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Behavioral Effects of Pergolide Mesylate on Food Intake and Body Weight

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GREENE, S. B., D. MATHEWS, E. M. HOLLINGSWORTH AND C. P. GARBIN. *Behavioral effects of pergolide mesylate on food intake and body weight.* PHARMACOL BIOCHEM BEHAV **23**(2)161–167, 1985.—In a crossover design experiment, pergolide mesylate significantly suppressed food intake and body weight in spayed female rats. Inhibition of food intake by a constant dose of pergolide progressively diminished with repeated administrations. Pergolide continued to suppress body weight with no indications of tolerance. When pergolide was discontinued, body weight increased sufficiently to compensate for the loss and failure to gain during drug treatment. A second experiment investigated the observation that animals injected first with vehicle showed greater anorexia when subsequently injected with pergolide than did animals injected first with pergolide. In addition, tolerance was further assessed by administering on two occasions a higher dose of pergolide. Following chronic pergolide treatment, this dose was insufficient to reinstate anorexia; however, after a period of abstinence, this dose produced anorexia comparable to that observed at the beginning of pergolide treatment. Due to pergolide mesylate's action as a postsynaptic dopamine agonist, a dopaminergic neural system is implicated in pergolide induced anorexia.

Pergolide mesylate Anorexia Dopamine agonist Food intake Body weight Tolerance

CONSIDERABLE pharmacological and neurophysiological evidence suggests that central nervous system dopamine (DA) neurons exert inhibitory control over food consumption [1, 2, 10, 14]. Drugs which act either directly or indirectly to stimulate the DA system are frequently effective anorectic agents, amphetamines being a classic example [13, 22, 23]. Amphetamine acts presynaptically to increase brain DA [9] and drugs which block neural DA receptors or inhibit DA synthesis attenuate amphetamine anorexia [4, 14, 19]. A variety of other DA agonists, these acting postsynaptically to stimulate directly DA receptors, have also been reported to exert dose and time dependent anorectic effects when acutely administered. These drugs include apomorphine, ergolines such as lisuride, lergotrile, and bromocriptine [7,14], and a piperonyl pyrimidil derivative, piribedil [6].

The purpose of the present study was to examine the effects of a new DA agonist, pergolide mesylate, on food intake and body weight. This drug, an N-propylergoline derivative, is a potent postsynaptic stimulator of DA receptors, particularly in the striatum and olfactory tubercle [12]. Behaviorally, this drug at high doses stimulates stereotypy, circling and vomiting [17], and is effective in reversing the symptoms of experimentally induced Parkinsonism in animal models [17]. Thus, pergolide seems to be very similar in its effects to other DA agonists. Biochemically, however, pergolide has some characteristics which some of the other DA agonists lack which may affect its efficacy as an anorectic agent. It is long acting, probably due to slow metabolism of the drug, and therefore capable of producing contralateral turning in unilaterally lesioned rats which lasts almost ten times as long as that seen with other DA agonists [12]. This would render it more effective in chronic administration than other DA agonists whose duration of action is quite short, necessitating more frequent drug administrations. In addition, unlike some of the other ergoline agonists, pergolide stimulates intrastriatal DA receptors linked to adenylate cyclase in cell-free homogenates of striatal tissue [12].

In the present study, we administered pergolide over an extended period of time (15–22 days) because it seemed to us that this would determine most clearly its potential as a long term anorectic drug, as well as demonstrate cumulative toxic effects. The specific hypotheses we examined were that (1) pergolide treatment would suppress food intake and therefore body weight, and (2) tolerance to the anorectic effects of pergolide, as with amphetamine, would develop with prolonged treatment.

EXPERIMENT 1

METHOD

Animals

The subjects were 16 naive Long-Evans Hooded female

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rats weighing 231–295 grams. Females were selected for this study because we intended to use them in additional studies on the effect of pergolide on sexual behavior. To control for estrogen induced fluctuations in body weight, all females were ovariectomized-hysterectomized using Chlorapent anesthesia (2.8 ml/kg of body weight, IP). Each female was caged individually and the colony was maintained on a reversed light-dark cycle with lights off between 12:00 and 22:00 hours. Following recovery from ovariectomy, food was restricted to the first four dark hours each day (12:00–16:00 hr) with water continuously available. After three weeks, body weight for all rats stabilized and experimental procedures began.

Drug Treatment

Pergolide mesylate (pergolide; Eli Lilly and Co., Indianapolis, IN) was dissolved in Krebs-Ringer solution (a buffered saline, hereafter referred to as "Ringer"). Overnight heating and continuous stirring were necessary to dissolve the pergolide. Half of the animals received the pergolide solution and the other half only the Ringer. All the rats were injected intraperitoneally with a volume of solution equal to 1 ml/kg of body weight at 11:30 hours daily. Pergolide was prepared as a 100 μg/ml solution. Both solutions were maintained at a pH of 7.2 at room temperature.

In administering the drug, we chose to employ a reversal design in which each group received both pergolide and Ringer injections. The rationale for this design was that treatment could be compared not only between subjects, but within subjects as well, thereby strengthening any statements regarding effects of the drug. The reversal design also allows the analysis of any "carryover" effects the drug itself may produce. This paradigm is employed in the clinical analysis of drug effects and is, we feel, equally applicable here in the animal model.

Procedure

During all phases of the experiment, food intake was determined daily after the 4 hours access (16:00) by subtracting the weight of leftover food in the bottom of the cage (plus spillage beneath the cage) from the initial amount of food placed in the cage. Body weight for all animals was measured at 16:15 hours daily.

After the initial baseline phase consisting of food and weight measurement for 5 days, the animals were divided into 2 groups balanced for body weight and food intake. On days 6 through 27, the Ringer-pergolide group was injected with the Ringer vehicle and the pergolide-Ringer group was injected with the pergolide solution 30 minutes before the food was made available. On days 28 through 42, the drug manipulations were reversed with the Ringer-pergolide rats receiving pergolide injections and the pergolide-Ringer rats receiving the Ringer at 11:30 hours, followed by food access from 12:00 to 16:00 and measurements after 16:00 hours. From day 43 onward, injections were discontinued, animals were allowed to feed freely and body weights were recorded daily for the next 7 days. To check for the possibility that pergolide induced a taste aversion to the lab chow, the 4 hour limited access to food was reinstated on days 47–49, with food intake and body weight recorded daily.

Data Analysis

The major purpose of the analyses were (1) to determine the effects of initial and prolonged daily injections of pergolide on food intake and body weight, and (2) to determine whether order of treatment (i.e., Ringer-pergolide versus pergolide-Ringer) produced an effect on food intake and body weight.

Food intake data was analyzed by collapsing the data into six aggregate data points, based upon average daily intake during blocks of time clustered around the days of treatment change. Block 1 consisted of the initial baseline period of 5 days; block 2 was the first four days of drug treatment (days 6–9); block 3 was the last four days of drug treatment (24–27); block 4 was the first four days of drug reversal (28–31); block 5 was the last four days of drug reversal (39–42); and, the sixth block was days 47–49, the three days of food measurement after treatment withdrawal. These data were initially analyzed with a mixed effects ANOVA and the expected interaction was further analyzed with Tukey Tests, which provide a conservative and powerful test in terms of a similar effects of treatment blocks within each treatment group and also within specific treatment phases using both *a priori* and *post-hoc* hypotheses [25].

Body weight data were similarly aggregated and analyzed, the only exception to the above was that block 6 was days 43–49, during which time weight was recorded but treatment was discontinued.

RESULTS

Food Intake

While the overall ANOVA revealed no group effect on food intake, $F(1,14)=1.08$, $p>0.3$, there was both a time block effect, $F(5,70)=19.01$, $p<0.001$, and a group by time block interaction, $F(5,70)=29.85$, $p<0.001$. Tukey analyses of simple main effects of food intake within each group demonstrated that pergolide clearly had an anorectic effect on food intake (Fig. 1). The Ringer-pergolide group showed no significant difference in food intake from block 1 to 2 (baseline to Ringer treatment) or from block 2 to 3 (first 4 days of Ringer to last 4 days of Ringer); however, this group did show a significant decrease in food intake from block 3 to 4 (last 4 days of Ringer to first 4 days of pergolide). A significant increase in food intake occurred from block 4 to 5 (first 4 days to last 4 days of pergolide), suggesting that tolerance to pergolide had occurred. The last comparison, from block 5 to 6, showed a significant recovery of food intake, $F(1,35)=10.69$, $p<0.05$, from the last 4 days of pergolide treatment to the 3 days of food measurement after drug withdrawal. Similarly, analyses of food intake in the pergolide-Ringer group showed a significant decrease in food intake when pergolide was administered, block 1 to 2, $F(1,35)=41.41$, $p<0.01$, and a significant increase in food intake with chronic administration of pergolide, block 2 to 3, $F(1,35)=13.89$, $p<0.01$, once again suggesting a tolerance effect.

Between group analyses of food intake during the same treatment phase revealed a significant order effect of drug administration (Fig. 1). During the first 4 days of pergolide treatment, food intake was similar for both groups. During the last 4 days of pergolide treatment however, the pergolide-Ringer group had returned to baseline levels of consumption, while the Ringer-pergolide group was still consuming significantly less, $F(1,35)=19.13$, $p<0.05$. During the Ringer's treatment phase, food intake for both groups was essentially the same, both the first and last 4 days of treatment.

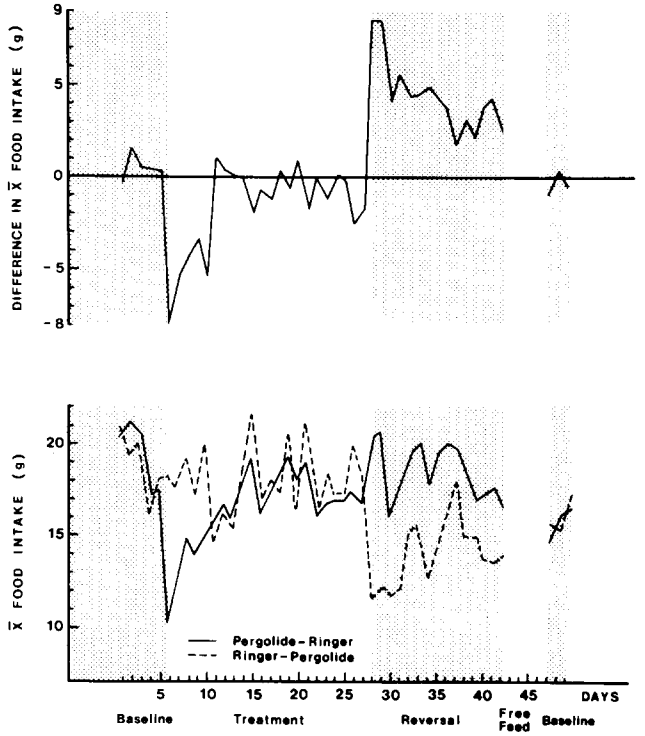

FIG. 1. Effects of pergolide mesylate on food intake. Lower panel represents the daily X̄ food intake for the Ringer-pergolide group (dotted line) which was injected with Ringer during treatment phase and pergolide during reversal and the pergolide-Ringer group (solid line) which was injected with pergolide during treatment and Ringer during reversal. Upper panel represents the difference in daily X̄ food intake between the 2 groups.

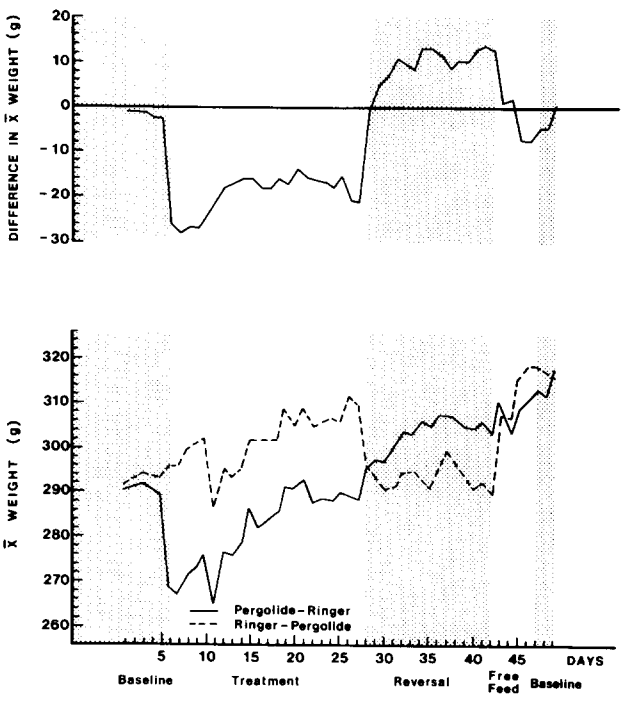

FIG. 2. Effects of pergolide mesylate on body weight. Lower panel represents the daily X̄ body weight for the Ringer-pergolide group (dotted line) which was injected with Ringer during treatment phase and pergolide during reversal and the pergolide-Ringer group (solid line) which was injected with pergolide during the treatment and Ringer during reversal. Upper panel represents the difference in daily X̄ body weight between the 2 groups.

Body Weight

Analysis of variance of between group differences in body weight indicated no group effect, $F(1,14)$, $p>0.6$ across all phases of treatment. There was both a significant time block effect, $F(5,70)=23.53$, $p<0.001$ and a group by time block interaction, $F(5,70)=14.63$, $p<0.001$. Within group Tukey analyses indicated that pergolide did produce sharp declines in body weight (Fig. 2) which were concomitant with declines in food intake (Fig. 1). Analyses of body weight in Ringer-pergolide animals revealed no significant difference between blocks 1 and 2 or from blocks 2 to 3. With the initiation of pergolide injections, significant decreases were exhibited from blocks 3 to 4, $F(1,35)=11.04$, $p<0.05$, but no significant increase was evident from block 4 to 5. Changes between time blocks 5 and 6 did show a significant recovery in body weight from the last 4 days of pergolide treatment to the next 4 days of recordings without the drug, $F(1,35)=24.41$, $p<0.01$. Body weight comparisons across time for the pergolide-Ringer group showed a significant decrease, $F(1,35)=44.81$, $p<0.05$, from baseline to pergolide treatment (block 1 to 2) and a significant increase in weight, $F(1,35)=37.61$, $p<0.01$, with chronic administration (block 2 to 3). When the drug was removed, weight continued to climb significantly from block 3 to 4, $F(1,35)=8.15$, $p<0.05$, but thereafter, body weight stabilized and no further changes in weight occurred during the remainder of the experiment.

While the ANOVA of body weight between groups revealed no significant effect over all phases of the experiment, a between group analysis comparing groups during the same treatment phase revealed an order effect of drug administration which was evident only during the first 4 days of Ringer treatment. Rats receiving pergolide first were significantly lighter during the first 4 days of Ringer treatment than rats receiving Ringer treatment first, $F(1,35)=43.62$, $p<0.05$. Body weight during the pergolide phase for both groups was comparable both during the first 4 and last 4 days of treatment. Body weight during the last 4 days of Ringer treatment was also comparable for both groups, indicating that although the pergolide-Ringer group had a lower initial average body weight during the Ringer phase, they made up for this difference by the last 4 days of this phase.

In the absence of both pergolide and Ringer, body weight immediately returned to baseline levels. In addition, when animals were allowed to free feed, body weight continued to increase beyond baseline levels, suggesting that the 4 hour limited access paradigm had suppressant effects upon food intake and hence body weight.

DISCUSSION

In the present experiment, pergolide mesylate significantly suppressed food intake and body weight in a reversal design in which rats were administered both pergolide and the vehicle, Ringer's buffered saline. However, the effects of the drug and vehicle were not symmetrical. The lack of

symmetry in body weight is understandable in that those rats administered pergolide first were of lighter weight at the beginning of the Ringer phase of treatment as compared to those beginning with Ringer due to pergolide's anorectic effects. It is of interest, however, that the weight reduced pergolide-Ringer animals quickly made up for the lost weight, although consuming food in the same amounts as did the other group during the previous treatment phase.

What is more difficult to understand, however, is the order effect of treatment phase on food intake. It is puzzling that those rats treated with Ringer first lost less weight overall when compared to the other group, but showed a more sustained suppression in food intake. This finding does not appear to be due to the development of a food aversion by the Ringer-pergolide group as animals in both groups ate comparable amounts during a return to baseline at the conclusion of treatment. However, this finding might result from a "preexposure effect" conditioned during the initial phase of treatment. Alternatively, perhaps the injections themselves are stressful and while insufficient alone to produce anorexia, potentiate pergolide's effects on food intake. We designed a second experiment to examine these possibilities. Since preexposure of animals to the Ringer injections appeared to potentiate pergolide's anorectic effects, in this second experiment, one group was "preexposed" to Ringer injections, then both groups were simultaneously administered pergolide. In addition, at the conclusion of pergolide treatment, all animals were subjected to a tolerance "challenge" in which they were injected with a second, higher dose of the drug. After a period of drug abstinence, all animals were again challenged with this higher dose to determine if its anorectic effect was again manifest.

EXPERIMENT 2

METHOD

Animals

Sixteen naive Long-Evans Hooded female rats were ovariectomized-hysterectomized and housed as described in Experiment 1. Prior to adaptation to the four hour feeding schedule, rats were divided into two groups balanced for body weight, with a mean weight of 213 g for the "preexposed" group and 215 g for the "naive" group.

Procedure

Following adaptation to baseline as described in Experiment 1, five days of Baseline measurements of food intake and body weight were made. During the next Pretreatment phase, one group was injected daily with Krebs-Ringer solution (1 ml/kg of body weight, IP) and the other group was untreated for a total of 7 days. Following the Pretreatment phase, rats in both groups were injected daily with pergolide (100 μg/kg of body weight) for ten days. On the eleventh and twelfth days of treatment, the injection and feeding regimen was changed in several ways. During the four hour feeding period, rats were moved to a new locale, with white noise and bright light present continuously. In addition, injections were made subcutaneously rather than intraperitoneally. At the end of the feeding period on both days, rats were removed to their home colony. On the thirteenth day of treatment, rats were injected with a new, higher dose of pergolide (500 μg/kg of body weight), but food and body weight measurements were made in the familiar environment.

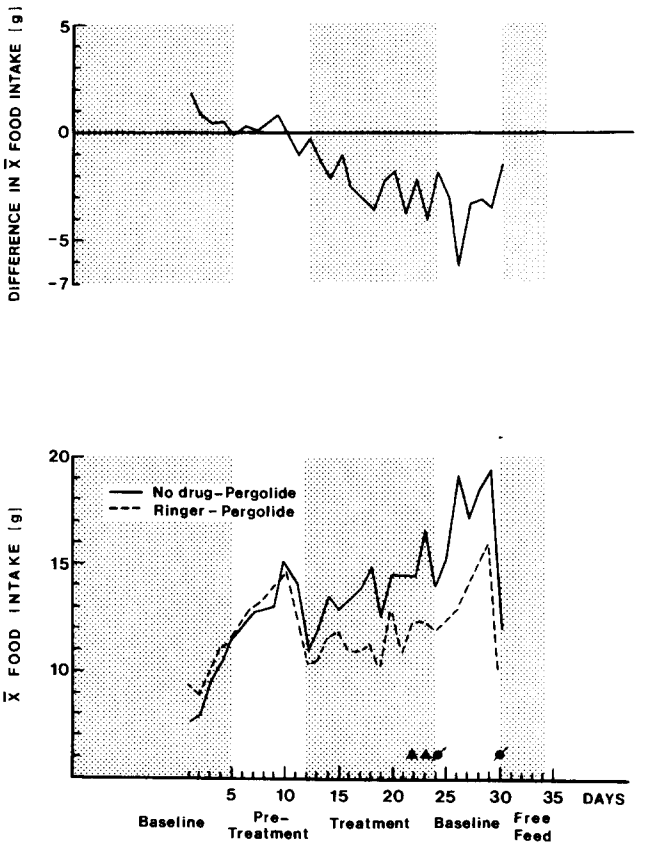

FIG. 3. Effects of preexposure to injections on food intake. Lower panel represents the daily X̄ food intake for the Ringer-pergolide group (dotted line) which was injected with Ringer during the pretreatment phase and pergolide during the treatment phase and the no drug-pergolide group (solid line) which was untreated during the pretreatment phase and injected with pergolide during the treatment phase. Upper panel represents the difference in daily X̄ food intake between the 2 groups. Symbols indicate days of either environmental change (▲) or increased pergolide dosage (💉).

For six days following this higher dose of pergolide, rats were returned to Baseline, with food and weight measurements made daily at the conclusion of the four hour feeding period, but with no drug administered. On the sixth day, as a final assessment of tolerance, the rats were again injected with the higher dose of pergolide and food and weight measurements were made.

Data Analysis

Data were analyzed using Student-Newman-Keuls *a priori* planned comparisons (pairwise F) to examine the between group differences during each experimental phase. Comparisons for both food intake and body weight were made by summing across days in each Baseline, Pretreatment, and Treatment phase.

RESULTS

Examination of Fig. 3 indicates that prior exposure to injections of Ringer saline potentiates the anorectic effect of pergolide when it is subsequently administered. *A priori* planned comparisons of food intake data revealed no signifi-

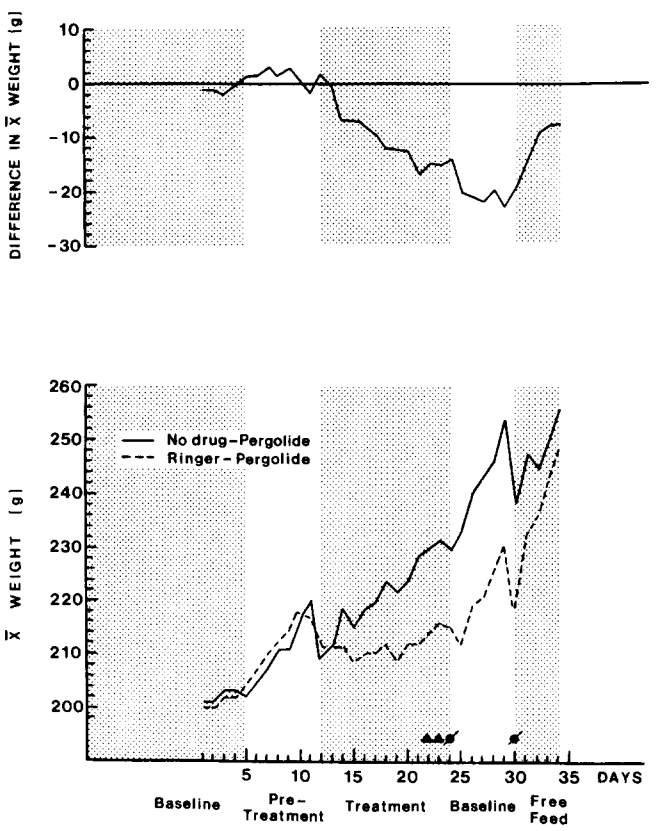

FIG 4. Effects of preexposure to injections on body weight. Lower panel represents the daily $\bar{X}$ body weight for the Ringer-pergolide group (dotted line) which was injected with Ringer during the pretreatment phase and pergolide during the treatment phase and the no drug-pergolide group (solid line) which was untreated during the pretreatment phase and injected with pergolide during the treatment phase. Upper panel represents the difference in daily $\bar{X}$ body weight between the 2 groups. Symbols indicate days of either environmental change (▲) or increased pergolide dosage (💉).

cant difference between groups during any experimental phase except the Treatment phase, during which the preexposed animals ate significantly less than the naive animals, $F(1,14)=9.41$, $p<0.008$. Analysis of body weight data revealed no significant difference between the groups during any phase, although examination of Fig. 4 indicates that body weight of the preexposed group was lower than the naive group both during pergolide treatment and the subsequent recovery (i.e., Baseline) period.

Inspection of Figs. 3 and 4 reveals that food intake and body weight for animals in both groups continued to increase throughout the study, suggesting that these animals were still in the dynamic growth phase of development. For this reason, within group comparisons to treatment phases earlier in the experiment must be made with caution and with this superimposed upward trend in mind. Hence, while the data suggest that there was little apparent effect of changing the feeding environment on food intake, one must entertain the possibility that the effect of our manipulations was cancelled by the superimposed increasing food intake. Perhaps more mature animals with a more stable baseline food intake may have demonstrated some change in consumption in the novel situation. In the case of the tolerance challenge of a higher dose of pergolide, it is probably most appropriate to compare food intake on both the first and second large dose administrations to the period immediately preceding the challenge, rather than baseline rates at the beginning of the study. With such analysis, it is clear that the first high dose of pergolide following an extended period of drug administration had little apparent effect on food intake in both groups. However, the second high dose of pergolide following a period of drug abstinence was relatively as effective (compared to Baseline 2) as the first low dose of pergolide administered to naive animals (compared to Baseline 1) in reducing food intake in both groups.

DISCUSSION

The data in Experiment 2 again clearly demonstrate both the anorectic drug effect and the potentiation of this effect in animals previously exposed to injections of Ringer's saline. While this robust effect replicates Experiment 1, its cause remains unclear. In both experiments, Ringer followed by pergolide may have increased discrimination learning or detection of relevant interoceptive (i.e., drug induced) cues during pergolide treatment because of Ringer preexposure, thereby enhancing the suppression of food intake by pergolide over time [5,18]. Alternatively in the pergolide-Ringer group of Experiment 1 and the no drug pergolide group of Experiment 2, lack of preexposure to the injection regimen may have resulted in a decrease of discrimination or ability to detect relevant cues and consequently a development of rapid tolerance during the pergolide phase [16].

While tolerance was clearly demonstrated in both Experiments 1 and 2 by the gradual decline in the anorectic effect of pergolide over repeated injections, we additionally demonstrated tolerance by administering a higher dose of pergolide. Immediately following chronic administration, a higher dose of pergolide was apparently insufficient to challenge tolerance. After drug abstinence, this same dose lead to suppression of food intake comparable to that at the beginning of pergolide treatment, further substantiating the occurrence of tolerance following chronic pergolide treatment.

In Experiment 2, body weight in the pretreated group was suppressed as compared to the naive group when both were pergolide treated, although the difference was not significant. The magnitude of weight loss overall in Experiment 2 was not as great as that in Experiment 1 and previous investigators [8] have suggested that anorectic agents are less effective in general in animals that have high metabolic demands, such as animals that have been previously food deprived or young developing animals particularly those with a body weight in the range of 200–250 g. The animals in the second experiment fell in this range and inspection of Figs. 3 and 4 reveals a continued upward trend in both food intake and body weight for these animals. It is probable therefore that the drug induced anorexia was somewhat diminished by the metabolic food demands of growth. It is possible that a significant difference in body weight during pergolide treatment in the second experiment would have been observed had the animals been heavier at the outset.

GENERAL DISCUSSION

In the present study, pergolide mesylate induced anorexia, decreasing food intake and body weight. These results are consistent with amphetamine experiments which have demonstrated that repeated administration of d- and

l-amphetamine temporarily suppress food consumption but maintain body weight reduction [3,20]. Food intake and body weight curves (lower panels of Figs. 1 and 2) generated by the pergolide data consistently track amphetamine generated curves from initial sharp declines to rapid tolerance display in the case of food and no indication of tolerance for weight [3,20]. When the drug was discontinued, pergolide and amphetamine rats exhibited compensatory weight increases sufficient for the loss and failure to gain during the drug phases [23,24]. These data are consistent with the hypothesis that drugs such as amphetamine and pergolide may have peripheral as well as central effects on weight maintenance, perhaps by increasing overall metabolism and energy expenditure [14].

Absence of a conditioned aversion to eating has also been demonstrated in both pergolide and amphetamine [23] studies. In order to establish an aversion to any drug, pairing must be with a novel stimulus [11, 15, 21]. High familiarity with standard rat chow pellets decreases conditionability of an aversion. With pergolide, absence of a taste aversion was demonstrated by reinstating the 4 hour feeding schedule. If an aversion to the pellets had been conditioned, intake would have remained suppressed. Instead, normal eating was exhibited, strengthening the argument that the anorexia produced by pergolide is not due to a noxious association between the drug and food.

The reversal design used in Experiment 1 is a vehicle for assessing drug effects. However, as this study demonstrates, there may be some inherent difficulties in using such a design when drugs are injected rather than administered orally. The stress of injection, while insufficient alone to produce anorexia, may potentiate the effects of an anorectic agent, perhaps via adrenal release of epinephrine. Injections may also provide a salient stimulus for discrimination learning. A plausible explanation for the order of treatment effect evident in our data is that rats exposed to an injection regimen prior to pergolide injections were preconditioned to attend to relevant internal cues. These cues enhanced discrimination learning during the drug treatment and potentiated the drug induced anorexia.

In summary, the data from the present study are consistent with other evidence suggesting that central DA neurons are involved in the mediation of food ingestion [1, 2, 4, 6, 7, 13, 14, 19, 22, 23]. These data demonstrate that pergolide decreases food intake and subsequently body weight, but that tolerance to its anorectic effects develops rapidly. In addition, the present study demonstrates that pergolide induced anorexia is not due to a conditioned food aversion and is potentiated by previous exposure to injections of drug vehicle, although the cause of this latter effect remains unclear at this time.

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