine, and an 8 h phase advance elicit subjectively similar unconditioned responses (subjective states) which are similar to the state which produces symmetrical cross-generalization between PTZ and hangover states.

Inasmuch as the discrimination task has been used as an animal analogue of the subjective effects in humans, these data may have implications for the successful treatment of interoceptive states related to EtOH "hangover," morphine withdrawal and "jet-lag."

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