Pharmacology Biochemistry & Behaviour, Vol. 54, No. 4, pp. 745–751, 1996

0091-3057/96 $15.00 + .00

ELSEVIER

SSDI 0091-3057(95)02228-7

Metergoline Antagonizes Fluoxetine-Induced Suppression of Food Intake But Not Changes in the Behavioural Satiety Sequence

J. C. G. HALFORD AND J. E. BLUNDELL[1]

Bio-Psychology Group, Department of Psychology, University of Leeds, Leeds LS2 9JT, UK

Received 14 June 1995; Revised 8 November 1995; Accepted 8 November 1995

HALFORD, J. C. G. AND J. E. BLUNDELL. *Metergoline antagonizes fluoxetine-induced suppression of food intake but not changes in the behavioural satiety sequence.* PHARMACOL BIOCHEM BEHAV **54**(4) 745–751, 1996.—In this study continuous monitoring was used to yield a true behavioural record. This allows a bidimensional account of drug effects on every unit of behaviour. Behavioural dimensions of duration (dur) and frequency (frq) measures were utilized to monitor the effects of an ED_{50} anorectic dose of fluoxetine (10 mg/kg IP) on the behavioural satiety sequence and the effect of a metergoline (1 mg/kg IP) challenge. Fluoxetine reduced food intake by 45% ($p < 0.005$). The local eating rate was also reduced ($p < 0.001$), demonstrating a marked slowing of eating behaviour. Eating behaviour was reduced (frq $p < 0.005$) as was grooming (frq $p < 0.05$) and activity. Resting was increased (dur $p < 0.05$) and temporally advanced. There was no gross disruption of behaviour and the profile was adjusted in a way consistent with the expression of satiety. Fluoxetine-induced changes were very similar to those produced by prefeeding. Metergoline antagonised fluoxetine's effect on intake and eating duration (dur $p < 0.05$). However, metergoline did not antagonise the effect of fluoxetine on the frequency of eating (frq $p < 0.005$), thus increasing the amount consumed per eating episode. Grooming (frq $p < 0.005$) and activity also remained reduced. At this dose fluoxetine-induced suppression of eating is serotonin dependent as it is reversed by metergoline. Fluoxetine-induced suppression of eating at this dose is consistent with the normal operation of satiety. Fluoxetine-induced slowing of behaviour appears to be mediated by a separate mechanism.

Feeding 5-HT Satiety Fluoxetine Metergoline Behavioural satiety sequence Continuous analysis

FLUOXETINE administration reduces food intake in both obese and nonobese mice while simultaneously increasing synaptic 5-HT (22). In addition to inhibition of 5-HT uptake, the fluoxetine R(−) enantiomer possesses a weak affinity for the 5-HT_{2C} receptor (21), a subtype specifically implicated in the food intake reducing action of certain serotoninergic compounds. It is as yet unclear whether this small secondary action augments or diminishes fluoxetine-induced suppression of intake (13), although there is some indication of a receptor blocking action (19).

Paradoxically, the fluoxetine-induced reduction in intake has not been blocked by various 5-HT antagonists or by hypothalamic 5-HT neurotoxin lesioning with 5,7 dihydroxytryptamine (8,20). *p*-Chlorophenylalanine also fails to inhibit the action of fluoxetine (13). Only combined pretreatment of metergoline and the catecholamine neurotoxin 6-hydroxydopamine has been shown to significantly antagonise fluoxetine-induced anorexia (7). Catecholamine antagonism does not, on its own, block fluoxetine-induced anorexia either. In addition, because fluoxetine blocks 5-HT uptake in vivo at doses much lower than those required to reduce intake (18), some researchers, quite reasonably, have questioned the significance of 5-HT functioning in fluoxetine-induced suppression of intake. Fluoxetine-induced anorexia does not appear to be solely mediated via indirect agonism of 5-HT feeding receptors, but is also dependent on the activation of catecholaminergic receptors. Recently, evidence has come to light that fluoxetine-induced suppression of food intake can be antagonised at least partially by metergoline (12). Fluoxetine-induced anorexia, from this evidence can produce partial anorexia solely via $5\text{-HT}_{1/2}$ receptors.

[1]To whom requests for reprints should be addressed.

The characteristic sequence of behavioural changes associated with the onset of satiety in the laboratory rat has often been used to investigate the possible underlying mechanisms of drug induced anorexia (5,6). This behavioural satiety sequence characterised by a transition from eating to resting via activity and grooming is associated with the natural cessation of feeding (2). The preservation or advancement of the satiety sequence by anorectic compounds has been taken to signify reduction of intake via the postingestive physiological mechanisms of satiety. It is noticeable that the suppression of intake by quinine adulteration of food or injection of lithium chloride disrupts the events of the satiety sequence (2,6). Interference with the behavioural sequence is, thus, hypothesised to signify disruption of satiety, and suggests a reduction of intake by nonphysiological processes.

Previous studies of the satiety sequence have used time-sampling procedures to record behavioural data (1,2). These techniques only record part of the behaviour actually occurring, so they are not true behavioural records, but representations of behavioural occurrence in the form of modified frequencies (17). Instantaneous (momentary) time sampling is currently used by most researchers studying the satiety sequence. The animal's behaviour is recorded at an instant at the end of a specified interval (if the interval is 15 s then the animal's behaviour is coded every 15th second). Momentary time sampling is unbiased in estimation and in large behavioural data sets it is accurate due to low random error (3,16). However, in the 5-min time bins that make up the statistical analysis of the satiety sequence random error is high making analysis over time problematic (14). Additionally, momentary time sampling is systematically biased in its estimation of behavioural frequency (14,15). Behaviours that are event-like in nature, such as frequently occurring short-lived behaviours (e.g., sniffing and rearing) are best measured in frequency (1). Thus, these active behaviours may not be reliably recorded by momentary time sampling. Finally, there may be a possible observational bias in the technique. This can be termed 'event over state observer bias.' If the animal is viewed at the instant in which it is in a transition between an event (e.g., activity) and state (e.g., resting) behaviour, the event behaviour is more likely to be coded due to its prominence.

In the present study it was intended to examine the action of fluoxetine on the continuously recorded behavioural satiety sequence and to disclose any possible antagonism of this action by a relatively nonspecific 5-HT receptor blocker (metergoline). In the study of the behavioural effects of fluoxetine there is a rationale for the analysis of both behavioural duration and frequency. Because it has previously been demonstrated that the suppression of eating induced by fluoxetine has a marked effect of the frequency of numerous behaviours (9), it seemed necessary to employ a system of continuous analysis of behaviour that gives true duration and true frequency of behaviour. This is particularly important because a recent study demonstrating a partial antagonism of the anorectic effect of fluoxetine by metergoline reported that only some aspects of meal taking were adjusted (12). Consequently, the effect of a receptor blocker on fluoxetine-induced changes in the behavioural sequence of satiety can be best studied using the true frequency and the true duration profiles (i.e., continuous recording, not time sampling). The drug effects on the behavioural satiety sequence can be compared with those produced by 5 min prefeeding the test animal before observation. Prefeeding naturally induces the process of satiety. Thus, the behavioural profile produced acts as a template against which drug action can be examined. The effects of both fluoxetine and metergoline on food intake and elements of eating behaviour have been studied numerous times. However, there is yet to be a detailed microstructural analysis of a successful antagonism of fluoxetine-induced suppression of food intake.

METHOD

Animals

Twelve male Lister hooded rats (250–300 g) from the colony of the Psychology department, Leeds University, were housed and monitored individually on a 12-h reversed light cycle (LO 0900 h). The animals were habituated to a brief period of food deprivation (4 h), injection procedures, the wet mash diet (CRM'X' labsure products, UK), and the observation tank and procedure for 2 full weeks before the start of the experiment proper. The wet mash diet was chosen as the animals find the diet highly palatable. The animals normally consume 50 g per day of this diet.

Design

A repeated measures design was employed with each animal's behaviour monitored on all three drugs and the saline control. The order of the four conditions was determined by a latin square to counterbalance drug treatments.

Drugs

Fluoxetine (Lilly, Indianapolis, IN) IP 10 mg/kg and metergoline (Farmitalia, Carlo Erba Limited, Milan, Italy) IP 1 mg/kg were dissolved into surgical saline. In a previous study a dose of 10 mg/kg of fluoxetine had been shown to reduce food intake 50% (9). Metergoline 1 mg/kg had previous been shown to partially block fluoxetine-induced suppression of intake (12). The drugs were injected at a volume of 1 ml/kg. Metergoline was injected 1 h before observation, fluoxetine half an hour before observation. Each animal acted as its own control. Because of the long half-life of fluoxetine and its active metabolites, at least 7 days separated any 2 test days. This is a necessary requirement of this type of study to avoid any contamination between successive test days.

Procedure

Four animals were monitored each day. On each experimental day food was removed from the animal's cage 4 h before monitoring. The animals were injected 1 h before the observation began. The observation tank (55 × 30 × 38 cm) provided freedom to move and explore, allowing full behavioural expression. The tank floor was covered in wood shavings and water was freely available. A low light intensity camera faced the tank at a 90° angle to the experimenter. The monitor provided a second alternative angle of view to aid behavioural coding. The camera and computer monitors were fitted with screen filters to prevent reillumination of the room. After 15 min re-exposure to the tank the observation began with the presentation of the food. Behaviour was exhaustively coded into eight categories—eating, drinking, grooming, sniffing, locomotion, rearing, resting, and other (11). Operational definitions of these behaviours are shown in Table 1. These were logged on to an IBM compatible PC using a specially designed data collection program ('KEETH') (10). Food was weighed at the start and at the end of each observation period. The behaviour was observed and coded live; the video recording only being used for confirmation of ambiguous behavioural events. As only one animal could be monitored at a time the

TABLE 1

BEHAVIOURAL CODES

1.	Eating:	Biting, gnawing, or swallowing food from dish or from front paws.
2.	Drinking:	Licking water bottle nozzle.
3.	Grooming:	Scratching, licking, or biting of the coat, whiskers, feet, or genitals
4.	Sniffing:	Head movements with rear limbs immobile; twitching of vibrissae at an aspect of the environment.
5.	Locomotion:	Movements involving all four limbs. walking around cage, or circling.
6.	Rearing:	Front paws raised from cage bottom. Can be supported by the tank side.
7.	Resting:	Inactive. Sitting or lying in a relaxed position or resting.

Based on definitions used by Antin et al., (2) and Kirkham and Blundell (11).

observations were staggered at 1 h intervals. The first observation started at 1300 h. Observation periods were 40 min long.

The effects of the various drug treatments on the behavioural profiles were compared to the effects of prefeeding that would naturally enhance the physiological processes of satiety. These prefed behavioural profiles were previously generated in a separate study using separate animals. These animals where maintained and observed under identical experimental conditions. However, they were not injected but allowed free access to food just prior to the start of the experimental observation.

Analysis

Food Intake and Eating Parameters. Mean intake (g) was calculated for each condition and this was statistically examined to confirm the effects of the particular treatments. Mean global eating rates (GER) (g/min), mean local eating rates (LER) (g/min), mean eating bout intake (MBI) (g), and mean eating bout length (MBL) (min) were also calculated for each drug condition. The global eating rate (GER) represents the rate of food consumption for the entire monitoring period (40 min). The local eating rate (LER) represents the rate of eating only during the time the animal is actually eating food (5). In earlier studies the local eating rate has been shown to be a sensitive indicator of the effect of a drug on eating behaviour. These eating parameters can only be calculated from a continuous behavioural analysis where there is a measure of true (actual) duration of time spent eating and true (actual) time spent eating. They represent underlying change in food intake, eating duration and eating frequency.

Specific Behavioural Measures. The mean number of episodes of all behaviours were calculated for each drug condition thereby providing a measure of the rate of behavioural change. The occurrence of each behaviour for each drug over the whole observation period was calculated and displayed according to its frequency and duration of occurrence. Due to the hydration of the diet, drinking occurred very infrequently.

Microstructural Analysis of Behaviour. To analyze the change in behaviour over time a SAS program divided the 40-min continuous record of each animal in each condition into 5-min periods (or time bins) and calculated the frequency and duration of each behaviour. Profiles were plotted. Drug effects on each behaviour over the whole period were analyzed on SAS using analysis of variance for both the continuous duration and continuous frequency data. For each drug a 2×8 analysis of variance has been carried out with drug (two levels) and time period (eight levels) as the main factors (two-tailed test).

RESULTS

Food Intake and Eating Parameters

The effects of the various conditions on food intake and eating parameters are shown in Table 2. Fluoxetine significantly reduced food intake by 45% ($p < 0.005$). The local eating rate was also significantly reduced ($p < 0.001$), demonstrating a marked slowing of eating. Metergoline alone had no effect on food intake. However, metergoline did significantly reduce local eating rate ($p < 0.01$) Metergoline did not significantly alter other eating parameters. Metergoline reversed the fluoxetine-induced suppression of intake to saline levels. However, the local eating rate remained at the same level and the mean intake per eating episode remained high showing fluoxetine was still slowing intake.

Specific Behavioural Measures

The effect of the various conditions on specific behaviours are shown in Tables 3 and 4. The fluoxetine-induced reduction in the frequency of eating proved highly significant ($p < 0.0001$). Fluoxetine reduced grooming (frequency $p < 0.05$) locomotion (duration $p < 0.0005$, frequency $p < 0.001$), rearing (duration $p < 0.0005$, frequency $p < 0.0005$), and sniffing (frequency $p < 0.005$). Resting was increased in duration ($p <$

TABLE 2

MEAN FOOD INTAKE (SE) AND EATING PARAMETERS—GER, LER, MBI AND MBL

	Food Intake	GER	LER	MBI	MBL
Saline control	8.0 g (0.423)	0.20 g/min	1.33 g/min (0.147)	0.36 g (0.060)	16.3 s (0.056)
Fluoxetine10.0 mg/kg	4.1 g* (0.910)	0.10 g/min	0.88 g/min* (0.127)	0.59 g (0.102)	40.1 s† (0.132)
Metergoline 1.0 mg/kg	7.9 g§ (0.724)	0.20 g/min	1.13 g/min† (0.095)	0.44 g (0.189)	23.2 s (0.205)
Flux 10.0 + meter 1.0	7.3 g¶ (0.797)	0.18 g/min	0.87 g/min* (0.082)	0.57 g (0.180)	39.3 s† (0.182)

Student's t-test: $*p < 0.005$, $\dagger p < 0.01$, $\ddagger p < 0.05$ change from control.
$\S p < 0.005$, $\P p < 0.01$, $\# p < 0.05$ increase from fluoxetine alone condition.

TABLE 3

MEAN DURATION OF SPECIFIC BEHAVIOURS OVER THE OBSERVATION PERIOD (S)

	Eat	Groom	Loco'	Rear	Sniff	Rest
Saline control	360 (31.2)	207 (46.3)	89 (11.8)	320 (43.2)	716 (67.4)	628 (114.5)
Fluoxetine 10.0 mg/kg	279 (57.6)	176 (32.4)	30*** (7.71)	77*** (23.6)	639 (100.9)	1127# (161.95)
Metergoline 1.0 mg/kg	419 (71.6)	99 (20.5)	76 (9.64)	96*** (22.81)	579** (82.5)	1129### (141.9)
Flux 10.0 meter 1.0	506# (76.6)	105 (20.3)	67 (10.8)	42*** (20.6)	626 (79.4)	1051## (114.5)

$F_{crit}(1, 11) = 4.84$. Significance from control #—increase, *—decrease: #/* = $p < 0.05$, ##/** = $p < 0.01$, ###/*** = $p < 0.005$.

0.05). Metergoline alone did not significantly alter the duration and frequency of eating behaviour as seen in the specific behavioural changes. However, metergoline decreased the frequency of grooming ($p < 0.05$) and rearing ($p < 0.0001$) and the duration of rearing ($p < 0.0001$) and sniffing ($p < 0.01$). Curiously the frequency of sniffing significantly increased ($p < 0.0001$) as did the duration of resting ($p < 0.005$). In the fluoxetine-metergoline condition the frequency of eating was still significantly reduced ($p < 0.005$); however, the duration of eating significantly increased to a level significantly higher than the control ($p < 0.05$). The animal may eat longer to compensate for the low rate of intake. In the fluoxetine-metergoline condition reductions from the saline control were still observed in grooming (frequency $p < 0.005$), locomotion (frequency $p < 0.05$), rearing (duration $p < 0.0001$, frequency $p < 0.0001$), and sniffing (frequency $p < 0.0001$). Resting was still significantly increased from saline levels in the fluoxetine-metergoline condition (duration $p < 0.005$).

Microstructural Profiles of Behaviour

The effect of the various conditions on behavioural profiles over time are shown in Figs. 1 (duration) and 2 (frequency). These can be compared to the behavioural profiles produced by prefeeding (duration and frequency), which naturally enhances the underlying processes of satiety (Fig. 3). Fluoxetine enhanced the behavioural profiles consistent with satiety (i.e., a shift in the profile to the left). Fluoxetine produced a behavioural profile similar to that produced by prefeeding. The fluoxetine-induced changes in behaviour were much more marked in frequency. This replicated previous results (20). Metergoline alone did not appear to alter the structure of the satiety sequence despite its significant effects on specific behaviours (see previous). The profile resembles that of the saline control more than that of prefeeding. In the fluoxetine-metergoline condition, the duration profile structure was similar to the saline control. However, the frequency profile structure remained similar to that of the prefeeding profile structure. (Note: the staggering of the four daily monitoring sessions did not appear to adversely affect the results. There was no apparent differences in food intake under saline or drug conditions between the first and last animal monitored each day.)

DISCUSSION

This experiment used a 5-HT drug and a 5-HT blocking agent to investigate the role of 5-HT mechanisms in the control of food intake *per se* and in the behavioural profile associated with eating. This behavioural profile is often regarded as being the *sine qua non* for establishing a natural mechanism for the adjustment of eating by a drug. Fluoxetine reduced intake and altered the behavioural satiety sequence in a way generally accepted to be consistent with the operation of natural mechanisms of satiety. However, fluoxetine also changed the overall behavioural profile; the drug reduced the frequency of all behaviour. Metergoline had no effect on food consumption or on the duration or rate of eating. However, metergoline did influence other components of behaviours—rearing, sniffing, locomotion, and resting; however, these changes did not interfere with eating. The sensitive behavioural assay demonstrated a biological effect of metergoline. Metergoline reversed the effect of fluoxetine on food intake but did not adjust the behavioural profile to that of the non drug state. Agonist plus antagonist is not equivalent to the placebo treatment (saline plus saline).

This experiment has demonstrated the first clear full reversal of fluoxetine-induced suppression of eating by a serotonin antagonist suggesting 5-HT is responsible for fluoxetine-induced anorexia. The clarity of this effect may well have been due to the decision to allow 1 full week between successive injections of fluoxetine. When using a within subjects design it is essential to allow time for the metabolites of fluoxetine to be cleared from the plasma and other tissues. If the interval between successive injections is short then the metabolites of fluoxetine will still be present when the further injection is made. However, metergoline did not antagonise all effects of fluoxetine on the behavioural satiety sequence. Therefore, there is an apparent dissociation between food consumption *per se* and the elements of eating behaviour through which the consumption takes place. Only a complete behavioural

TABLE 4

MEAN NUMBER OF EPISODES OF SPECIFIC BEHAVIOURS OVER THE OBSERVATION PERIOD

	Eat	Groom	Loco'	Rear	Sniff	Rest
Saline control	22.14 (2.45)	21.43 (3.74)	63.15 (6.65)	64.95 (7.44)	82.76 (9.01)	18.05 (2.71)
Fluoxetine 10.0 mg/kg	6.96*** (1.22)	11.7*** (2.96)	24.5*** (7.05)	18.8*** (6.70)	45.06*** (12.96)	18.77 (3.38)
Metergoline 1.0 mg/kg	18.10 (2.28)	8.78* (2.22)	56.8 (7.02)	19.9*** (3.76)	123.9### (7.91)	19.78 (2.04)
Flux 10.0 + meter 1.0	12.88*** (1.78)	7.70*** (1.65)	44.51* (5.02)	10.4*** (2.35)	40.51*** (5.43)	15.33 (1.56)

$F_{crit}(1, 11) = 4.84$. Significance from control #—increase, *—decrease: #/* = $p < 0.05$, ##/** = $p < 0.01$, ###/*** = $p < 0.005$.

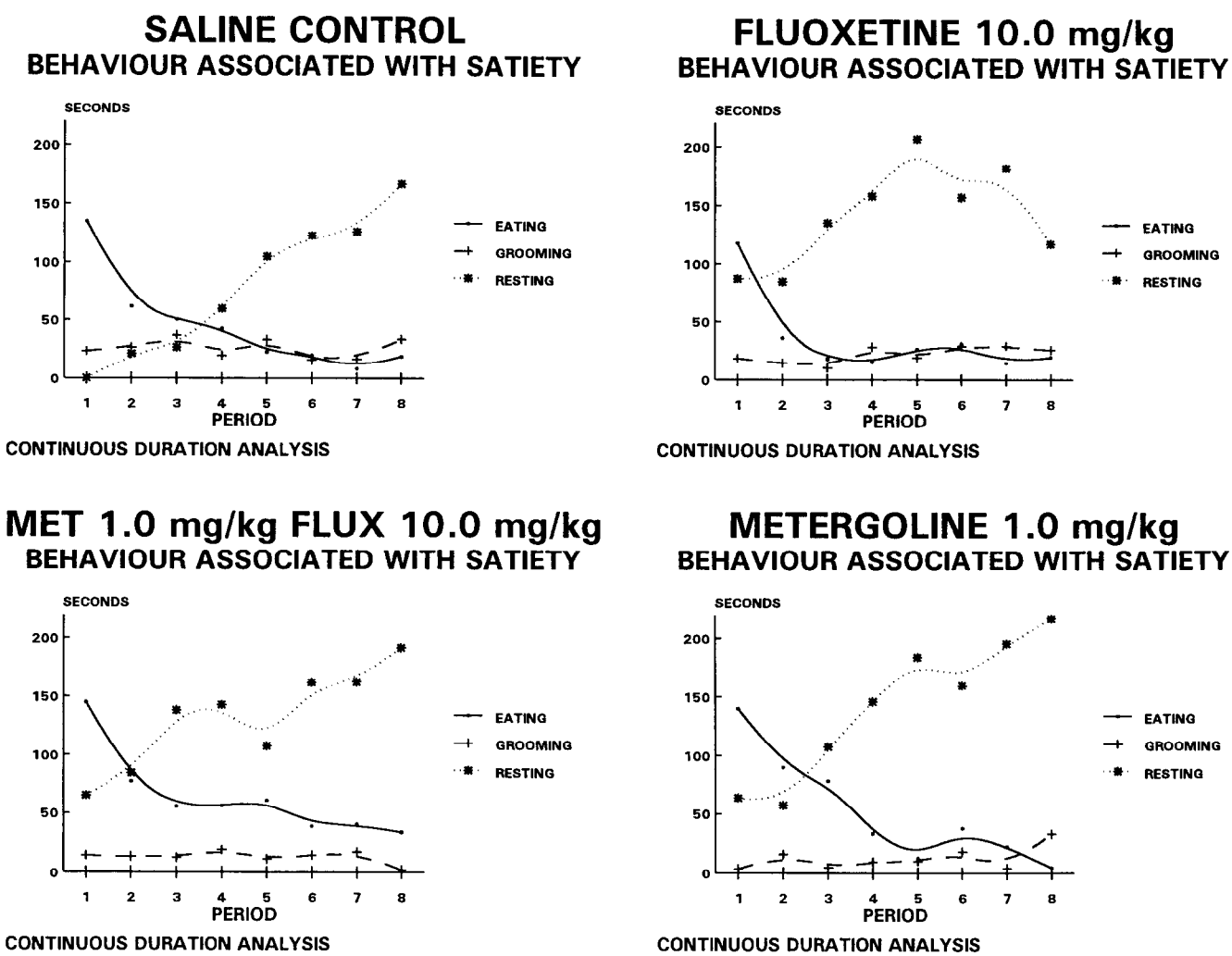

FIG. 1. Satiety profiles produced by saline control, fluoxetine 10.0 mg/kg, metergoline 1.0 mg/kg, and the fluoxetine and metergoline condition (analysis by duration).

analysis has the power to identify these behavioural changes and to disclose changes in both duration and frequency measures. Both are required to give a picture of the action of a drug and, more importantly of the antagonism between drug and blocker.

The fluoxetine-induced suppression of food intake in this study appears to be serotonin dependent, as it was reversed by the 5-$HT_{1/2}$ antagonist, metergoline. Therefore, serotonin reuptake inhibition does appear to be the mechanism by which fluoxetine induces anorexia at this particular dose. This experimental result is only consistent with the work of Lee and Clifton (12). In both studies low doses of fluoxetine were employed. The slowing effect of fluoxetine on eating behaviour did not appear to be due to the activation of 5-$HT_{1/2}$ receptors. As food intake was restored to a normal level by metergoline, the duration of eating actually increased above saline control levels. However, this effect was similar to the reported effect of the dopamine antagonist pimozide (6). Pimozide was reported not to effect food intake but reduced the frequency of eating while increasing its duration. Thus, it may be possible that fluoxetine possesses an additional side effect not mediated by 5-$HT_{1/2}$ receptors. The dose employed in this study would indicate that this effect did not substantially disrupt the structure of feeding behaviour.

However, we can speculate that fluoxetine, at a higher dose, may additionally reduce food intake via severe sedation in addition to fluoxetine's existing effects on satiety. At the dose employed in both this and a previous study (9), fluoxetine sharply reduced the frequency of behaviour. Severe sedation (decreased locomotor activity and massive increase in resting) induced by the 5-HT_2 agonist, MK-212 has been shown reduce intake (Halford and Blundell, unpublished results). But unlike fluoxetine, severe sedation produced by an equi-anorectic dose of MK-212 does disrupt the structure of the behavioural satiety sequence. Fluoxetine at a higher dose may do the same. This is possibly why researchers using larger doses of fluoxetine have failed to block its anorectic effects. In large doses, fluoxetine may possess a doubly potent anorectic action via two pharmacologically distinct mechanisms of satiety and sedation. In such an experimental situation both mechanisms would need to be blocked to reverse fluoxetine-induced anorexia. This is consistent with the study by Grignaschi et al. (7), in

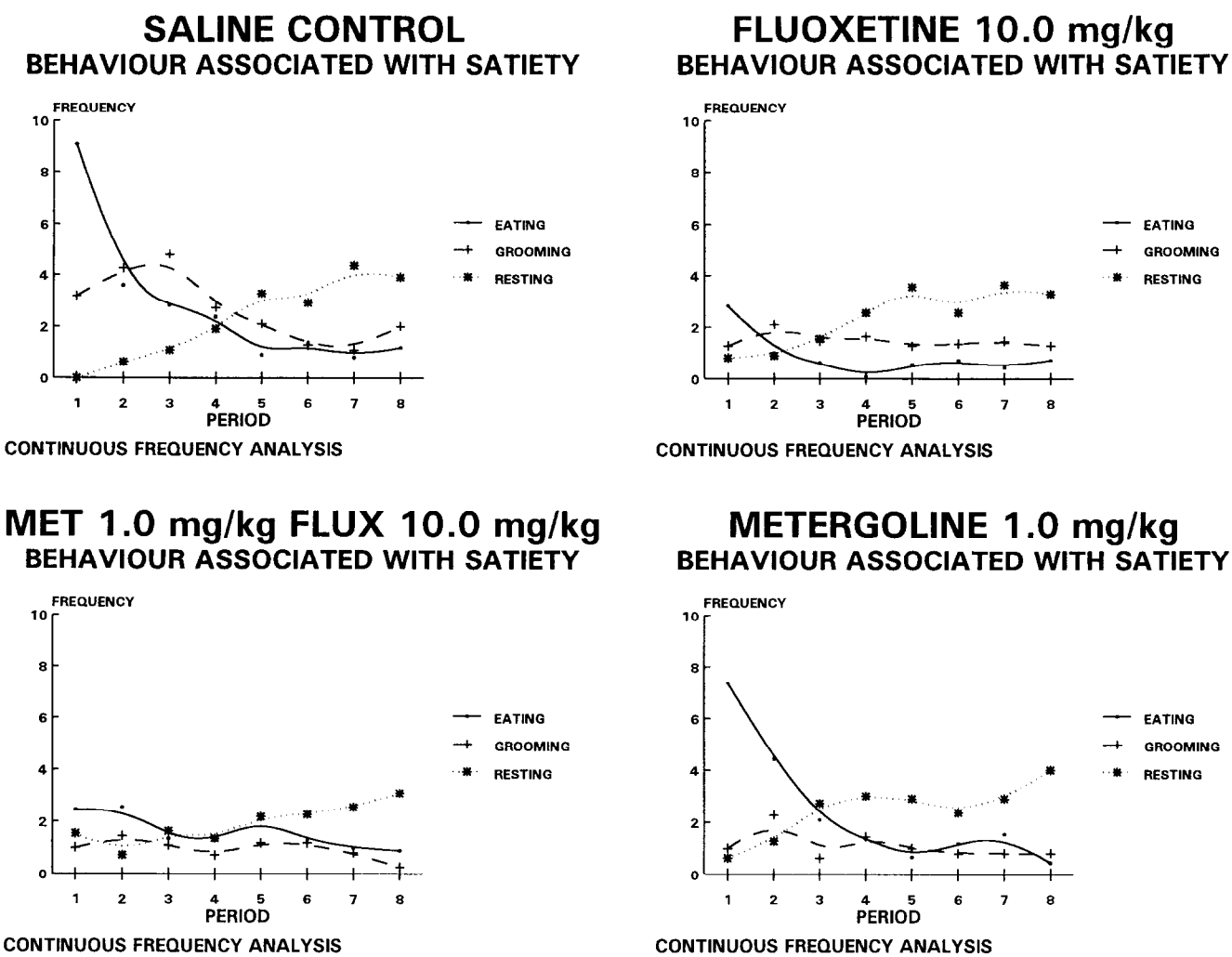

FIG. 2. Satiety profiles produced by saline control, fluoxetine 10.0 mg/kg, metergoline 1.0 mg/kg, and the fluoxetine and metergoline condition (analysis by frequency).

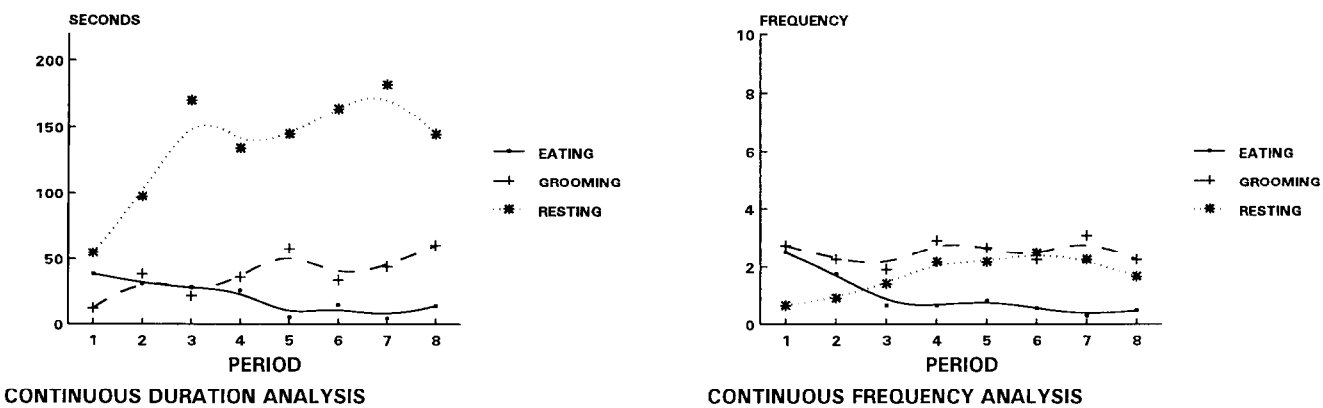

FIG. 3. Satiety profile produced by 5 min prefeeding. These can act as a template by which the anorectic action of various drug conditions can be judged (analysis by duration and frequency).

which the anorectic effect of fluoxetine was only reversed by a combined serotoninergic and catecholaminergic blockade. Consequently, sedation may be induced by an unspecified catecholaminergic mechanism.

In conclusion, the results of this study have established that fluoxetine induced suppression of eating, at a dose of 10 mg/kg, is serotonin dependent as it is completely reversed by metergoline. Fluoxetine-induced suppression of eating at the dose level used, is consistent with the normal operation of satiety. The drug, at this dose, does not substantially disrupt the behavioural satiety sequence but does alter the structural expression of other aspects of behaviour. The action of metergoline reversed the effect on food intake but did not reverse the effect of fluoxetine on aspects of the behavioural profile or on eating rate. This pharmacological study has, therefore, separated two aspects of eating control: how much food an animal eats (quantitative effect on ingestion) and how the animal eats it (qualitative effects on the pattern of ingestive behaviour).

ACKNOWLEDGEMENTS

The authors are grateful to Dr. Victoria Burley, Dr. Clare Lawton (BioPsychology Group), Paul Nicholson (University of Leeds Computer Service), and Dr. Colin Hendrie (Ethopharmacology Lab, Dept Psychology, Leeds) for help and advice, and to Sandy Briggs and Neil Lowley for technical support.

REFERENCES

1. Altmann, J. Observational study of behavioural-sampling methods. Behaviour 49:227–267; 1974.
2. Antin, J.; Gibbs, J.; Holt, J.; Young, R. C.; Smith, G. P. Cholecystokinin elicits the complete behavioural sequence of satiety in rats. Physiol. Behav. 19:761–766; 1975.
3. Ary, D. Mathematical explanation of error in duration recording using partial interval, whole interval, and momentary time sampling. Behav. Assess. 6:221–228; 1984.
4. Blundell, J. E.; Latham, C. J. Characterization of the behavioural changes underlying the effects of amphetamine and fenfluramine on food consumption, and the antagonism by pimozide and metergoline. Pharmacol. Biochem. Behav. 12:717–722; 1980.
5. Blundell, J. E.; McArthur, R. A. Behavioural flux and feeding: Continuous monitoring of food intake and food selection, and the video-recording of appetitive and satiety sequences for the analysis of drug action. In: Samanin, R.; Garattini, S., eds. Anorectic agents; Mechanisms of action and of tolerance. New York: Raven Press; 1981:19–43.
6. Blundell, J. E.; Tombros, E.; Rogers, P. J.; Latham, C. J. Behavioural analysis of feeding: Implications for the pharmacological manipulation of food intake in animals and man. Neuropsychopharmacology 4:319–326; 1980.
7. Grignaschi, G.; Petrini, A.; Neill, J. C.; Samanin, R. Evidence for an involvement of brain serotonin and catecholamines in the feeding suppressant effect of fluoxetine. (Unpublished results).
8. Grignaschi, G.; Samanin, R. Role of serotonin and catecholamines in brain in the feeding suppressant effect of fluoxetine. Neuropharmacology 31(5):445–449; 1992.
9. Halford, J. C. G.; Blundell, J. E. 5-Hydroxytryptaminergic drugs compared on the behavioural sequence associated with satiety. Br. J. Pharmacol. 100s:95p; 1993.
10. Hendrie, C. A.; Bennett, S. A microcomputer technique for the detailed behavioural and automatic statistical analysis of animal behaviour. Physiol. Behav. 30:233–235; 1984.
11. Kirkham, T. C.; Blundell, J. E. Dual action of naloxone on feeding revealed by behavioural analysis: Separate effects on initiation and termination of eating. Appetite 5:45–52; 1984
12. Lee, M. D.; Clifton, P. G. Partial reversal of fluoxetine anorexia by the 5-HT antagonist metergoline. Psychopharmacology (Berlin) 107:359–364; 1992.
13. Lightowler, S.; Kennett, G. A.; Wood, M. D.; Brown, A. M.; Glen, A. Blackburn, T. P.; Tulloch, I. F. Hypophagic effect of fluoxetine in rats is not mediated by inhibition of 5-HT reuptake or an agonist action at 5-HT_{2C} receptors. Br. J. Pharmacol. 112s:310p; 1994.
14. Pöyäs, H. Measuring time budgets with instantaneous sampling. A cautionary note. Anim. Behav. 40(4):317–318; 1991.
15. Quera, V. A generalised technique to estimate frequency and duration in time sampling. Behav. Assess. 12:409–424; 1990.
16. Rhine, R. J.; Linville, A. K. Properties of one-zero scores in observational studies of primate social behaviour: The effect of assumptions on empirical analysis. Primates 21(1):111–122; 1980.
17. Sackett, G. P. Measurement in observational research. In: Sackett, G. P., ed. Observing behaviour, vol. 2. Baltimore: University Park Press; 1978:25–43.
18. Sugrue, M. F. Neuropharmacology of drugs affecting food intake. Pharmacol. Ther. 32:145–182; 1987.
19. Wood, M. D.; Glen, A.; Blackburn, T. P.; Lee, J. A.; Sutiphong, J. A.; Carey, J.; Robinson, J. ( )-Fluoxetine has a high affinity for the cloned rat and human 5-HT_{1C} receptor and the human 5-HT_2 receptor. Br. J. Pharmacol. 100s:99p; 1993.
20. Wong, D. T.; Reid, L. T.; Threlkeld, P. G. Suppression of food intake in rats by fluoxetine: Comparison of enantiomers and effects of serotonin antagonists. Pharmacol. Biochem. Behav. 31: 475–479; 1988.
21. Wong, D. T.; Threlkeld, P. G.; Robertson, D. W. Affinities of fluoxetine, its entantiomers, and other inhibitors of serotonin uptake for subtypes of serotonin receptors. Neuropsychopharmacology 5:43–47; 1991.
22. Yen, T. T.; Wong, D. T.; Bemis, K. G. Reduction of food consumption and body weight of normal and obese mice by chronic treatment with fluoxetine: A serotonin reuptake inhibitor. Drug Dev. Res. 10:37–45; 1987.