

Chronic Antidepressant Drug Regimes and Food and Water Intake in Rats

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DURCAN, M. J., J. R. McWILLIAM, I. C. CAMPBELL, M. C. NEALE AND G. DUNN. *Chronic antidepressant drug regimes and food and water intake in rats*. PHARMACOL BIOCHEM BEHAV 30(2) 299-302, 1988.—Food and water consumption were measured in rats prior to and during a course of antidepressant drug administration. Desmethylimipramine (DMI, 10 mg/kg/day), clorgyline (1.0 mg/kg/day) or saline were injected IP for 30 days. Food and water intake in the DMI- and clorgyline-treated rats was initially and significantly decreased but progressively returned towards pretreatment levels over the course of the drug administration. The effects of these antidepressant drug treatments on food and water intake appeared to consist of two components: (a) a rapid suppressive effect, possibly associated with an acute central action of these drugs (and perhaps a slight initial stress effect related to the drug administration) and (b) an adaptive effect over the course of the treatment which may involve changes in monoaminergic neurotransmitters or receptor status in those brain regions associated with feeding behavior. The similarities of the results of these treatments and those seen with chronic stress are discussed.

Feeding Drinking Antidepressants Desmethylimipramine Clorgyline Hypothalamus Rats

THE regulation of feeding behavior in the rat is mediated by opposing systems located in the medial and lateral hypothalamus [1,10]. Discrete lesioning of sites in the rat brain have shown that the paraventricular nucleus is involved in the mediation of feeding [11], whereas the perifornical area is associated with the suppression of feeding [13].

There is substantial evidence to suggest that noradrenergic mechanisms may play a physiologically important role in the modulation of feeding behavior. Microinjection of noradrenaline, pharmacological agents which potentiate the release of noradrenaline, or agonists that act directly on alpha-adrenoceptors all increase feeding when injected into the paraventricular nucleus [3, 10, 11, 14]. Feeding behavior is suppressed by microinjection of noradrenaline into the perifornical area; this system operating via beta-adrenoceptor stimulation [10,13].

Changes in feeding behavior in the rat have previously been reported to occur during chronic stress and this effect was correlated with the beta-adrenoceptor number in the hypothalamus [19]. It is now established that chronic antidepressant regimens are also associated with a decrease in central beta-adrenoceptors ([20] for review). The effect of chronic antidepressant drug administration was investigated here using the monoamine oxidase (MAO) inhibitor clorgyline and the tricyclic desmethylimipramine (DMI). These drugs were administered at doses and over a time course that has previously been reported to cause a decrease in beta-

adrenoceptor number [4, 5, 16] and the rationale for choosing the doses, since only one dose of each drug was used, was based on these reported changes. The aim of this investigation was to monitor any changes in feeding behavior over the time course of the daily administration of these drugs in order to compare these changes with those seen with the administration of chronic stress [19]; the effect on feeding and drinking behavior of the withdrawal of these treatments was also investigated.

METHOD

Subjects

Twenty-five male rats from an outbred Wistar stock were randomly allocated to three treatment groups; DMI (N=7), clorgyline (N=9) and saline (N=9). These animals were housed singly in metal cages (25.4×22.7×21.5 cm) and maintained on a 17:7 hr light:dark cycle at 22±2°C and 55±5% relative humidity with food (pelleted rat diet RM3E, supplied by Wm. Lillico & Son Ltd., UK) and water available ad lib. The mean weight of the animals was 285±4 g at the commencement of the study.

Measurement of Food and Water Intake

Food in grammes and water intake in millilitres was monitored daily by providing the animals with measured amounts each day and recording the amount remaining after 24 hr.

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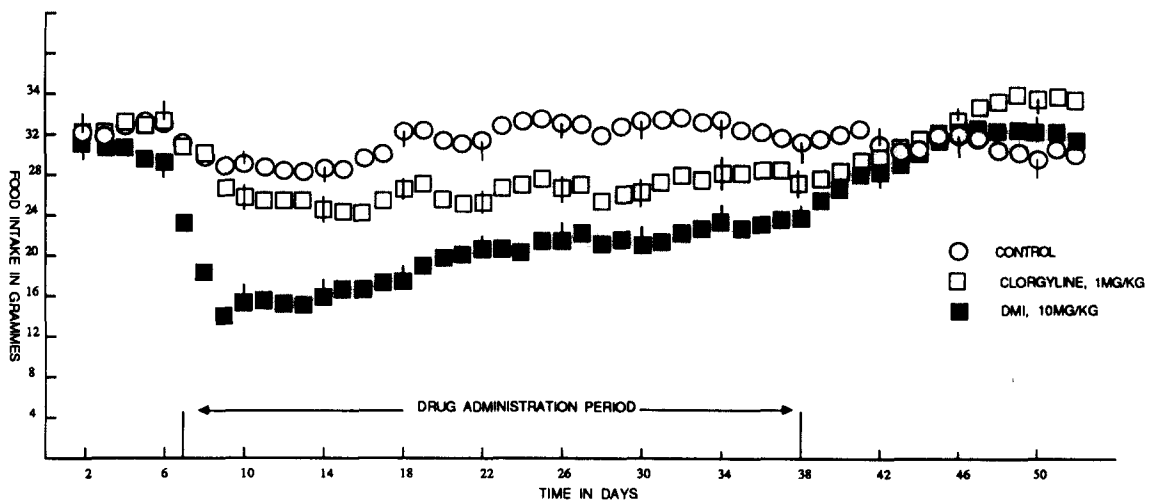


FIG. 1. The mean smoothed food intake data for the control, clorgyline and DMI treatment groups for each day of the experiment. Standard errors shown every fourth day.

TABLE 1
MEANS AND STANDARD ERRORS OF THE FOOD AND WATER INTAKE MEASURES

	INITIAL LEVEL	DROP	TIME (days)
Food Intake			
Control (N=9)	32.3 ± 1.6 g	5.5 ± 1.1 g	8.1 ± 3.2
DMI (N=7)	29.3 ± 0.9 g	17.3 ± 1.2 g†	4.0 ± 1.2
Clorgyline (N=9)	32.0 ± 0.9 g	9.4 ± 0.4 g‡	9.3 ± 1.8
Water Intake			
Control (N=9)	37.3 ± 1.3 ml	7.7 ± 0.7 ml	5.1 ± 1.3
DMI (N=7)	38.2 ± 2.2 ml	21.2 ± 1.6 ml‡	5.0 ± 1.9
Clorgyline (N=9)	37.2 ± 0.9 ml	11.7 ± 0.7 ml‡	12.4 ± 2.7*

INITIAL LEVEL, mean pretreatment consumption; DROP, mean difference between the initial level and the minimum consumption; TIME, the mean in days of the time taken for each subject to reach the minimum consumption point.

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$ vs. control treatment.

The animals were weighed three times in the seven day pre-drug period and daily thereafter.

Drug Administration

Seven days after the commencement of the study each animal was injected (at a volume of 1 ml/kg) IP with one of the three treatments, i.e., 10 mg/kg DMI (Sigma), 1 mg/kg clorgyline (May and Baker) or saline control and thereafter injected once a day. Thirty-eight days after the beginning of the study the drug administration was discontinued but the daily measurement of food and water intake was continued for a further 15 days. All measurements and treatments took place between 09.00 and 11.00 hr.

Data Analysis

The data collected for each measure were smoothed using a linear moving average in order to reduce the effects of random day to day variation and therefore to facilitate the finding of a minimum food intake point, i.e., the minimum intake point for food and water of each subject during the course of the experiment. This was achieved by making each data point the average of itself, the value for the previous day and the value for the following day: for example feeding data point 1 = the food consumed on day 1 + day 2 + day 3 divided by three; feeding point 2 = the average consumption on days 2, 3 and 4 and so on. The following variables were then investigated for food and water consumption (a) INITIAL LEVEL, this was calculated as the mean (in grammes for food and millilitres for water) of the six data points prior to the drug administration; (b) DROP, this was calculated as the difference between the initial level and the minimum consumption point (in grammes for food and millilitres for water) for each subject and (c) TIME, this was the time in days taken for each subject to reach its minimum consumption point after the commencement of the drug regimen.

RESULTS

The means for each treatment of the food consumption data are plotted as Fig. 1; water intake shows an essentially similar pattern.

There were no significant differences found in the INITIAL LEVEL of either food or water consumption [$F(2,22) = 1.70$ for food, and $F(2,22) = 0.13$ for water]. A large difference between the groups was seen for the variable DROP on the feeding measure, $F(2,22) = 37.70$, $p < 0.001$, with both the DMI ($p < 0.01$) and the clorgyline ($p < 0.001$) groups differing significantly from the saline-injected controls. A similar result was found for DROP on water consumption, $F(2,22) = 61.14$, $p < 0.001$ and again both DMI ($p < 0.001$) and clorgyline ($p < 0.001$) treated animals differed from controls.

There were no significant differences for the variable TIME between the groups on the feeding measure though the DMI group did appear to show a more rapid decline in con-

sumption. However, for the drinking measure there was an overall drug effect to TIME, $F(2,22)=4.28$, $p<0.05$, but only the clorgyline animals differed from saline-treated controls. The means and standard errors of the variables INITIAL LEVEL, DROP and TIME are shown in Table 1 for both the feeding and drinking measures.

As can be seen in Fig. 1 the drug-treated animals returned to normal feeding and no significant differences in the overall mean food and water intake were seen after the drug administration was discontinued.

DISCUSSION

Antidepressant drug administration had significant effects on feeding and drinking behavior in these animals with the observed suppression being maximal during the initial course of the treatment. Since only one dose of each drug was used the conclusions drawn for these results must be tempered by the absence of full dose-response curves. However, notwithstanding this weakness in the study, both clorgyline and DMI do potentiate central catecholamine levels, either by preventing their further metabolism or their reuptake [5,8], and increased catecholamine levels at post-synaptic dopamine or beta-adrenoceptors in the perifornical region of the hypothalamus could be responsible for the rapid initial suppression of feeding. The effect is similar to the anorexic effect produced by amphetamine administered directly into this area or given peripherally [12].

The parallel but much smaller reduction in feeding and drinking in response to the control treatment may be due to the mild stressor of IP injections to which there may be a subsequent adaptation [15]; it might have been preferable to adapt the animals to saline injections and stabilise the food and water intakes prior to the commencement of the drug treatments.

Applying chronic stress to rats has previously been re-

ported to inhibit feeding in a way similar to that seen here after chronic antidepressants [19], and in experiments in our laboratory immobilisation stress has caused reductions in food intake (Durcan, unpublished observations). Over the course of the antidepressant drug administration a gradual reduction in the suppression of food and water intake was apparent which is again similar to the effects reported during chronic stress [19]. Changes in catecholamine receptors may be responsible for these behavioral effects; both chronic stress and antidepressant drug administration being associated with a reduction of beta-adrenoceptors in the hypothalamus [16,19]. During chronic immobilisation stress in rats, beta-adrenoceptor loss in the hypothalamus was maximal between 4-7 days and was found to precede receptor losses in the cortex and brainstem. This loss of beta-adrenoceptors may account for the gradual return towards pretreatment consumption by adapting to increased central catecholamine levels.

The results of this experiment show that chronic treatment with antidepressants causes an initial (acute) drop in food and water intake followed by a gradual adaptation to the treatment which is similar to the effects on feeding seen during chronic stress [19] and the similarity in effects of the two treatments (stress and antidepressants) lends support to the hypothesis of Stone [17,18] that antidepressant therapy is a form of adaptation to stress. However some caution must be expressed in interpreting the results of this experiment as suggesting that adrenergic mechanisms are solely responsible for the feeding and drinking changes noted. Other neurotransmitter systems have been implicated in the control of feeding and drinking [7] and, particularly at the doses used, other monoamine systems may be being altered by these treatments. For example both DMI and clorgyline may be influencing serotonergic mechanisms which have also been implicated in feeding responses [2, 6, 9].

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