Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 1, pp. 119–125, 1994

0091-3057/94 $6.00 + .00

0091-3057(93)E0012-S

# Autonomic and Behavioral Thermoregulation in the Golden Hamster During Subchronic Administration of Clorgyline

CHRISTOPHER J. GORDON*[1] AND WALLACE C. DUNCAN, JR.†

*Neurotoxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711*

†*Clinical Psychobiololgy Branch, National Institute of Mental Health, Bethesda, MD 20892*

Received 26 April 1993

GORDON, C. J. AND W. C. DUNCAN, JR. *Autonomic and behavioral thermoregulation in the golden hamster during subchronic administration of clorgyline.* PHARMACOL BIOCHEM BEHAV **48**(1) 119–125, 1994.—Chronic administration of clorgyline, a type-A monoamine oxidase inhibitor, leads to a decrease in peritoneal (i.e., core) temperature of golden hamsters. To better understand the mechanisms of clorgyline's thermoregulatory effects, autonomic and behavioral thermoregulatory effectors were measured in Syrian hamsters following chronic infusion of clorgyline via a minipump (2 mg/kg/day). Metabolic rate, evaporative water loss, motor activity, and core temperature were measured after 60 min of exposure to ambient temperatures ($T_a$) of 5, 20, 30, and 35°C. Behavioral thermoregulatory responses were assessed by measuring selected $T_a$ and motor activity of the same animals in a temperature gradient over the course of 23 h. Metabolic rate and motor activity were significantly elevated in clorgyline-treated hamsters exposed to a $T_a$ of 5°C. There were no effects of clorgyline on evaporative water loss. In the temperature gradient the mean selected $T_a$ of clorgyline-treated hamsters was nearly equal to that of the saline-treated hamsters, 30.7 and 31.2°C, respectively. On the other hand, the mode of selected $T_a$ in the clorgyline group was 2.8°C higher than that of the saline group. Motor activity in the gradient was significantly elevated and food consumption was depressed by clorgyline treatment. Overall, these findings indicate that chronic clorgyline treatment in the golden hamster results in novel autonomic and behavioral modification; it stimulates metabolic thermogenesis during cold exposure, but appears to increase the behavioral zone of thermoneutrality. This latter effect may mean an improvement in heat tolerance, suggesting that this drug might assist in the adaptation to warm temperatures.

Temperature regulation  Behavior  Metabolic rate  Core temperature  Food consumption
Motor activity  Antidepressant  Chronic treatment

THE antidepressant drug clorgyline [*N*-Methyl-*N*-propargyl-3-(2,4-dichlorophenoxy)-propylamine hydrochloride, MW 308.6], a monoamine oxidase inhibitor, selectively and irreversibly binds to type A monoamine oxidase (MAO), preventing the deamination of serotonin, norepinephrine, and dopamine (10,11). In addition to its antidepressant effects, clorgyline treatment leads to a variety of behavioral changes (5,6,9,20,23,24,27). Recently, several thermoregulatory effects of chronic clorgyline treatment have been described. One week of clorgyline treatment decreases the mean 24 h body temperature and minimal metabolic rate in the golden hamster (6,8). Chronic clorgyline treatment is also associated with reduced rapid eye movement (REM) sleep and increased non-REM sleep. These effects on sleep patterns are concomitant with the clorgyline-induced hypothermia (8). Because numerous studies have found marked interactions between thermoregulation and sleep patterns (22,25), it is possible that clorgyline's effect on thermoregulation is related to the changes in sleep–wake pattern (6,8).

Acute and chronic dose response studies in rats indicate that both low (1 mg/kg/day) and high doses (10 mg/kg/day) of clorgyline produce complete inhibition of MAO activity (7). Clinical doses of clorgyline used in this study (2 mg/kg/day) produce marked inhibition (80%) of type A MAO during the first 2 weeks of minipump infusion (26), and central levels of serotonin and dopamine are subsequently elevated by 200% and 50%, respectively (21). Similar doses of clorgyline produce numerous clinical and behavioral effects (5,6,9,20,23,

[1] Requests for reprints should be addressed to Dr. C. J. Gordon, MD-74B, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711.

24,27). Because central administration of 5-HT elicits changes in body temperature of the hamster and other species (4,18), it is likely that clorgyline's effects on thermoregulation are related to altered 5-HT levels in the CNS.

Little is known regarding the effects of clorgyline on behavioral and autonomic thermoregulation. To better understand the mechanism of clorgyline's effect on autonomic thermoregulation, it would be useful to measure the thermoregulatory responses under a wide range of ambient temperatures ($T_a$) such that the thermoregulatory effectors are either activated or suppressed. Moreover, to understand if clorgyline has an effect on the set point for the control of body temperature, it is necessary to evaluate the effect of clorgyline on behavioral thermoregulation (12). That is, if cloryline reduces the set point, then one would predict a preference for cooler $T_a$s concomitant with a reduction in body temperature. On the other hand, if clorgyline reduces body temperature without affecting set point, then one would predict a preference for warmer $T_a$s. Hence, the purpose of this investigation is to measure autonomic and behavioral thermoregulatory responses in the golden hamster treated with chronic clorgyline.

## METHOD

Animals used in this study were male golden hamsters obtained from Sasco Laboratories (Omaha, NB) at an age of 36 days. The hamsters were housed in groups of three in cages lined with wood shavings at a $T_a$ of 22°C, 50% relative humidity, and a LD 14 : 10 photoperiod (lights on at 0800 h). The animals were maintained in these housing conditions for at least 11 days before being tested.

Clorgyline (Research Biochemical Inc., Natick, MA) was administered subcutaneously with an osmotic minipump (Alzet, model 2002) in a physiological saline vehicle at a dose of 2.0 mg/kg/day. Hamsters were anesthetized by inhalation of metofane. A small incision was made for SC insertion of the minipump in the interscapular region, the incision was closed with wound clips, and the hamster was returned to its original housing. Control hamsters were implanted with identical minipumps filled with 0.9% saline.

Saline- and clorgyline-treated hamsters were brought to the laboratory and evaluated for behavioral and autonomic thermoregulatory responses during the second week of drug treatment. This treatment week is associated with a 0.3°C decrease in core temperature when monitored in undisturbed hamsters using a radiotelemetry system (8).

### *Autonomic Responses*

Autonomic responses included metabolic rate (MR), evaporative water loss (EWL), motor activity, and core temperature measured at $T_a$s of 5, 20, 30, and 35°C as described earlier (15). The effects of the four $T_a$s were evaluated during the daytime (0900 to 1600 h) on 2 consecutive days. Animals were exposed to each $T_a$ for 60 min. MR, EWL, and motor activity were sampled for 2.0 min intervals. MR was measured by indirect calorimetry by recording the change in oxygen concentration of the environmental chamber as described previously (15). EWL was determined by first measuring the dew point temperature of the effluent air from the chamber and then converting to EWL in dimensions of mg $H_2O$/ml consumed oxygen. Motor activity was measured using a Doppler-type system which operated with a frequency of 10 g GHz [see (15)]. Core temperature was measured at the end of the test period by inserting a thermocouple in the esophagus for ~5 s. This procedure gave a rapid measure of the hamster's core temperature using a digital recorder [Physitemp model BAT-10; see (14)]. Six hamsters were treated with either saline or clorgyline. Because of technical difficulties, one hamster from each group was dropped from the analysis.

### *Behavioral Responses*

Behavioral thermoregulatory responses were measured using a temperature gradient previously described in detail (16). Briefly, the gradient measured selected ambient temperature and motor activity each minute over a 23 h period while food (Agway 3000) and water were provided ad lib. After the hamster had been tested for its autonomic responses as described above, it was placed in a wire mesh runway positioned inside the temperature gradient. The gradient ranged from approximately 16 to 35°C. Food cups were positioned at the warm and cold ends of the runway. A water tube was positioned in the middle of the gradient. The testing period began at approximately 1000 h and continued for 24 h. Selected $T_a$ and motor activity data were collected at 60 s intervals and stored for later analysis. At the end of the test period the hamster was removed from the gradient and its esophageal temperature was measured as described above. The food cups from the warm and cold ends of the gradient were weighed to the nearest 0.1 g to estimate the amount of food taken. It was not possible to account for the spillage of food from dispensers to calculate food consumption. Food spillage was generally quite minimal in the gradient. Five saline and clorgyline animals were tested in the gradient.

### *Data Analysis*

The autonomic parameters were analyzed for statistical significance using a two-way repeated measures ANOVA which tested for significant effects of treatment and $T_a$ (GB-STAT, Bethesda, MD). Significant interactions between treatment and $T_a$ were then evaluated with a Tukey's protected $t$-test to evaluate significant effects of treatment at a given $T_a$.

Analysis of the behavioral data was conducted using parametric and nonparametric techniques. The selected $T_a$ and the time-normalized motor activity data (i.e., meters $h^{-1}$) were averaged into hourly means. These data were then analyzed for statistical significance using a two-way ANOVA with repeated measures that tested for effects of drug treatment and hours in the gradient. In addition, frequency histograms of the 60 s selected $T_a$ data collected over the 23 h period were constructed to determine the distribution of selected $T_a$ for each hamster. The frequency distributions were compared using nonparametric procedures. The mode of each distribution as well as the percentage of time that the hamsters spent either below a $T_a$ of 28°C or above 32°C [i.e., the approximate lower and upper critical $T_a$s, respectively; see (13)] were calculated and tested for significance using a two-tailed Mann–Whitney test. Mean selected $T_a$ over the entire test period, total motor activity (i.e., distance moved during the entire test period), core temperature after removal from the gradient, and food taken from the warm and cold ends of the gradient were also analyzed using a Student's $t$-test.

## RESULTS

### *Autonomic Responses*

Clorgyline treatment and ambient temperature produced numerous effects on the autonomic parameters (Fig. 1). There were significant main effects of clorgyline treatment, $F$ =

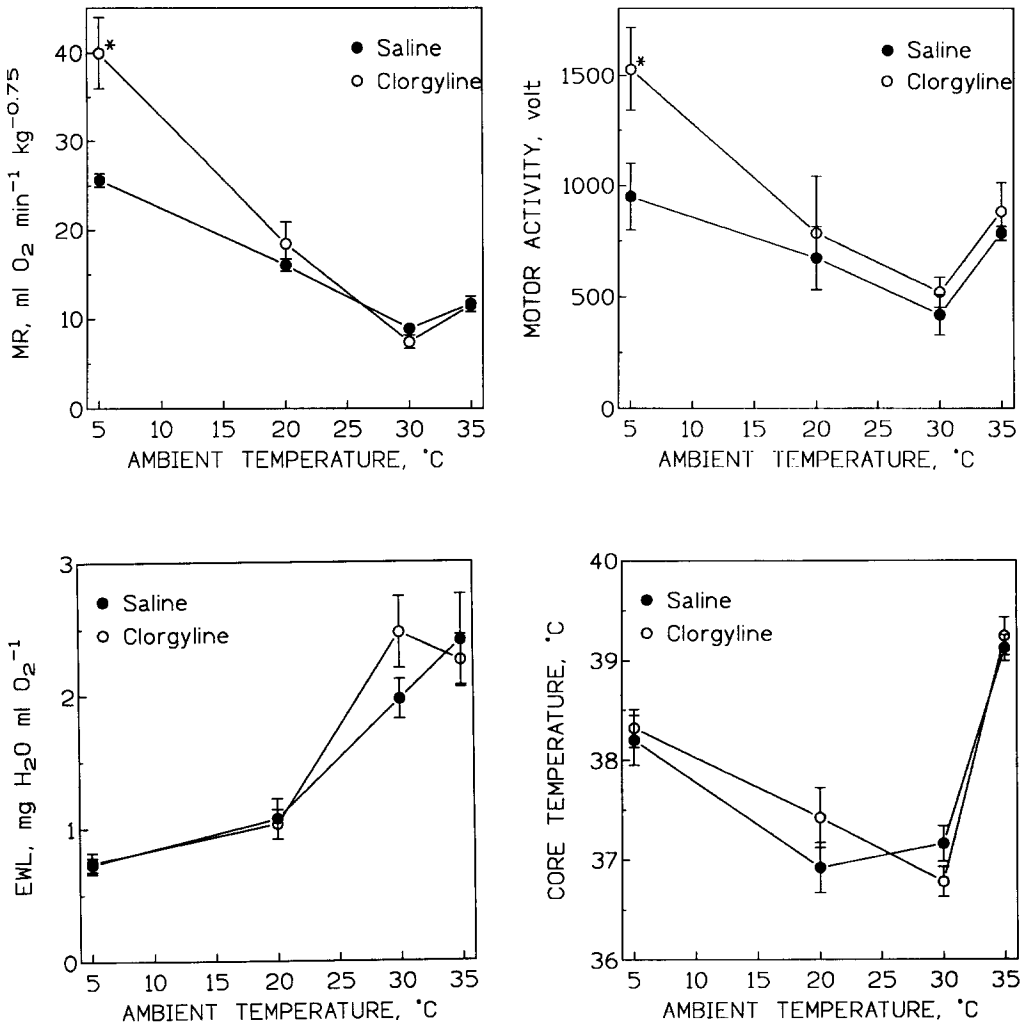


FIG. 1. Effect of 7 to 8 day infusion of saline or clorgyline on metabolic rate (MR), evaporative water loss (EWL), core temperature, and motor activity of golden hamster maintained for 60 min at ambient temperatures of 5 to 35°C. $n$ = 5 per group. Asterisks indicate significant difference between treated and control groups.

11.9, $p$ = 0.008, $T_a$, $F$ = 71.6, $p < 0.0001$, as well as significant interactions between $T_a$ and drug treatment, $F$ = 7.9, $p < 0.007$, on metabolic rate. For both clorgyline-treated and saline-treated animals, minimal and maximal metabolic rates were observed at $T_a$s of 30 and 5°C, respectively. The metabolic rate of the clorgyline-treated group was 56% greater than that of the saline group when tested at a $T_a$ of 5°C. Otherwise, metabolic rate at the warmer $T_a$s was the same between the two treatment groups. There was a marginally significant effect of clorgyline on motor activity, $F$ = 4.5, $p$ = 0.06, but a marked effect of $T_a$ on this parameter, $F$ = 9.3, $p$ = 0.0003 (Fig. 1). Tukey's $t$-test indicated a significant elevation in motor activity in the clorgyline group at a $T_a$ of 5°C ($p < 0.05$). Core temperature and EWL were significantly affected by $T_a$, $F$ = 49, $p < 0.0001$; $F$ = 47, $p < 0.0001$, respectively, but not by clorgyline treatment.

Regression analysis of the motor activity and metabolic rate data indicated a best-fitting relationship using a hyperbolic function (Y = 1/(mX + b) (Fig. 2). For both saline- and clorgyline-treated hamsters, metabolic rate appears to increase only when motor activity increases above a critical level. It is interesting to note that the intercept of the polynomial equations for both treatment groups is equal to approximately 10.5 ml $O_2$/(min $kg^{0.75}$), which is close the the minimal (i.e., basal) metabolic rate.

Clorgyline also had a significant effect on body weight. Saline animals weighed 145.4 g at surgery and 151.0 g at first testing; clorgyline animals weighed 144.6 g at the time of surgery and 134.3 g at first testing. The loss in body weight of the clorgyline group was significant when compared to the presurgical weights (paired $t$-test, $t$ = 2.77, $p < 0.039$).

### *Behavioral Responses*

The selected $T_a$ responses recorded each minute reveal dynamic behavioral patterns of the hamsters when placed in the temperature gradient for 1 day (Fig. 3). In these examples, both saline- and clorgyline-treated hamsters preferred warm over cold ends of the gradient, and this preference shifted with time of day. During the first 2 hours in the gradient

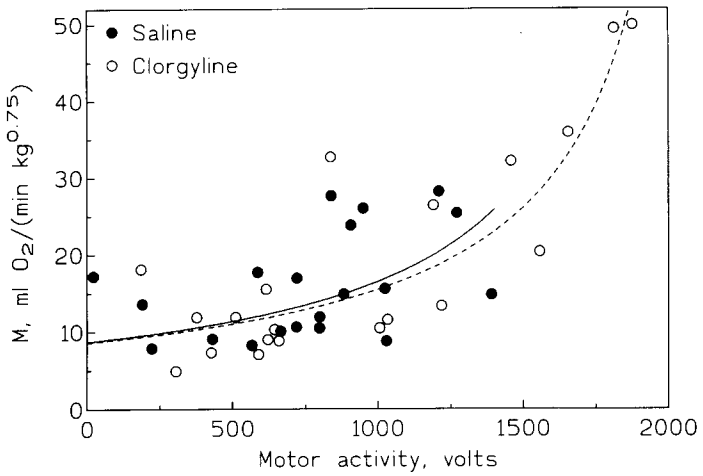


FIG. 2. Correlation between motor activity and metabolic rate in saline and clorgyline hamsters exposed to ambient temperatures of 5, 20, 30, and 35°C. Data were fit with a hyperbolic relationship: saline group, Y = 1/(−5.45E−05*X + 0.115), $r^2$ = 0.3; clorgyline group, Y = 1/(−5.22E−05*X + 0.116), $r^2$ = 0.77).

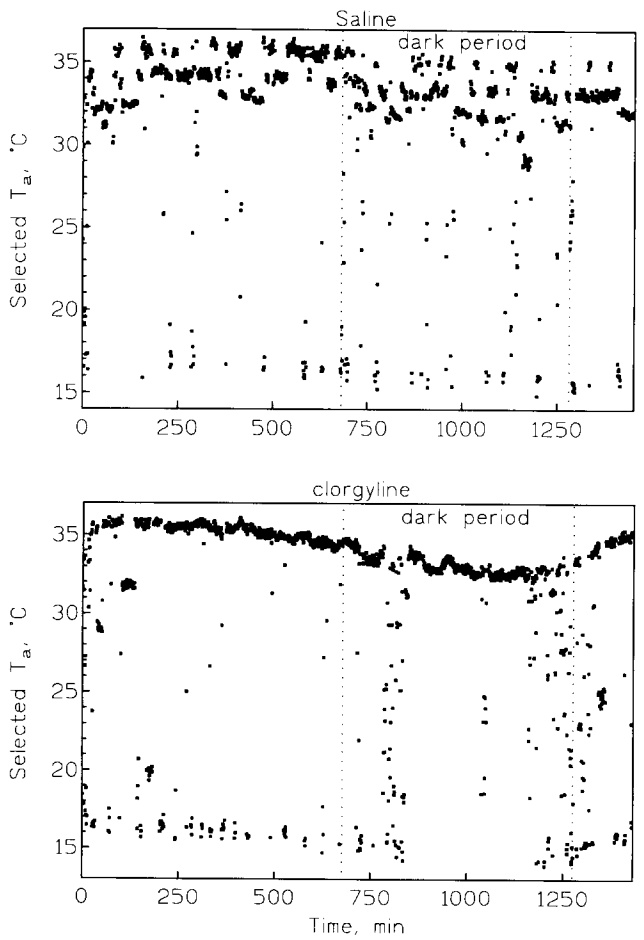


FIG. 3. Examples of the selected $T_a$ response recorded each minute in a saline- and clorgyline-treated hamster placed in the temperature gradient.

hamsters selected warm $T_a$s of ~ ~32°C. At the onset of the dark cycle, the hamsters exhibited a decrease in selected $T_a$ that was concomitant with an increase in motor activity. Compared to the saline-treated hamsters, the clorgyline-treated hamster preferred a narrower band of warm $T_a$s as evidenced by the dense clustering of selected $T_a$s (Fig. 3). Increased motor activity at dusk and dawn in the clorgyline-treated hamsters is evident by the vertical bands of points at the beginning and end of the dark period.

Repeated measures ANOVA of the 60 min averages of these data indicated that selected $T_a$ was significantly affected by hour in the gradient ($F$ = 3.7, $p$ < 0.0001) but unaffected by clorgyline treatment ($F$ = 1.0, $p$ = 0.33; Fig. 4). Motor activity in the gradient was significantly affected by both clorgyline treatment ($F$ = 6.9, $p$ = 0.029) and hour ($F$ = 4.5, $p$ < 0.0001). Motor activity of the clorgyline group showed two distinct peaks, one at the beginning and one at the end of the dark period. Motor activity of the saline group displayed a single peak at the onset of the dark period. Total motor activity reflected the time-average data presented in Fig. 4 (120.6 ± 5.7 meters for the saline group and 229.6 ± 30 meters for the clorgyline group; $p$ < 0.05).

Nonparametric analysis of the selected $T_a$ data demonstrated significant effects of clorgyline treatment. The frequency distribution of selected $T_a$ was markedly altered by clorgyline treatment (Fig. 5). The mode of selected $T_a$ in the saline group was nearly equal to the mean, whereas in the clorgyline group the mode was 2.8°C greater than the mean $T_a$ (Table 2). The Mann–Whitney $U$-test indicated that clorgyline produced an upward shift in the mode of $T_a$ relative to saline ($p$ = 0.008). This shift in distribution is clearly seen in the selected $T_a$ frequency plot (Fig. 5). Nonparametric analysis of these data indicate that clorgyline caused a significant increase in the percentage of time spent at $T_a$s below and above the normal thermoneutral zone (Table 3).

While housed in the temperature gradient, total food taken by the clorgyline group was only 39% of that taken by the saline group (Table 1). Moreover, the saline animals took 6.45 times as much food from the warm end as from the cold end of the gradient, whereas this ratio was only 0.9 in the clorgy-

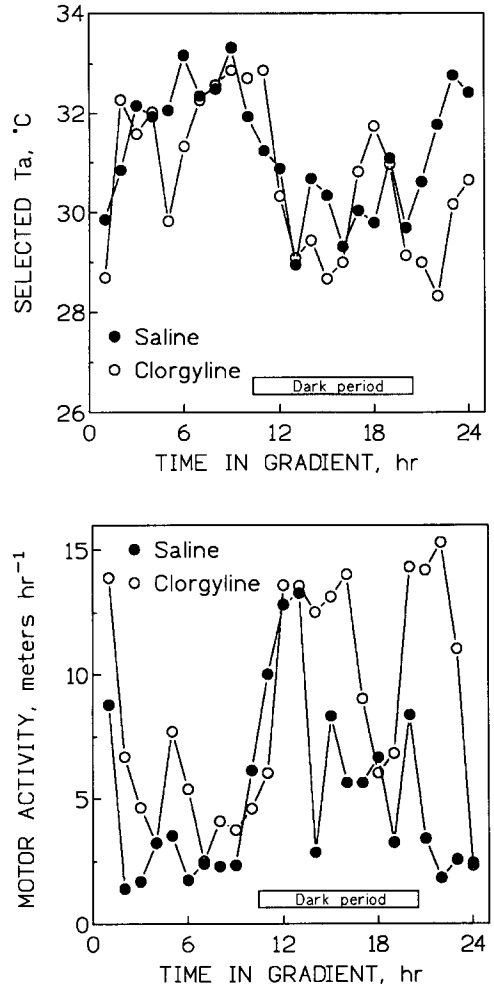


FIG. 4. Time course of 60 min averages of selected $T_a$ and motor activity of golden hamsters treated with saline or clorgyline. $n = 5$ for each group.

line group. Core temperature after removal from the temperature gradient was not significantly different between the two groups (37.6 ± 0.25°C for the saline group and 37.1 ± 0.12°C for the clorgyline group).

## DISCUSSION

To the best of our knowledge, this is the first attempt to characterize the changes in behavioral and autonomic thermo-

TABLE 1

TOTAL FOOD TAKEN FROM THE WARM AND COLD END OF TEMPERATURE GRADIENT*

| Treatment | Food Taken from Dispenser, g | | |
|---|---|---|---|
| | Total | Cold | Warm |
| Saline | 21.6 ± 2.8 | 2.9 ± 1.0 | 18.7 ± 2.6 |
| Clorgyline | 8.4 ± 0.7† | 4.5 ± 1.3 | 3.9 ± 1.4† |

*Calculation of food taken from dispensers did not take into account the spillage of food.

†$p < 0.05$ when compared to saline group.

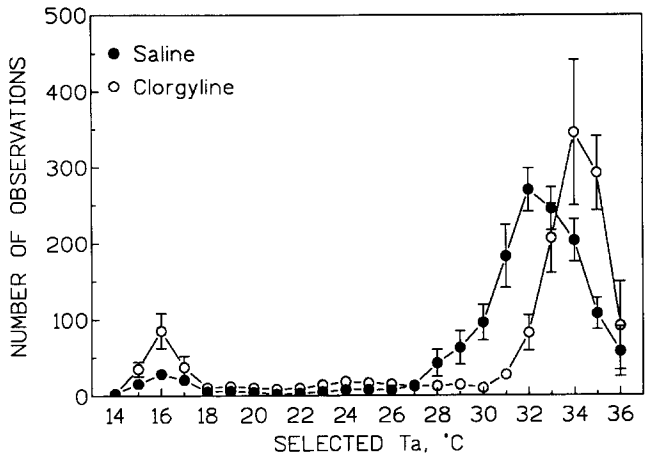


FIG. 5. Average frequency distribution of selected $T_a$ data observed at 60 s intervals from hamsters treated with saline or clorgyline and placed in the temperature gradient for 23 h. Data plotted as mean ± SE. ($N = 5$ per treatment group).

regulatory responses of a rodent subjected to chronic clorgyline treatment. A major change in autonomic thermoregulation occurred during exposure of clorgyline animals to a relatively cold $T_a$ of 5°C. Clorgyline treatment resulted in a marked elevation in metabolic rate at this $T_a$ but had no effect at warmer $T_a$s of 20, 30, and 35°C. Clorgyline had no effect on EWL of hamsters exposed to a $T_a$ of 35°C. A $T_a$ of 35°C is likely to pose a mild heat stress to hamsters because they normally select $T_a$s of 32–33°C during the daytime [see Fig. 4 and (17)]. In view of the increase in mode of selected $T_a$ in the clorgyline-treated hamsters, it will be of future interest to study the sensitivity of hamsters to severe heat stress following clorgyline treatment.

On the other hand, behavioral thermoregulatory responses appeared to be affected in several ways by clorgyline. Although the mean selected $T_a$ was unaffected, it was clear that clorgyline-treated hamsters in the gradient had an altered distribution in selected $T_a$. There was an upward shift in the mode of selected $T_a$, suggesting an elevation in the zone of

TABLE 2

INDIVIDUAL MODE AND MEAN SELECTED $T_a$ DETERMINED BY ANALYSIS OF SELECTED $T_a$ RESPONSES AT 60 s INTERVALS*

| Hamster No. | Treatment | Mode $T_a$, °C | Mean $T_a$, °C |
|---|---|---|---|
| 1 | Saline | 31 | 30.4 |
| 2 | Saline | 33 | 32.0 |
| 3 | Saline | 31 | 30.5 |
| 4 | Saline | 32 | 31.2 |
| 5 | Saline | 32 | 31.4 |
| 1 | Clorgyline | 34 | 31.6 |
| 2 | Clorgyline | 34 | 31.8 |
| 3 | Clorgyline | 35 | 29.0 |
| 4 | Clorgyline | 35 | 31.0 |
| 5 | Clorgyline | 35 | 30.0 |

*Mann–Whitney tests showed significant increase in mode of selected $T_a$ in clorgyline group ($p < 0.0008$).

TABLE 3
MANN-WHITNEY RESULTS OF SELECTED $T_a$ RESPONSE

| Treatment | No. | Percent Time < 28°C | Rank | Percent Time > 32°C | Rank |
|---|---|---|---|---|---|
| Saline | 2 | 9.8 | 4 | 65.4 | 6 |
| Saline | 5 | 9.1 | 3 | 45.7 | 4 |
| Saline | 1 | 8.3 | 1 | 26.8 | 1 |
| Saline | 4 | 8.7 | 2 | 42.7 | 3 |
| Saline | 3 | 11.4 | 5 | 37.6 | 2 |
| | | mean = 9.5 | | mean = 43.6 | |
| Clorgyline | 4 | 19.7 | 8 | 69.6 | 8 |
| Clorgyline | 2 | 12.8 | 6 | 78.2 | 10 |
| Clorgyline | 3 | 33.2 | 10 | 54.8 | 5 |
| Clorgyline | 5 | 26.7 | 9 | 69.3 | 7 |
| Clorgyline | 1 | 12.8 | 7 | 69.7 | 9 |
| | | mean = 21.0 | | mean = 68.3 | |

Percent time hamsters spent below $T_a$ of 28°C and above 32°C has been calculated and ranked. *Ranks show that compared to saline treatment the clorgyline hamsters spent a greater percentage of time at $T_a$s less than 28°C ($p = 0.008$) and greater than 32°C ($p < 0.05$).

thermoneutrality. However, there was also a tendency for clorgyline-treated hamsters to prefer colder $T_a$'s (Table 3). Clorgyline-treated hamsters were also more active than saline-treated hamsters in the gradient.

The effects of clorgyline on behavioral thermoregulation were complex. On the one hand, selected $T_a$s were lower during the night than during the day in both the saline and clorgyline treatment groups, a response that has been reported for both rat and golden hamster (2,17). Furthermore, the 24 h mean selected $T_a$ was not statistically different between the two groups, possibly because of the more pronounced bimodal distribution of selected $T_a$s in the clorgyline animals. On the other hand, there was a marked elevation in the mode of selected $T_a$ for the clorgyline group. Analysis of this frequency distribution indicated that relative to the saline-treated hamsters, clorgyline treatment led to a significant increase in the percentage of time spent above 32°C, as well as below 28°C, the upper and lower limits of the hamster's thermoneutral zone (13).

This unusual thermoregulatory behavior could be related to clorgyline's effects on body temperature, metabolic rate, and motor activity. The increase in the mode of the selected $T_a$ coupled with an increase in motor activity in the temperature gradient is, indeed, a novel response. Normally, rodents in a temperature gradient display a reduced selected $T_a$ concomitant with increased motor activity at night (17). In view of the increased motor activity, we would have expected an overall reduction in selected $T_a$ of the clorgyline group. Thus, the increase in mode of the selected $T_a$ may be unrelated to the hamster's motor activity. The fact that chronic clorgyline treatment lowers peritoneal and brain temperature should also be considered in evaluation of the behavioral response. Based on the inverse relationship between body temperature and selected $T_a$ over a 24 h period (2,17), a reduction in body temperature would lead one to expect an increase in the selected $T_a$ if thermal sensory processes are operating normally. Thus, it is possible that an increased mode of selected $T_a$ is a mechanism of cold defense in the clorgyline-treated hamster. Finally, one should not preclude the possibility that an altered distribution in selected $T_a$ is an indication of dysfunction of the central neural processing of thermal information. An impairment in heat sensitivity would conceivably lead to an increase in the mode of the selected $T_a$. A recent study has found that chronic clorgyline treatment identical to that of the present study leads to a doubling of hypothalamic serotonin levels in the hamster (21). Such marked neurochemical changes in the CNS could lead to altered behavioral thermoregulatory patterns.

Using an esophageal temperature probe, we were unable to statistically confirm the hypothermic effect of clorgyline that was previously observed in hamsters. Using noninvasive radiotelemetry techniques, it was observed that clorgyline treatment led to a 0.4°C decrease in core temperature of the Syrian hamster (8). Because handling stress and insertion of probe can cause transient elevations in core temperature (1), it is likely that the procedures used in this study (i.e., esophageal temperature and metabolic measurements in this study were made after a 60 min test period in the environmental chamber) caused enough stress to obviate the effect of clorgyline on body temperature, a thermoregulatory pattern that is amenable to detection in undisturbed animals using radiotelemetry. Alternatively, it has been observed during radiotelemetry studies that at some phases during the light there were no differences in core temperature of clorgyline- vs. saline-treated hamsters (8).

It is not clear why clorgyline treatment resulted in an elevation in metabolic rate in the cold. There are two possible explanations for this elevation. First, as shown by the regression analyses of motor activity and metabolic rate, increased activity is associated with higher metabolic rates (Fig. 2). In view of the higher motor activity of the clorgyline hamsters tested at 5°C, it could be concluded that the higher metabolic rates in this group was a reflection of their increased motor activity. A second possibility is that clorgyline increased the development of brown adipose tissue (BAT) thermogenesis. Preliminary data suggests that chronic clorgyline treatment (e.g., <2 weeks) initially enhances BAT development in the hamster, but continued treatment (e.g., >4 weeks) leads to BAT atrophy (Duncan and Gordon, unpublished observations). If BAT hypertrophy occurs, then one would expect an increased metabolic rate during cold exposure, as occurs in rodents acclimated to cold $T_a$s (19). Further, one would also expect an increase in basal metabolism measured at thermo-

neutrality, but this was not observed in the present study (Fig. 1). With regard to BAT atrophy, it is interesting to note that minimal metabolic rate (i.e., metabolic rate during inactivity) measured over a 24 h period at a $T_a$ of 22°C was reduced in hamsters treated with clorgyline for 1 month (6), which was a longer treatment course that could have resulted in diminished BAT thermogenesis and metabolic rate. The fact that the clorgyline effect on metabolic rate was seen only during cold exposure could represent an unusual aspect of this drug that deserves further study.

To summarize, we found that chronic infusion of clorgyline in the hamster produced behavioral and autonomic thermoregulatory changes. Clorgyline caused a significant elevation in metabolic rate in hamsters exposed to a cold $T_a$ of 5°C, a response that may be related to clorgyline's effect on motor activity and/or BAT thermogenesis. Behavioral thermoregulation appears to be affected by clorgyline treatment. The clorgyline-treated animals were more active in the temperature gradient, spent more time outside of the normal zone of thermoneutrality, and had a significantly higher mode of their selected $T_a$. This behavioral response indicates an upward shift in the zone of thermoneutrality and perhaps an improvement in the ability to adapt to warm $T_a$s during clorgyline treatment. The fact that clorgyline treatment enhanced cold-induced thermogenesis and increased preference for warm $T_a$s may improve our understanding of the drug's thermoregulatory properties.

ACKNOWLEDGEMENTS

This paper has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

We thank L. Fogelson for providing technical assistance. We also thank Drs. T. Wehr and N. Ozaki for their review of the manuscript.

## REFERENCES

1. Berky, D. L.; Meeuwsen, K. W.; Barney, C. C. Measurements of core temperature in spontaneously hypertensive rats by radiotelemetry. Am. J. Physiol. 258:R743–R749; 1990.
2. Briese, E. Rats prefer ambient temperatures out of phase with their body temperature circadian rhythm. Brain Res. 345:389–393; 1985.
3. Campbell, I. C.; Robinson, D. S.; Lovenberg, W.; Murphy, D. L. The effects of chronic regiments of clorgyline and pargyline on monoamine metabolism in the rat brain. J. Neurochem. 32: 49–55; 1979.
4. Clark, W. G.; Lipton, J. M. Changes in body temperature after administration of adrenergic and serotonergic agents and related drugs including antidepressants: II. Neurosci. Biobehav. Rev. 10: 153–220; 1986.
5. Duncan, W. C.; Tamarkin, L.; Sokolove, P. G.; Wehr, T. A. Chronic clorgyline treatment of Syrian hamsters: An analysis of effects on the circadian pacemaker. J. Biol. Rhythms 3:305–322; 1988.
6. Duncan, W. C.; Gao, B.; Wehr, T. A. Light and antidepressant drugs: Interactins with vigilance states, body temperature and oxygen consumption in Syrian hamsters. In: Horne, J., ed. Sleep '90. Bochum: Pontenagel Press; 1990:356–359.
7. Felner, A. E.; Waldmeir, P. C. Cumulative effects of irreversible MAO inhibitors in vivo. Biochem. Pharmacol. 28:995–1002; 1979.
8. Gao, B.; Duncan, W. C.; Wehr, T. A. Clorgyline-induced reduction in body temperature and its relationship be vigilance states in Syrian hamsters. Neuropsychopharmacology 4:187–197; 1991.
9. Garrick, N. A.; Redmond, D. E.; Murphy, D. L. Primate-rodent monoamine oxidase differences. In: Singer, T. P.; Von Korf, R. W.; Murphy, D. L., eds. Monoamine oxidase: Structure, function, and altered functions. New York: Academic Press: 1979: 351–359.
10. Garrick, N. A.; Murphy, N. L. Species differences in the deamination of dopamine and other substrates for monoamine oxidase in brain. Psychopharmacology (Berlin) 72:27–33; 1980.
11. Garrick, N. A.; Murphy, D. L. Monoamine oxidase type A: Differences in selectivity towards l-norepinephrine compared to serotonin. Biochem. Pharmacol. 31:4061–4066; 1982.
12. Gordon, C. J. A review of terms and proposed nomenclature for regulated vs. forced, neurochemical-induced changes in body temperature. Life Sci. 32:1285–1295; 1983.
13. Gordon, C. J.; Fehlner, K. S.; Long, M. D. Relationship between autonomic and behavioral thermoregulation in the golden hamster. Am. J. Physiol. 251:R320–R324; 1986.
14. Gordon, C. J.; Fogelson, L. Comparative effects of hypoxia on behavioral thermoregulation in rats, hamsters, and mice. Am. J. Physiol. 260:R120–R125; 1991.
15. Gordon, C. J.; Fogelson, L. Comparison of rats of the Fischer 344 and Long-Evans strains in their autonomic thermoregulatory response to trimethyl tin administration. J. Toxicol. Environ. Health 32:141–152; 1991.
16. Gordon, C. J.; Lee, K. A.; Chen, T. A.; Killough, P.; Ali, J. Dynamics of behavioral thermoregulation in the rat. Am. J. Physiol. 261:R705–R711; 1991.
17. Gordon, C. J. 24-hour rhythms of selected ambient temperature in rat and hamster. Physiol. Behav. 53:257–263; 1993.
18. Jansky, L. Time sequency of physiological changes during hibernation: The significance of serotonergic pathways. In: Wang, L. C. H.; Hudson, J. W., eds. Strategies in cold. New York: Academic Press; 1978:299–326.
19. Kopecky, J.; Sigurson, L.; Park, I. R.; Himms-Hagen, J. Thyroxine 5'-deiodinase in hamster and rat brown adipose tissue: Effect of cold and diet. Am. J. Physiol. 251:E1–E7; 1986.
20. Lipper, S.; Murphy, D. L.; Slater, S.; Buchsbaum, M. Comparative behavioral effects of clorgyline and pargyline in man: A preliminary evaluation. Psychopharmacology (Berlin) 62:123–128; 1979.
21. Ozaki, N.; Duncan, W. C.; Johnson, K. A.; Wehr, T. A. Diurnal variation of serotonin and dopamine levels in discrete brain regions of Syrian hamsters and their modification by chronic clorgyline treatment. Brain Res. 627:41–48; 1993.
22. Parmeggiani, P. L. Interaction between sleep and thermoregulation: An aspect of the control of behavioral states. Sleep 10:426–435; 1987.
23. Pickar, D.; Murphy, D. L.; Cohen, R. M.; Campbell, J. C.; Lipper, S. Selective and nonselective monoamine oxidase inhibitors. Arch. Gen. Psychiatry 39:535–540; 1982.
24. Potter, W. Z.; Murphy, D. L.; Wehr, T. A.; Linnoila, M.; Goodwin, F. K. Clorgyline. A new treatment for patients with refractory rapid cycling disorder. Arch. Gen. Psychiatry 39:505–510; 1982.
25. Szymusiak, R.; Satinoff, E. Maximal REM sleep time defines a narrower thermoneutral zone than does minimal metabolic rate. Physiol. Behav. 26:687–690; 1981.
26. Wirz-Justice, A.; Campbell, I. C. Antidepressant drugs can slow or dissociate circadian rhythms. Experentia 38:1301–1309; 1982.
27. Zametkin, A.; Rapoport, J. L.; Murphy, D. L.; Linnoila, M.; Ismond, D. Treatment of hyperactive children with monoamine oxidase inhibitors. Arch. Gen. Psychiatry 42:962–966; 1985.