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Effects of Diurnal Phase and Pimozide on Cholecystokinin-Elicited Hypoactivity in the Hamster

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SCHNUR, P., M. ESPINOZA AND R. FLORES. *Effects of diurnal phase and pimozide on cholecystokinin-elicited hypoactivity in the hamster.* PHARMACOL BIOCHEM BEHAV 43(4) 979–984, 1992. – Locomotor activity in golden Syrian hamsters was measured following IP injections of cholecystokinin (CCK; 25 μg/kg) and pimozide (0.5 mg/kg), the dopamine receptor antagonist. In addition, animals were tested during either the dark or light phase of the diurnal cycle in either dark or light running wheel environments. Results indicated that CCK-elicited hypoactivity was blocked by pimozide and that the effect of CCK was evident only among animals tested during the light phase of the daily cycle. Ambient lighting conditions in the test environment did not modify the drug effects. Independently of any drug effect, locomotor activity was affected by diurnal phase and ambient lighting in the test environment. Animals were more active when tested during the dark phase than during the light phase and locomotor activity was higher under dark than under light ambient conditions. It is concluded that diurnal phase modulates CCK's effect on hamster locomotion and that CCK's effect on locomotion is mediated, in part, by dopaminergic mechanisms.

Cholecystokinin Pimozide Locomotor activity Circadian rhythm Hamster Dopamine

CHOLECYSTOKININ (CCK) is a gastrointestinal and brain octapeptide that produces a variety of behavioral effects (36,41). Previously, we demonstrated that CCK, at systemic doses ranging from 25–75 μg/kg, inhibits locomotor activity in hamsters, is more potent given IP than SC, and antagonizes morphine-elicited activity by acting, in part, independently of morphine to produce opposite behavioral effects (24,25). In a recent study (24), we investigated CCK's effects in three experiments. Although CCK inhibited locomotor activity in each experiment, its effect was diminished in the third experiment, where baseline levels of activity were elevated compared to the first two experiments. Because animals were tested during the dark phase of the diurnal cycle in Experiment 3 and during the light phase in Experiments 1 and 2, we hypothesized that diurnal phase modulated the effect of CCK on activity. The present experiment tests this hypothesis by manipulating diurnal phase as an independent variable. Moreover, the present experiment investigates the effect of ambient lighting on locomotor activity. Ambient lighting in the test environment conceivably could modulate CCK's effect on activity independently of diurnal phase or it might interact with diurnal phase to modulate the drug effect.

In the brain, CCK is colocalized in dopaminergic neurons and intracerebral administration of CCK has been found to modulate the effects of dopamine agonists on activity (3–5,7,8,10,11). Furthermore, CCK has been reported (39) to inhibit rearing and locomotion when microinjected at a dose of 10 μg into the ventral tegmentum, an area rich in dopaminergic cell bodies. Thus, CCK may be acting centrally through dopamine-containing neurons to reduce locomotor activity. Alternatively, CCK may be acting peripherally to reduce locomotion by activating vagal afferents (5,10,11,28,29). The present study was designed to test the hypothesis that CCK-elicited hypoactivity in the hamster is mediated by dopaminergic mechanisms. Half the animals given CCK in the experiment below were pretreated with the dopamine receptor blocker pimozide (PIM) and half were pretreated with a tartaric acid (TTA) vehicle.

METHOD

Subjects

Thirty-two golden Syrian hamsters (30 female, 2 male) with a mean weight of 116 g were used. Hamsters were derived from animals obtained from Sasco, Inc. (Omaha, NE). They were housed individually in stainless steel cages in separate rooms in a temperature-controlled vivarium, given free access to Purina rodent lab chow and tapwater, and maintained on a 12 L : 12 D cycle. For half the animals (light phase), the vivar-

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ium lights were turned on at 0800 h and off at 2000 h; for the remainder (dark phase), the vivarium lights were turned off at 0800 h and on at 2000 h. Experiments were conducted in accordance with NIH guidelines for the use and care of laboratory animals.

Apparatus and Material

The apparatus consisted of 32 activity wheels (Wahmann Co., Baltimore, MD; Model LC-34) housed in plywood enclosures that isolated the wheels visually from one another. Noise from ventilation fans in each enclosure (approximately 70 dB re: 0.0002 dynes/cm^2) provided auditory masking. Movements of each wheel were detected by microswitches, transduced by an interface (Lafayette Instruments, Lafayette, IN, Model 1180-0I), and recorded on Apple II+ computers. Sixteen activity wheels were located in each of two adjoining rooms. In one room (dark test environment), there was no ambient illumination. In the other room (light test environment), a 25-W incandescent bulb mounted above the running wheel in each enclosure provided direct illumination and fluorescent room lights provided indirect illumination.

CCK, a gift from Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, NJ, SQ 19,844; batch NN026NC, Lot B), was dissolved in 0.9% saline and administered in a dose of 25 μg/kg. Pimozide (Sigma Chemical Co., St. Louis, MO) was dissolved in a 3% solution of tartaric acid and administered in a dose of 0.5 mg/kg. All injections were given IP in a volume of 1 ml/kg.

Procedure

Animals were assigned randomly to the eight treatments created by the factorial combination of diurnal phase (dark or light), ambient lighting in the test environment (dark or light), and drug (CCK or saline); that is, because the experiment was conducted between 1100 and 1400 h, half the animals were tested during the dark (D) phase and half during the light (L) phase of the daily lighting cycle. Half of each of these groups was tested in a dark (d) running wheel environment and half in a light (l) running wheel environment. Finally, half of each group was given CCK and half saline on the test day.

On the first 3 days of the experiment, all animals were given an IP injection of saline 10 min before being placed in the running wheels for a 3-h baseline session. The purpose of these sessions was to acclimatize hamsters to the handling and injection procedures. In addition, these sessions provided data for the effects of phase and test environment lighting on locomotor activity. On day 4 (test day 1), half the animals received an injection of CCK and half saline 10 min before being placed in the running wheels for a 3-h test session. Locomotor activity was cumulated every 20 min.

Following the first test day, animals received 3 additional days of saline baseline sessions as described above. On the next day, they were tested again (test day 2): Half the animals in each of the groups received an injection of PIM and half received an injection of the TTA vehicle 4 h prior to an injection of CCK or saline. Ten minutes after CCK or saline injection, they were placed in the running wheels for a 3-h session. Locomotor activity was cumulated every 20 min. Data were analyzed using analysis of variance (ANOVA), supplemented by posthoc tests where appropriate. A $p < 0.05$ level of significance was adopted throughout.

RESULTS

Baseline Days

Prior to each test day, animals in the dark and light phases of their diurnal cycle were observed for 3 days in dark and light running wheel environments following saline injections. The effects of phase and ambient lighting conditions on hamster locomotor activity are evident on these days. A two (phase) × two (test environment) × nine (time blocks) mixed-factorial ANOVA was used to analyze the data. Figure 1 (top) shows mean locomotor activity pooled over saline baseline days 2 and 3 (day 1 data were lost due to computer failure). Figure 1 (bottom) shows mean locomotor activity pooled over saline baseline days 4, 5, and 6. Prior to the first test day (fig. 1, top), animals in the dark phase of the daily cycle were more active than animals in the light phase of their daily cycle, $F(1, 28) = 34.83$. Although animals were more active in dark than in light running wheel environments, these differences were not significant. In addition, locomotor activity increased early in the test session and then decreased, $F(8, 224) = 9.53$, an effect that was particularly evident among animals tested during the light phase of the diurnal cycle, $F(8, 224) = 11.62$. Prior to the second test day (Fig. 1, bottom), animals in the dark phase of the daily cycle were more active than animals in the light phase of the daily cycle, $F(1, 28) = 6.60$. Moreover, animals were more active when tested in a dark running wheel environment than when tested in a light running wheel environment, $F(1, 28) = 50.18$. As on the first baseline days, locomotor activity was curvilinearly related to time blocks, $F(8, 224) = 16.11$, particularly for light-phase-tested animals, $F(8, 224) = 2.04$. Moreover, the interaction between time and test environment, $F(8, 224) = 7.89$, was significant.

Test Day 1

Test day data were analyzed using a two (phase) × two (test environment) × two (drug) × nine (time blocks) mixed-factorial ANOVA. Figure 2 indicates that animals given CCK were less active than those given saline during the first 80 min of the test session, an effect independent of phase and running wheel environment lighting, $F(8, 192) = 5.92$. Posthoc comparisons using Fisher's least significant differences (LSD) test ($p < 0.05$, one tailed) indicated that group CCK was less active than group SAL during each of the first three time blocks.

The dose of CCK used in this experiment, 25 μk/kg, is higher than that used in mice and rats (2–10 μg/kg). This dose in the hamster is necessary to observe effects in the running wheel that last for 1 h or more [cf. (25)]. In addition, the effects that were evident on the previous baseline days continued to be manifest on the test day, that is, animals in the dark phase of the daily cycle were more active than those in the light phase, $F(1, 24) = 41.92$. Furthermore, the effect of time blocks, $F(8, 192) = 3.29$, and the interaction between phase and time blocks, $F(8, 192) = 4.87$, were significant. The significant interaction between phase and time blocks reflects the fact that dark-phase animals increased their activity during the test session whereas the activity of light-phase animals decreased during the test session.

Test Day 2

A two (drug 1) × two (drug 2) × two (phase) × two (test environment) × nine (time blocks) ANOVA was used to analyze the data from the second test day. Figure 3 shows the effects of pimozide and CCK on locomotor activity as a func-

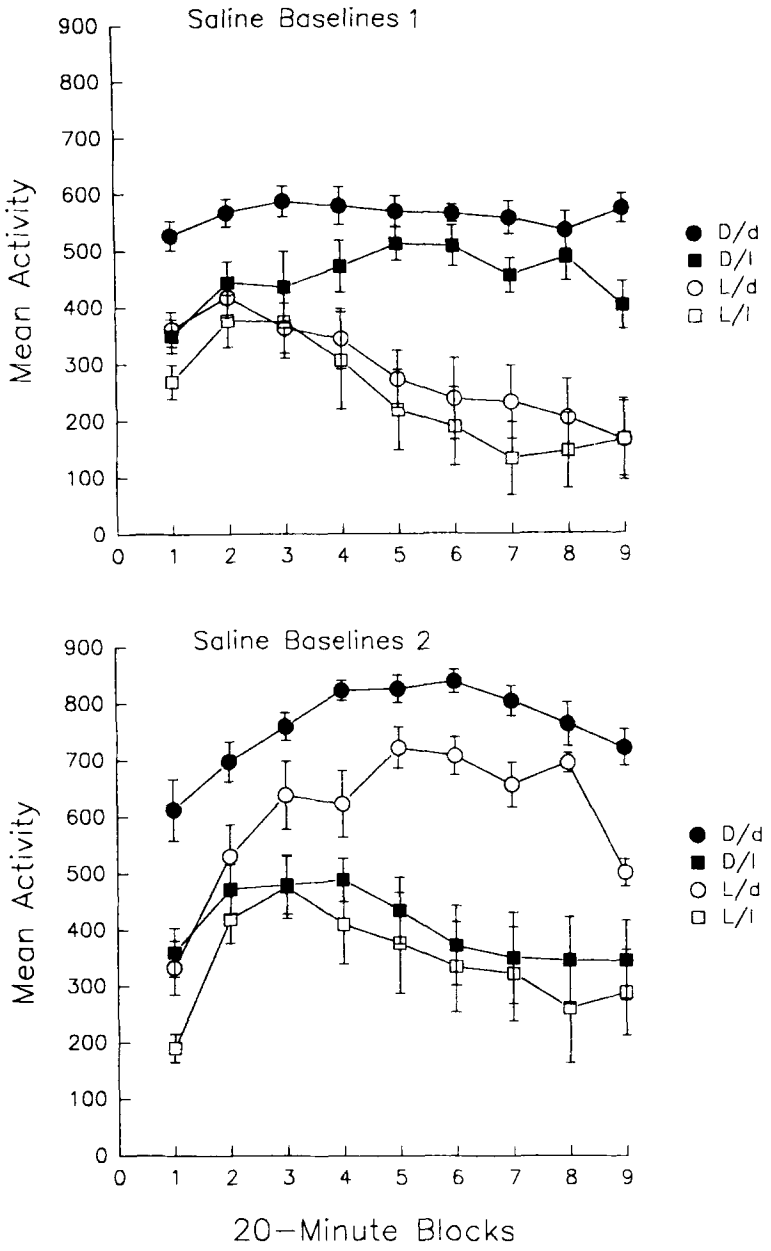

FIG. 1. Mean (± SE) activity in dark (D)- and light (L)-phase animal tested in dark (d) or light (l) environments as a function of 20-min time blocks on saline baseline days 2 and 3 (top) and on saline baseline days 4, 5, and 6 (bottom).

tion of time blocks, collapsed across phase and test environment lighting. It is evident that CCK produced hypoactivity and pimozide attenuated CCK-induced hypoactivity: Group TTA/CCK was less active than group TTA/SAL, whereas group PIM/CCK was more active than group TTA/CCK, $F(8, 128) = 2.18$. Posthoc comparisons using Fisher's LSD test indicated that group TTA/CCK was significantly less active than group TTA/SAL at each time block except the first and last. Furthermore, group PIM/CCK was significantly more active than group TTA/CCK during time blocks 3, 5, 6, 7, and 8.

The effects of phase and test environment lighting continued to influence locomotor activity as they had on the previous 3 baseline days. Animals in the dark phase of the daily cycle were more active than animals in the light phase of the daily cycle, $F(1, 16) = 6.99$. Also, animals were more active in a dark running wheel environment than in a light running wheel environment, $F(1, 16) = 10.64$. In addition, the effect of time blocks was significant, $F(8, 128) = 4.61$, as were the interactions between time blocks and test environment, $F(8, 128) = 4.23$, and among time blocks, phase, and test environment, $F(8, 128) = 2.53$.

Figure 4 shows the effect of CCK and pimozide on activity as a function of phase. ANOVA indicated that the interaction

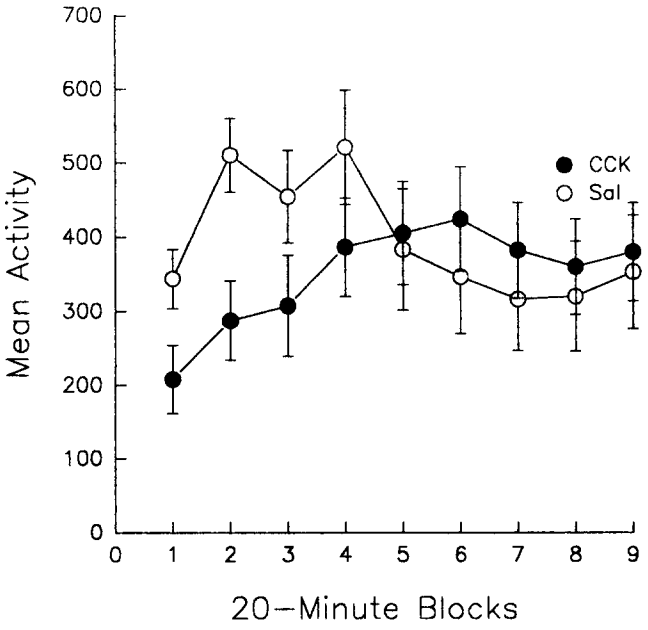

FIG. 2. Mean (±SE) activity on test day 1 as a function of 20-min time blocks for animals given cholecystokinin (CCK) or saline; data collapsed across diurnal phase and ambient lighting conditions.

among drug 1, drug 2, and phase was significant, $F(1, 16) = 4.38$. Among animals tested during the light phase of the daily cycle, CCK produced hypoactivity (group TTA/CCK vs. group TTA/SAL) that was attenuated by prior injection of pimozide (group TTA/CCK vs. group PIM/CCK). Posthoc comparisons using Fisher's LSD test indicated that group TTA/CCK was hypoactive compared both to group TTA/SAL and to group PIM/CCK. Group PIM/SAL was not hypoactive compared to group TTA/SAL. Among animals tested during the dark phase of the daily cycle, none of the pairwise comparisons was significant.

DISCUSSION

The present results confirm our previous finding that CCK has an inhibitory effect on hamster locomotor activity (24,25). Moreover, the present study indicates that diurnal phase modulates CCK's effect on locomotor activity, as we had hypothesized. On the second test day, CCK elicited hypoactivity among animals tested during the light phase of the diurnal cycle but not among those tested during the dark phase of the diurnal cycle (Fig. 4). In our previous study and on the first test day here, CCK-elicited hypoactivity occurred in all groups but its magnitude was greater among animals tested during the light phase of the diurnal cycle than among those tested during the dark phase. A circadian variation in the effect of CCK has been reported in mice (20), wherein CCK (10 μg/kg, IP) elicited hypoactivity in mice tested in the afternoon (1700 h) but not in those tested in the morning (1100 h). In a possibly related finding, it has been reported that the effects of food deprivation on endogenous levels of CCK in brain vary depending upon whether rats are food deprived during the light or dark portion of the diurnal cycle (13). In contrast to the effect of diurnal phase, ambient lighting at the time of test does not affect CCK-elicited hypoactivity.

Hamster locomotor activity was potently affected by diurnal cycle and lighting conditions at the time of test, independently of any drug effect. These effects were evident on baseline days preceding the test days. On both test days, animals tested during the dark phase were more active than animals

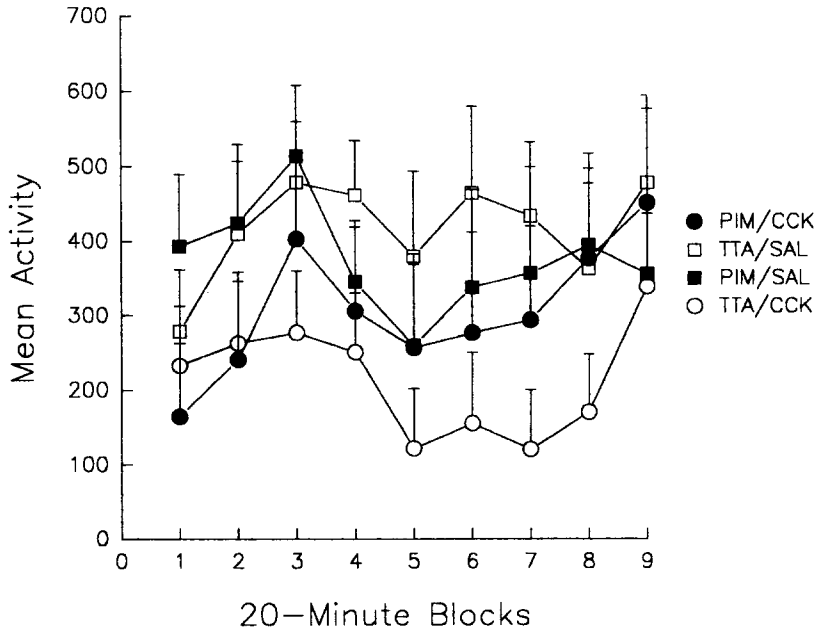

FIG. 3. Mean (±SE) activity on test day 2 as a function of 20-min time blocks for groups PIM/CCK, TTA/CCK, TTA/SAL, and PIM/SAL; data collapsed across diurnal phase and ambient lighting conditions. PIM, pimozide; CCK, cholecystokinin; TTA, tartaric acid; SAL, saline.

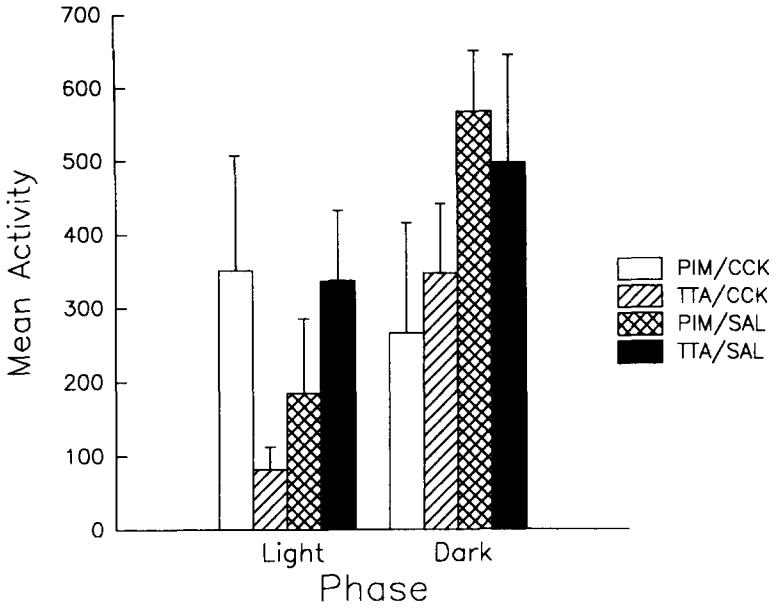

FIG. 4. Mean (±SE) activity on test day 2 as a function of diurnal phase for groups PIM/CCK, TTA/CCK, PIM/SAL, and TTA/SAL; data collapsed across ambient lighting conditions. PIM, pimozide; CCK, cholecystokinin; TTA, tartaric acid; SAL, saline.

tested during the light phase of the diurnal cycle. These results are consistent with what is observed when hamsters have access to a running wheel throughout the day. Under such conditions, 99% of the activity occurs during the dark phase (42). On the second test day, moreover, ambient lighting conditions affected locomotor activity with dark conditions producing more activity than light. This was true both for dark- and light-phase animals; that is, diurnal phase did not interact with the ambient lighting in the running wheel. At present, it is not known how ambient lighting affects hamster locomotor activity, but a similar effect has been reported in rats and mice tested in the open field (34). Perhaps, the relatively low lighting conditions prevailing at the time of high diurnal activity become associated with high levels of activity whereas the relatively high lighting conditions prevailing at the time of low diurnal activity become associated with low levels of activity. Then, independently of diurnal phase, ambient lighting conditions might serve as elicitors of high or low levels of conditioned activity.

The overall increase in activity between baselines 1 and 2 (Fig. 1) reflects a practice or warm-up effect. In numerous studies with hamsters in the running wheel, we have noticed that locomotor activity increases to an asymptote in 4–5 days (22,23). By contrast, the increase in the effect of ambient lighting on locomotor activity (Fig. 1) appears to reflect an adaptation to low illumination, that is, for both dark- and light-phase animals running in the light environment did not change between baselines 1 and 2. Rather, for both groups locomotor activity increased dramatically between baselines 1 and 2 in the dark ambient lighting condition.

The present results suggest that CCK's effect on locomotor activity is mediated, in part, by dopaminergic mechanisms. On the second test day, CCK-elicited hypoactivity was blocked by prior administration of the dopamine receptor blocker pimozide. These results are consistent with other reported interactions between CCK and dopaminergic functioning in the CNS. Not only is CCK found in dopamine-containing neurons in the nucleus accumbens (14) but it has been found that CCK regulates a variety of behavioral, neurochemical, and electrophysiological effects (2,12,16–18,21,26,27,31,33,35,37,38,40) that are under dopaminergic control. For example, CCK alters the release of dopamine from mesolimbic terminals in the nucleus accumbens (18,20,33,36,39) and intraaccumbens injections of CCK potentiate dopamine-induced hyperactivity (9) whereas intra-ventral tegmental area injections of CCK potentiate dopamine-induced hypoactivity (6). However, because pimozide has some activity at D_1 as well as at D_2 receptors (and perhaps on other neurotransmitter systems), future research using highly selective D_1 (e.g., SCH 23390) and D_2 (sulpiride) receptor blockers will be necessary to determine whether CCK-elicited hypoactivity is mediated by one or another receptor type in the hamster. Similarly, CCK is known to act through A and B receptor types. The CCK_A receptor is present in the periphery and the brain, where it may be responsible for mediating CCK's inhibitory effects on food intake (19,30) and locomotion (1,15,20,32). The CCK_B receptor is distributed widely in the brain, including nucleus accumbens, and is responsible presumably for some of CCK's effects on mesolimbic pathway regulation. Research currently underway in our laboratory using selective receptor antagonists (e.g., devazepide, L-365,260) is designed to determine whether CCK-elicited hypoactivity in the hamster is mediated principally by CCK_A or CCK_B receptor types.

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