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The 5-HT_2 Receptor Agonist MK-212 Reduces Food Intake and Increases Resting but Prevents the Behavioural Satiety Sequence

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HALFORD, J. C. G., C. L. LAWTON AND J. E. BLUNDELL. *The 5-HT_2 receptor agonist MK-212 reduces food intake and increases resting but prevents the behavioural satiety sequence.* PHARMACOL BIOCHEM BEHAV **56**(1) 41–46, 1997.—The 5-HT_{2C} receptor is implicated in the relationship between serotonin and satiety. However, anorexia induced by the 5-HT_2 receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) has been shown to delay, not advance behaviours associated with the onset of satiety, fragmenting eating behaviour. 6-chloro-2-(1-piperazinyl)pryazine (MK-212) is also a selective agonist at the 5-HT_2 receptor sites. MK-212 has greater affinity for 5-HT_{2C} receptor sites than DOI. The effects of an ED50 dose of MK-212 (5.0 mg/kg i.p.) on the eating and other behaviours of the fasted rat were continuously monitored following the presentation of food. Continuous monitoring provides the most powerful and valid form of behavioural analysis. Temporal profiles of behaviour duration (dur) and frequency (frq) were generated. Food intake was reduced 54% by MK-212 ($p < .001$). The frequency of grooming was reduced ($p < .01$). Locomotion (dur $p < .001$, frq $p < .001$), rearing (dur $p < .0005$, frq $p < .005$) and sniffing (dur $p < .05$, frq $p < .0001$) were all reduced. The duration of resting increased ($p < 0.01$). This is consistent with enhanced satiety. However, the Behavioural Satiety Sequence was not present after the administration of MK-212 (5.0 mg/kg). The temporal structure of behaviour produced by MK-212 was quite different from that produced by pre-feeding. Initially resting dominated the behavioural profile. Eating increased over time from a suppressed state in the initial stages of the observation period. This lack of appearance of the Behavioural Satiety Sequence is more similar to a state of hyper-sedation than to DOI induced hyper-activity. The time course of this sedation would not have been picked up by a simple categorical analysis of behaviour. Hence, temporal analysis is an essential tool in understanding of drug induced anorexia. **Copyright © 1997 Elsevier Science Inc.**

MK-212 5-HT_2 Behavioural satiety sequence Sedation Food intake

THE behavioural sequence associated with satiety has been used to investigate the anorectic activity of various drugs (6, 9–12,17–20,25,26). This behavioural satiety sequence was first defined by Antin et al. (1). Following the termination of eating behaviour, animals appeared to engage in a brief period of activity, and then grooming, before commencing with resting behaviour. The work of the group of G.P. Smith has established that the preservation of the structure of this stochastic sequence can be taken to signify the reduction of food intake by a post-ingestive physiological mechanism of satiety. Such adjustments in the Behavioural Satiety Sequence can be brought about by gastric pre-loading or pre-feeding the animal (1). More recent work by Dourish (9,17) and Simansky (25) has established the value of the satiety sequence for understanding drug induced anorexia. Disruption of the sequence demonstrates that a drug reduces food intake by mechanisms other than satiety (e.g. via the induction of nausea, pain, sedation or hyper-activity). Thus, anorectic drugs can be divided into those which preserve the satiety sequence and those which disrupt it.

Researchers have tended to use various time sampling techniques of behaviour recording. Research into the analysis of observation data suggests that these techniques may be unsuitable (22) due to sampling bias and/or random error. Statistical analysis of time sampling data may also be problematic (7, 21). Alternatively, continuous analysis can be utilised. This makes the analysis exhaustive (all behaviour is coded) and bi-dimensional (analysed by the behavioural dimensions of

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TABLE 1
BEHAVIORAL CODES EMPLOYED IN LIVE CODING

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 resting position.

Based on definitions used by Antin *et al,*. (1) and Kirkham and Blundell (17).

duration and frequency). Intermittent sampling procedures, such as time interval sampling techniques are most commonly used to monitor the behavioural satiety sequence, the animals' behaviour being recorded at the end of a specified interval (at the end of every 15th or 30th second). Time interval sampling has three distinct flaws. First, Quera (22) comments that time interval data has been repeatedly shown to be biased in its estimation of the true frequency of behaviour. This is critical to the analysis as both hyper-activity and sedation are signified by striking changes in behavioural frequency. Second, although time interval data is unbiased in its estimation of true duration of behaviour, large degrees of random error occur in the 5 min time bins used to analysis the sequence (13). This makes statistical analysis between these time bins problematic (7,21). Finally, there is 'event over state observer bias' (13). Basically, the observer is more prone to code an event-like behaviour (such as locomotion) than a state-like behaviour (such as resting) if the instant of observation falls on a transition between the two (13). As Quera (22) concludes 'The use of time sampling and post hoc correction is not justifiable when the observations are videotaped or when live observations can accurately record the frequencies and the onsets and offsets of behaviours'.

The role of serotonin (5-HT) in satiety has now been long established (2). Serotoninergic drugs appear to induce satiety via the activation of both 5-HT_{1B} and 5-HT_{2C} (formally 5-HT_{1C}) receptors (17). Investigation of the precise role both these individual receptors have in controlling eating behaviour still remains unclear as there are no highly selective agonists particularly for the 5-HT_{2C} receptor. Agonists for the 5-HT_{2C} receptor also have affinity for 5-HT_{1B} receptors or other 5-HT_2 receptors. MK-212 (6-chloro-2-(1-piperazinyl)pryazine), a 5-HT_2 receptor agonist, has been shown to reduce food intake (8). MK-212 possesses a particularly high affinity for 5-HT_{2C} receptors (15) known to be implicated with satiety. MK-212 has also been shown to decrease locomotion (24). These effects would appear to be similar to the actions of the 5-$HT_{1B/2C}$ agonist mCPP ((1,3-chlorophenyl)piperazine). mCPP has been reliably shown to preserve the behavioural satiety sequence (13,17,25). This would suggest that MK-212 reduces feeding via the activation of a common 5-HT_{2C} satiety mechanism. Another 5-HT_2 agonist, DOI, has been shown to increase activity and fragment eating behaviour (17,25). Consequently, resting behaviour is delayed and the satiety sequence is disrupted. DOI induced anorexia appears to be mediated by 5-$HT_{2A/2B}$ receptors rather than 5-HT_{2C} receptors (23).

The effects of MK-212 on the structure of feeding behaviour have not been studied in depth. From the existing data it would appear reasonable to assume that MK-212 would induce behavioural changes similar to those induced by mCPP and not DOI. MK-212 is known to decrease locomotion and increase sedation; these effects tend to suggest a natural modulation. Indeed the early occurrence of resting on its own has been regarded as an index of natural satiety (18–20,26,). In this study the effects of MK-212 on the continuously monitored satiety sequence will be examined. The temporal behavioural profile produced by MK-212 can be compared with that produced by the natural physiological stimulus of pre-feeding. This pre-feeding behavioural profile acts as a template against which the anorectic action of drugs can be interpreted.

METHOD

Animals

12 male Lister hooded rats (250–300g) from the colony of the Psychology department, Leeds University were housed and monitored individually on a 12 h reversed light cycle (lights out: 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, consuming approximately 50 g of it per day.

Drugs

MK-212 (Merck Sharp and Dohme, Harlow, UK) 5.0 mg/kg was dissolved into surgical saline which also acted as control. Both saline and MK-212 were administered i.p.. The drugs were injected at a volume of 1 ml/kg. Drug dosing was separated by 72 h to allow full metabolite flush out. This dose was chosen as it had previously been shown to reduce intake by 50% (13).

TABLE 2
MEAN AND ± SE FOR INTAKE, LOCAL EATING RATE (LER), MEAN EATING BOUT INTAKE (MBI), MEAN EATING BOUT LENGTH (MBL)

	Intake (g)	LER (g/min)	MBI (g)	MBL (s)
Saline control	8.92 (1.31)	1.32 (0.10)	0.59 (0.12)	26.9 (5.37)
MK-212 5.0 mg/kg	4.33*** (0.81)	0.81*** (0.10)	0.44 (0.04)	21.8 (3.08)

Student's *t*-test.
Decreases from saline control— * = $p < 0.05$, ** = $p < 0.05$, *** = $p < 0.005$; Increases from saline control - # = $p < 0.05$, ## = $p < 0.01$, ### = $p < 0.005$.

TABLE 3

MEAN AND ± SE OF DURATION OF EACH BEHAVIOUR OVER THE OBSERVATION PERIOD (SECS)

	Eat	Groom	Loco'	Rear	Sniff	Rest
Saline control	405 (60.62)	371 (47.15)	79 (12.75)	243 (31.07)	786 (75.03)	511 (61.98)
MK-212 5.0 mg/kg	320 (48.25)	371 (69.14)	18*** (4.83)	80*** (18.53)	556* (75.94)	1042## (129.2)

ANOVA $F_{crit(1,11)} = 4.84$; Decreases from saline control– * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.005$; Increases from saline control– # = $p < 0.05$, ## = $p < 0.01$, ### = $p < 0.005$.

Design

A repeated measures design was employed with each animal's behaviour monitored on both drug and the saline control. Each animal consequently acted as its own control. The order of the two conditions was determined by a latin square to counterbalance drug treatments.

Procedure

Four animals were monitored each day. On each experimental day food was removed from the animal cage 4 h before monitoring. The animals were injected one hour before the observation began. The observation period was 40 mins long. The observation tank (55 cm × 30 cm × 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 illumination 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 (see Table 1). These were logged on to an IBM compatible PC using a specially designed data collection program ('KEETH')(14). 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 observations were staggered at one hour intervals. The first observation started at 1300 h.

The effects of the drug treatment on the behavioural profiles were compared to the effects of pre-feeding which would naturally enhance the physiological processes of satiety. Prefeeding or gastric pre-loading have often been used experimentally as a positive control in studies examining the enhancement of satiety. These pre-fed behavioural profiles were generated in a previous study. The animals where maintained and observed under identical experimental conditions. However, they were not injected but allowed free access to food for 5 min just prior to the start of the experimental observation.

Analysis

A. 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 local eating rates (LER)(g/min), mean intake per eating behaviour episode (MBI)(g) and mean eating bout length (MBL)(min) were also calculated for each drug condition. The local eating rate (LER) represents the rate of eating only during the time the animal is actually eating food (4,5). In earlier studies the local eating rate has been shown to be a sensitive indicator of the effect of a drug on eating behaviour. Changes in intake and the three eating parameters were analysed using four two-tailed student's *t*-tests.

B. 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. The changes in behaviour were judged significant from the main condition effects of the condition by period ANOVAs used in the microstructural analysis in section c (below).

C. Microstructural analysis of behaviour. To analyze the change in behaviour over time a 'SAS' (Statistical Analysis Systems Inc.) 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 individual behaviour. Profiles were plotted. Drug effects on each individual behaviour over the whole period were analyzed on 'SAS' using analysis of variance for both the continuous duration and continuous frequency data. For each behaviour a 2 × 8 repeated measures analysis of variance was carried out with drug (two levels - control and MK-212 5.0 mg/kg) and time period (eight levels - period 1 to 8) as the two factors.

RESULTS

A. Food intake and eating parameters. The effect of MK-212 on food intake and eating parameters are shown in Table 2. The reduction in food intake induced by MK-212 was 54% of the control value and was highly significant ($p < 0.001$, $t = -3.58$). The reduction in local eating rate was also significant ($p < 0.005$ $t = -3.51$). Despite this significant slowing of

TABLE 4

MEAN NUMBER AND ± SE OF EPISODES OF EACH BEHAVIOUR OVER THE OBSERVATION PERIOD

	Eat	Groom	Loco'	Rear	Sniff	Rest
Saline control	19.7 (2.69)	24.6 (2.29)	47.1 (7.46)	47.8 (6.95)	94 (9.60)	17.2 (2.05)
MK-212 5.0 mg/kg	13.7 (1.33)	13.1** (2.55)	10.8*** (2.55)	14.1*** (2.60)	39.5*** (4.30)	12.4 (12.4)

ANOVA $F_{crit(1,11)} = 4.84$.
Decreases from saline control— * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.005$.

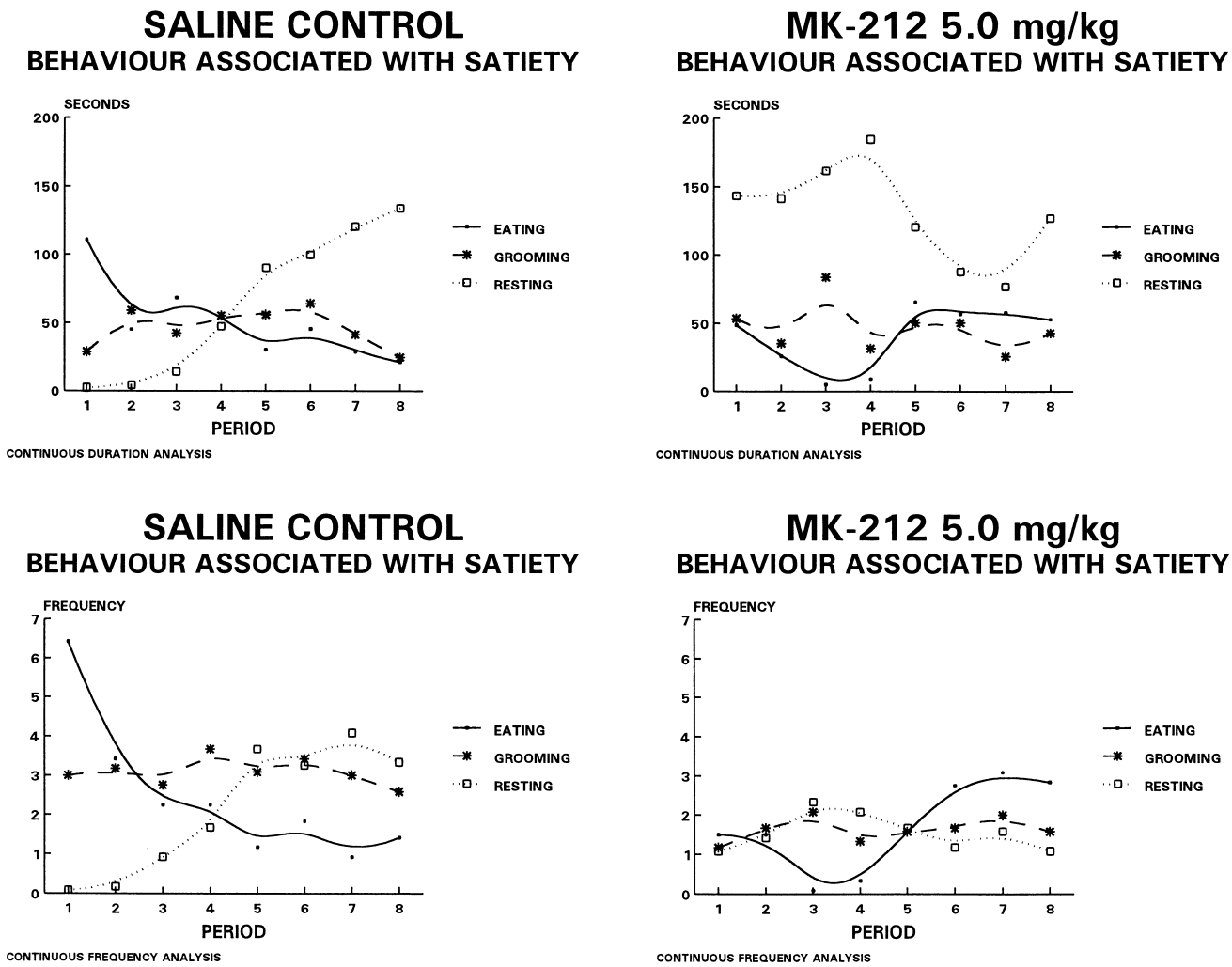

FIG. 1. Satiety profiles produced by saline control and by MK-212 5.0 mg/kg (Analysis by duration and frequency).

eating, neither the reduction in the duration nor frequency of eating was statistically significant (Tables 3 and 4).

B. Specific behavioural measures. The effect of MK-212 on the duration and frequency of other behaviours (along with eating) are shown in Tables 3 and 4. MK-212 decreased grooming (frequency $p<0.01$, $F = 11.49$), locomotion (duration $p<0.001$, $F = 20.28$, frequency $p<0.001$, $F = 22.84$), rearing (duration $p<0.0005$, $F = 26.22$, frequency $p<0.005$, $F = 17.70$) and sniffing (duration $p<0.05$, $F = 8.80$, frequency $p<0.001$, $F = 22.55$). MK-212 increased the duration of resting ($p<0.01$, $F = 11.01$). These overall behavioural changes are not inconsistent with the operation of satiety. Drinking and other behaviours occurred so rarely they were not analysed.

C. Microstructural analysis of behaviour. The behavioural profiles produced by MK-212 are shown in Fig. 1 (duration and frequency). The profiles can be compared with those produced by 5 min pre-feeding shown in Fig. 2 (duration and frequency). MK-212 did not preserve the structure of the satiety sequence. MK-212 did not advance the behavioural profiles in a manner consistent with pre-feeding. From the start of the observation period resting dominated the behavioural profile. As time passed eating behaviour rebounded from an initially low starting point. Activity also slowly increased over time. This clearly contrasts with the profiles generated by pre-feeding. In the 5 min pre-feeding condition the decline in eating over time was still apparent. Additionally, the onset of resting had been enhanced but it still increased over time.

DISCUSSION

MK-212 potently reduced food intake like other direct 5-$HT_{1/2}$ agonists. This is consistent with the role of 5-HT in satiety (2). However, MK-212 failed to permit the appearance of the behavioural satiety sequence in a manner consistent with pre-feeding. This suggests that MK-212 may not act on the underlying processes of satiety to reduce the intake of food. The behavioural adjustments of the profile induced by MK-212 were distinct and quite dissimilar from the fragmentation of the sequence produced by the 5-$HT1_{A/1B}$ agonist RU-24969 (5,13,17) or another 5-HT_2 agonist DOI (17,25). The effect of MK-212 on the satiety sequence was also dissimilar to the effect of the direct 5-$HT_{1B/2C}$ agonists mCPP and TFMPP (13,17,25), and other more general serotoninergic agonists such as d-fenfluramine, fluoxetine, sertraline and sibutramine

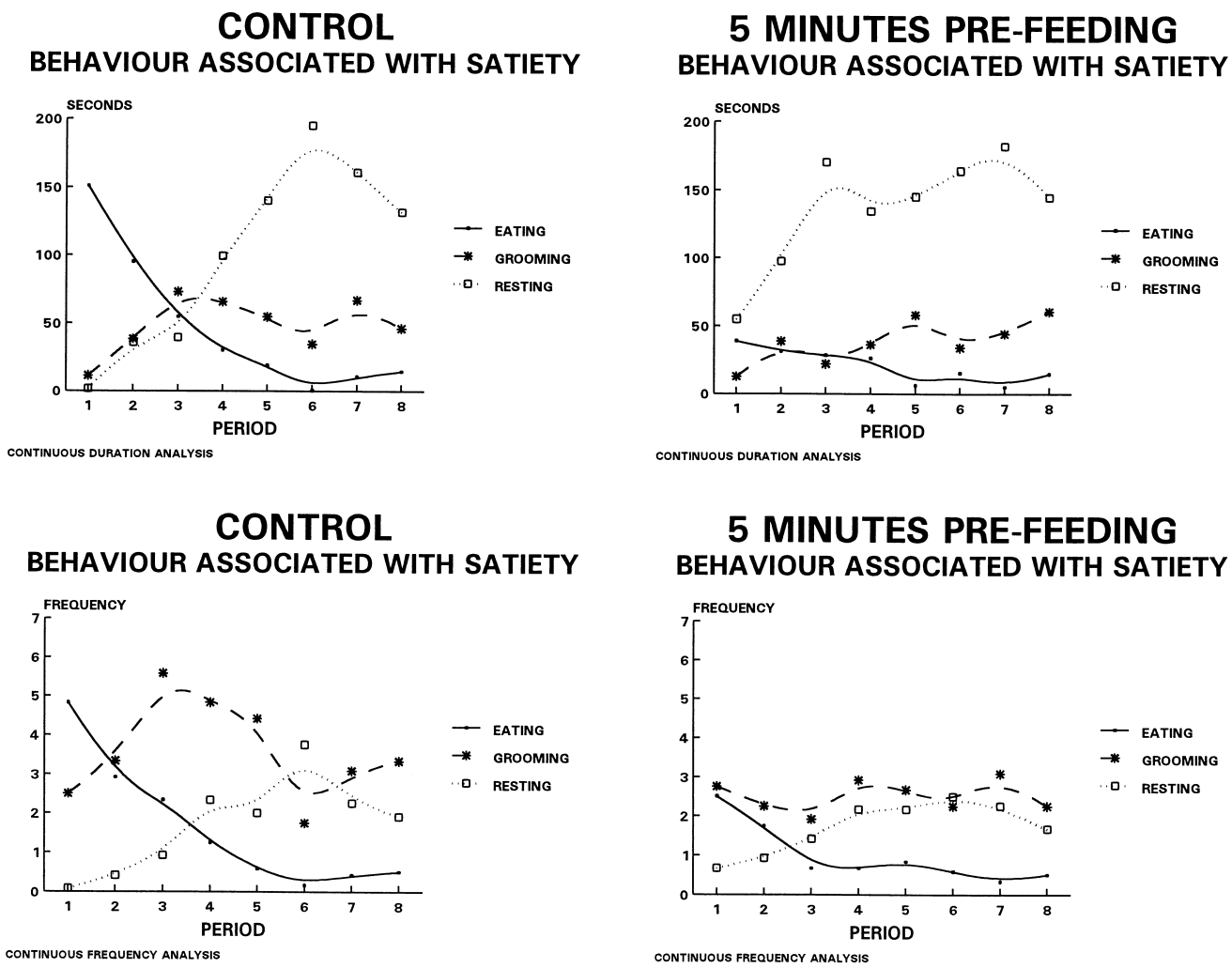

FIG. 2. Satiety profiles produced by 5 min prefeeding. These can act as a template by which the anorectic action of MK-212 can be judged (Analysis by duration and frequency).

(11–13,25). On the basis of a categorical analysis of behaviour, MK-212 reduced eating time (and food intake) and increased resting. These features are normally strongly suggestive of the preservation of the satiety sequence. Greater sedation in the later part of the Behavioural Satiety Sequence suggests enhanced satiety (see pre-feeding profiles). However, the temporal profile revealed that the sequence was in fact reversed. The behavioural profiles suggest instead that MK-212 suppressed food intake by suppressing activity and the rate of behavioural expression (i.e. the animals were very sedated). This is clearly demonstrated in the temporal profiles of behaviour. When first presented with food animals failed to eat but displayed a high level of sedation (high % resting, low % active behaviour). The animals only started to eat as the sedation started to weaken over time. We have previously observed that smaller, non-anorectic doses of MK-212 produced 'pimozide like' effects on eating behaviour (13). Pimozide is a dopaminergic antagonist with a sedative action which slows eating behaviour without affecting the total amount of food consumed (4). Strong sedation will, it appears, potently reduce food intake. Consequently, the disruption of food intake by severe sedation can be defined by a distinct behavioural profile. The initial feeding behaviour of the animal appears very suppressed and only slowly increases, along with active and grooming behaviours, over time. The overall occurrence of all behaviour is reduced and the eating rate is slowed. The difference between the behavioural effects MK-212 and DOI is problematic as both drugs activate the same 5-HT_2 receptors. MK-212 has a greater affinity for 5-HT_{2C} receptor and a lesser, but still potent affinity for other 5-HT_2 receptors. The primary role of 5-HT_{2A} and 5-HT_{2B} receptors in the anorectic action of DOI has been demonstrated (23). This pharmacological difference between the two drugs seems the most likely reason for the differences between the behavioural profiles produced by these two 5-HT_2 agonists. However, it is still far from clear exactly how the individual contribution of both 5-HT_{2A} and 5-HT_{2B} receptors could disrupt feeding behaviour in such markedly differing ways. Why does the activation of these 5-HT_{2A} and 5-HT_{2B} receptors induce sedation in the case of MK-212 and hyper-activity in the case of DOI?

It is important to note that using the traditional microstructural analysis of behaviour, gross behavioural changes

over time, this dose of MK-212 appeared to be altering behaviour in a manner consistent with satiety (as seen in Tables 1 to 3). MK-212, like most other 5-HT agonists, direct or indirect, produces a remarkably similar pattern of changes in many of the measures traditionally used to assess drug action on feeding mechanisms (4,5,17). MK-212 reduces intake and eating behaviour, slows eating rate, reduces activity and grooming and increases resting. Only the temporal profiles used to examine the Behavioural Satiety Sequence (Fig. 1) revealed the abnormal effects of MK-212 on behaviour. Therefore, temporal analysis of the Behavioural Satiety Sequence could be considered a necessary procedure for determining the nature of the action of an anorectic drug. General reductions in eating rate, grooming and activity, and increases in resting cannot be assumed to signify satiety when these measures so demonstrably fail to discriminate severe sedation.

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