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Review

# Meal patterning in rodents: psychopharmacological and neuroanatomical studies

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## Abstract

Studies of meal patterning have made an important contribution to our understanding of ingestive behaviour. This paper initially reviews studies of normal meal patterning in rodents, with an emphasis on the determination of suitable meal criteria. Studies of serotonergic mechanisms in the control of meal size and feeding rate suggest important roles for the 5HT<sub>1B</sub> and 5-HT<sub>2C</sub> receptor. Analysis of dopaminergic mechanisms show that dopamine D<sub>2</sub> receptor blockade is associated with enhancement of meal size and decrease of meal frequency; this probably represents a failure to switch from feeding to other behaviour when a meal is expected to terminate. Finally studies are described demonstrating that lesions of several forebrain structures, including hippocampus and nucleus accumbens, lead to a similar syndrome of short, frequent meals with little evidence of a deficit in body weight regulation. These structures may play a role in the organisation of meal patterning. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* Meal pattern; Meal size; Feeding rate; Rat; Mouse; Serotonin; 5-HT; Dopamine; Nucleus accumbens; Hippocampus

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## 1. Introduction

Physiological and behavioural studies of feeding and drinking have been an enduring feature of the Laboratory of Experimental Psychology at Sussex University since its inception in 1965.<sup>1</sup> Early members of the Laboratory included David Booth, Keith Oatley and Frederick Toates, whose interests at that time ranged from the modelling of physiological processes [5] to the conditioning of flavour–calorie relationships [4]. Later Mic Burton moved to Sussex

after completing his doctorate with Edmund Rolls (e.g. Ref. [6]) and initiated a psychopharmacological approach to the study of meal patterning, with a particular emphasis on serotonin (e.g. Ref. [7]). More recently my colleagues and I have continued this approach, with a particular emphasis on fine grain behavioural analyses, and it is some of these studies which form the subject of the present review. In order to account for meal patterning at a causal level we need first to have the appropriate descriptive methods, and then use the tools provided by psychopharmacology and behavioural neuroscience as appropriate probes, so I shall turn initially to the analysis of normal feeding patterns.

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<sup>1</sup> This paper is dedicated to the memory of Stuart Sutherland, founding Chair of the Laboratory of Experimental Psychology at Sussex, who died on 8th November 1998; though Stuart's own cynicism about empirical studies in psychology became legendary, he nevertheless remained an extremely supportive colleague to those who remained in the laboratory!

## 2. Studies of 'normal' meal patterning

Studies of meal patterning at Sussex have been strongly

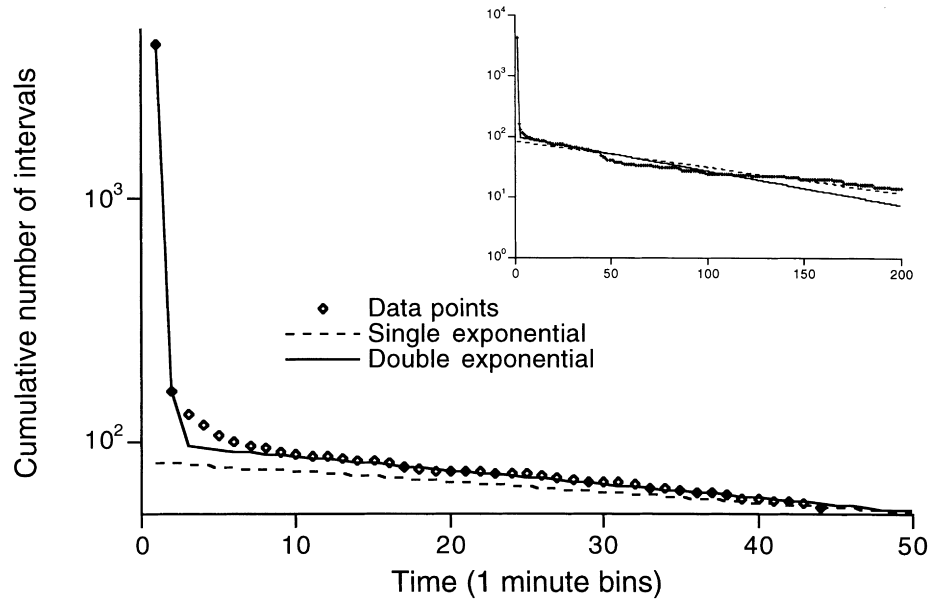


Fig. 1. A log-survivor plot for data, cumulated over 4 days, from eight individual rats, together with the best-fitting single and double exponential curves (see text). Inset: the same data plotted on an extended linear time axis.

influenced, at both technical and theoretical levels, by the pioneering contributions of Kissileff and Blundell [3,30]. In all of the studies reviewed below, we have used a large home cage equipped with an 'eatometer' [30] and a 'lickometer' [48] for measurement of food and fluid intake, respectively. The eatometer is an adaptation of a conventional pellet delivery system for operant studies that delivers pellets into a V-shaped trough fitted with infrared beams to detect presence of a pellet. In general, another pellet is made available immediately after the rat removes one from the trough, although delays in replacement bring feeding rate under experimental control and provide an interesting experimental manipulation [8]. The drinkometer combines a standard capacitive detector for tongue presence on a

spout with hardware to switch a peristaltic pump supplying fluid to the spout. Together with a microprocessor-based data collection system, the equipment provides a precise record over a 24 h period of both food and fluid intake (for further detail see Refs [9,10]).

In this environment, using a 12:12 h photoperiod, rats show very stable diurnal patterns of intake in which both food and fluid intake are at a maximum at the beginning and end of the dark phase and are at a minimum level during the light phase. Ingestion of both food and water is clustered into bouts (referred to here as meals and draughts, respectively). We have used log-survivorship analysis [45] as the initial method to suggest an appropriate criterion beyond which intervals between either feeding or drinking fall

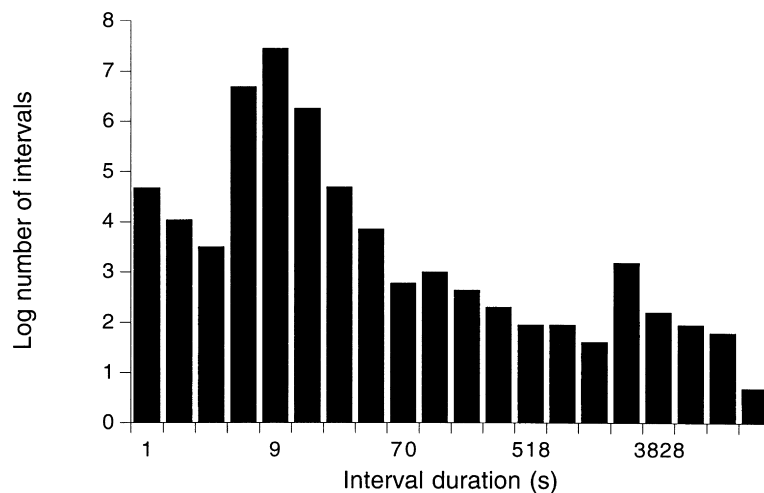


Fig. 2. The same data set as Fig. 1, but not cumulated and plotted on a log–log axis to reveal a possible log-normal distribution with a mode beyond the expected meal criterion.

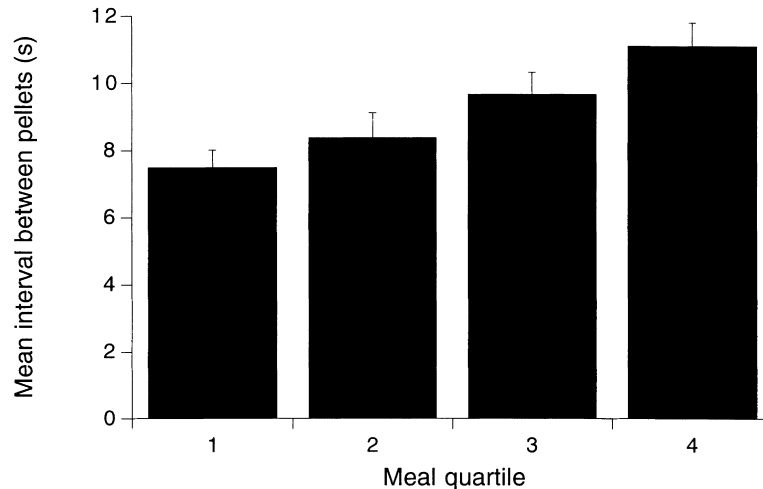


Fig. 3. Changes in feeding rate during the first meal of the night phase, from the data set shown in Figs. 1 and 2. Individual meals were divided into quartiles, based on quantity consumed, and feeding rate within them calculated by dividing their duration by the number of pellets consumed.

between meals or draughts. Fig. 1 shows typical data for feeding collected over 4 days within the same experiment, together with the best fitting single and double exponential curves. It is clear that the single exponential curve is an extremely poor fit; however the double exponential curve accounts for greater than 98% of the variance in the distribution. A meal criterion just beyond the break point of the curve will minimise the number of misassigned intervals [9,46] and suggests a criterion of 2–3 min. Sibley [44] has noted that although the log-survivorship method remains a good visual method for choosing a meal criterion, statistical procedures that depend on cumulative data suffer from lack of independence between successive data points. He recommends instead that all statistical analyses are performed on the non-cumulated distribution and we follow that recommendation. We have normally used grouped data to generate these distributions since individual differences are not marked, and also because use of individual criteria would provide difficulties of interpretation when additional manipulations, such as drug treatment, are investigated.

Tolkamp et al. [50] have recently suggested that the log-survivorship method makes an inappropriate assumption about the likely distributions of intervals between feeding or drinking. The assumption is that, at least beyond the time required to eat a single food item, the distribution is modelled by a slow Poisson process. Tolkamp et al. argue that it may be inappropriate to expect a Poisson distribution, but that instead a log-normal distribution may provide a better fit to the data. They come to this conclusion on two grounds: first they note that, in data recording visits to a feeder collected from dairy cattle, log-normal distributions provided a better fit than Poisson distributions. Second, they suggest that satiety would be expected to be a prolonged state and not have a constant probability of ending.

Fig. 2 shows the data from Fig. 1 plotted in the recommended way [50]. These data do not provide any strong justification for treating the hypothesised slow Poisson

distribution as log-normal and also suggest that a meal criterion of between 2 and 5 min is much more appropriate than one of 20–30 min used in some older studies [35]. The difference between our data and those reported by Tolkamp is most probably explained by variation in the organisation of ingestive behaviour between ruminant and non-ruminant species. Since feeding and rumination alternate in cattle, it is not surprising to find that intervals between feeds are fitted by a skewed normal distribution, but there is no obvious reason why this should occur in a non-ruminant species.

It has been reported previously that within-meal feeding rate remains constant throughout a meal [7]. However, if meals that occur at about the same time of day are grouped, then small but significant decreases in feeding rate are apparent as the meal progresses. Fig. 3 shows a statistically reliable ( $F_{3,17} = 5.85$ ,  $p = 0.006$ ) increase in mean inter-pellet interval in the four quartiles of the first meal of the dark phase for the same data set shown in Figs 1 and 2. Such changes are more easily recognised in animals fed on a series of scheduled meals and may provide a useful index of within-meal satiety [33].

Feeding rate is also a variable that can be brought under experimental control and shown to affect the characteristics of meal patterns. Studies by Collier's group (e.g. Ref. [20]), in which rats worked either for access to a meal, or for individual food items, indirectly suggested this possibility. Animals working for access to a meal showed the expected increase in meal size and decrease in meal frequency that reduces the work requirement for a given quantity of food. Less expected, from an ecological/economic perspective, was the finding that increasing work requirements for individual food items led to decreases in meal size. However, such data could be explained simply as a consequence of increasing delays between consumption of individual food items. For example, Wiepkema [53] argued that, at the beginning of a meal, a short duration positive feedback process from consumption of individual food items leads

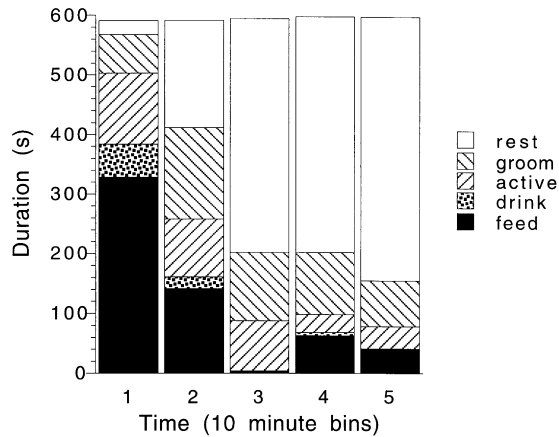


Fig. 4. Satiety sequence following consumption of freely initiated meals at the beginning of the night phase. Data originally presented in Ref. [19]. The animals ( $N = 8$ ) had received sham lesions (saline infusion) of the hippocampus.

to an enhancement of bout size; increases in the time between presentation of each item would be expected to reduce summation of such effects during the early phase of the meal. In addition, a major problem for control theory approaches to feeding [5] lies in the delay between consumption of food and its post-ingestional consequences. Slowing the rate of intake would be expected to reduce such delays, and allow the animal to “catch up” with post-ingestional consequences of feeding. In fact, using delays of 8 and 20 s between each 45 mg pellet, Clifton et al. [8] demonstrated a graded decrease in meal size accompanied by a corresponding increase in meal frequency. We also showed [8], by implementing a model based on Booth and Toates [5], that the data could be accurately predicted by reduction of feedback delays. In a subsequent report Lucas and Timberlake [36] reproduced and extended these findings. They argued that, since the major change in meal size occurred over a small range of short inter-pellet delays, an explanation in terms of disruption of positive feedback was more likely.

Recently we have combined the recording of behavioural satiety sequences with meal pattern studies [19]. Individual animals were video-recorded during the first hour of the dark phase, in addition to the usual long-term recording of food and water intake. The data was subsequently transcribed using a software package in which the observer’s key presses trigger direct encoding of time from the video tape recorder, thus allowing rapid scanning through periods of rest. Our rats typically initiate a meal within 10 min of lights-off thus providing synchrony between individual records. The behavioural categories are derived from those initially described by Antin et al. [1] and subsequently used by Blundell [3] and ourselves [10]. Fig. 4 shows data taken from a group of eight animals given sham hippocampal lesions [19]. It is clear that the satiety sequence has a very similar form to that usually obtained when animals feed on a damp, palatable mash that is presented only

once a day (see Ref. [10]). The implication is that the sequence that results in the latter situation is not an artefact produced by abnormally high consumption of palatable food, but is characteristic of normal postprandial behaviour in the rat.

In the studies reviewed below we have used these methods to examine the effects of a variety of pharmacological and neural manipulations on meal patterning. When pharmacological challenges were used they were routinely administered 20–30 min before the beginning of the dark phase of the photoperiod, at a time at which baseline intake is high. In all cases food (45 mg pellets) and water were available ad libitum, and meals and draughts were defined using a 2 min criterion with no imposed minimum meal size for inclusion in the data set.

### 3. Serotonergic contributions to meal patterning

The majority of meal patterning studies in the literature have used drugs that stimulate serotonergic systems in a relatively non-specific way. Fenfluramine is known to both enhance the release of serotonin and to inhibit reuptake [42]. More recently it has been shown that the D isomer is metabolised to a potent 5-HT<sub>2C</sub> agonist, D-norfenfluramine, which may account for some of the hypophagic effect of this drug [21]. Burton et al. [7] provided a detailed examination of meal patterns following administration of DL-fenfluramine. They confirmed the earlier report of Blundell and Latham [3], demonstrating a dose-related reduction in both meal size and feeding rate.

At present it seems likely that these effects are independent. Ritanserin, a 5-HT<sub>2</sub> antagonist, reduces fenfluramine-induced depression of feeding rate, but has little effect on the fenfluramine-induced reduction of meal size [27]. By contrast, cyanopindolol, a 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> antagonist, opposes the effects of fenfluramine on meal size, but has little effect on the depression of feeding rate [27]. Since low doses of the selective 5-HT<sub>1A</sub> agonist 8-OH-DPAT tend to increase food intake [23], it has been argued that 5-HT<sub>1B</sub> receptor stimulation mediates the reduction in meal size following fenfluramine treatment. However, it should be recognised that the hyperphagic effect of 8-OH-DPAT is only seen when baseline intake is low; similar doses used in a test situation in which baseline intake is high will reduce food intake, and this effect is also antagonised by the selective 5-HT<sub>1A</sub> antagonist WAY 100,635 [51]. It was therefore plausible that there might be a 5-HT<sub>1A</sub> receptor-mediated component to fenfluramine-induced hypophagia. In fact, using the satiety sequence paradigm, we could find no evidence that WAY 100,635 reduced D-fenfluramine-induced hypophagia [51]. This makes it much less likely that WAY 100,635 would antagonise D-fenfluramine induced reductions in meal size. In addition, the selective 5-HT<sub>1B</sub> agonist CP94,253 reduces food intake and produces a normal advancement of the satiety sequence [34] and may

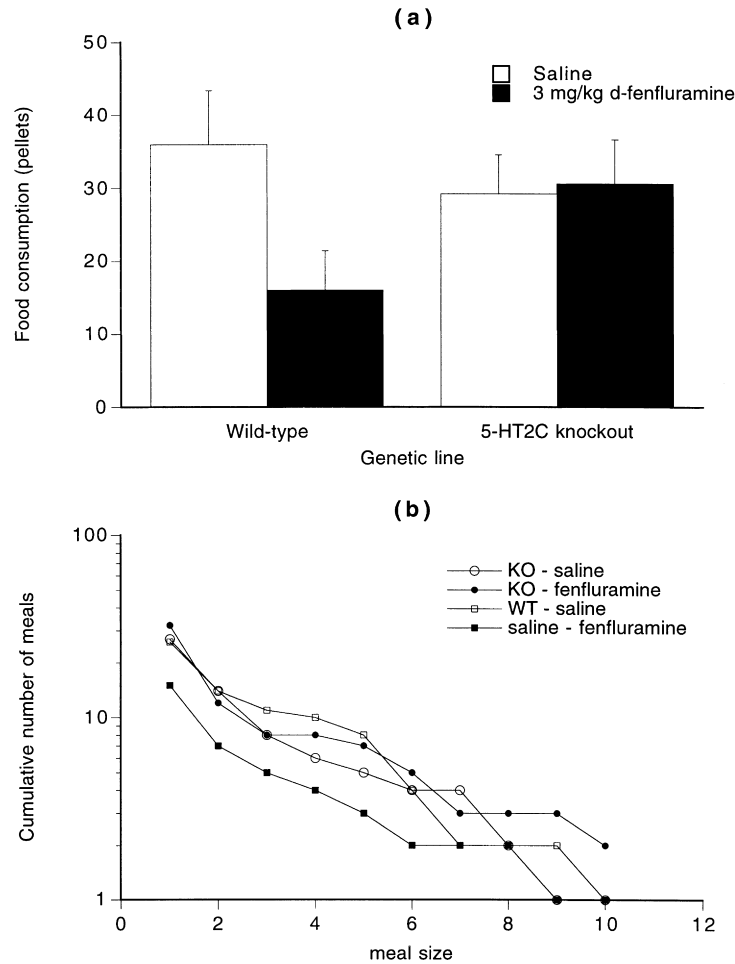


Fig. 5. (a) Mean food intake in 3 h following d-fenfluramine challenge (3 mg/kg) in wild-type (WT) and 5-HT<sub>2C</sub> knockout (KO) mice. (b) Log-survivor plots for meal size within the data set shown in (a). Data originally presented in Ref. [24].

therefore reduce meal size. Nevertheless, in the absence of meal pattern data from experiments using fenfluramine and selective 5-HT<sub>1B</sub> antagonists, this conclusion must remain provisional.

Clifton et al. [10] demonstrated that the selective serotonin reuptake inhibitor fluoxetine substantially reduced meal size but had no effect on meal frequency. This drug also reduced feeding rate, and the overall similarity of the behavioural syndrome to that produced by DL-fenfluramine [7] and by the mixed 5-HT<sub>1B/2C</sub> agonist mCPP [14] suggested a similar underlying mechanism. It would be predicted that serotonin antagonists should attenuate the hypophagic effect of fluoxetine and other selective serotonin reuptake inhibitors such as sertraline. However, simple intake studies using sertraline and serotonin antagonists have been successful in some cases, but unsuccessful in others [18,21,28]. Grignaschi and Samanin [26] were also unable to reverse fluoxetine-induced hypophagia with serotonin antagonists. Lee and Clifton [32] demonstrated a partial reversal of the effects of fluoxetine on milk and wet chow intake. We also showed, using the meal pattern paradigm, that fluoxetine increased the latency to feed following drug treatment,

and reduced meal size and feeding rate. Metergoline fully reversed the increased latency, and partially reversed the decrease in meal size but potentiated the fluoxetine-induced reduction of feeding rate. Lee [33] further demonstrated that this potentiation was dose related, increasing from a 17% reduction in feeding rate with a low dose of metergoline (6 mg/kg fluoxetine: 0.2 mg/kg metergoline) to a 32% reduction with a higher dose of metergoline (6 mg/kg fluoxetine: 5 mg/kg metergoline).

One problem in pursuing antagonist studies with fenfluramine, fluoxetine and similar compounds is that some recently described drugs, such as the highly selective 5-HT<sub>2C</sub> antagonist SB242,084, are not generally available. An alternative strategy, which we are pursuing, is provided by the development of detailed behavioural studies of ingestive behaviour in transgenic animals. Tecott et al. [49] have described a mild obesity syndrome in 5-HT<sub>2C</sub> receptor knockout mice. In a recent collaborative study with Tecott [52] we have shown, using the satiety sequence paradigm, that these animals are insensitive to the hypophagic effect of d-fenfluramine, although they show *enhanced* sensitivity to the motor stereotypy induced by a high dose of this drug.

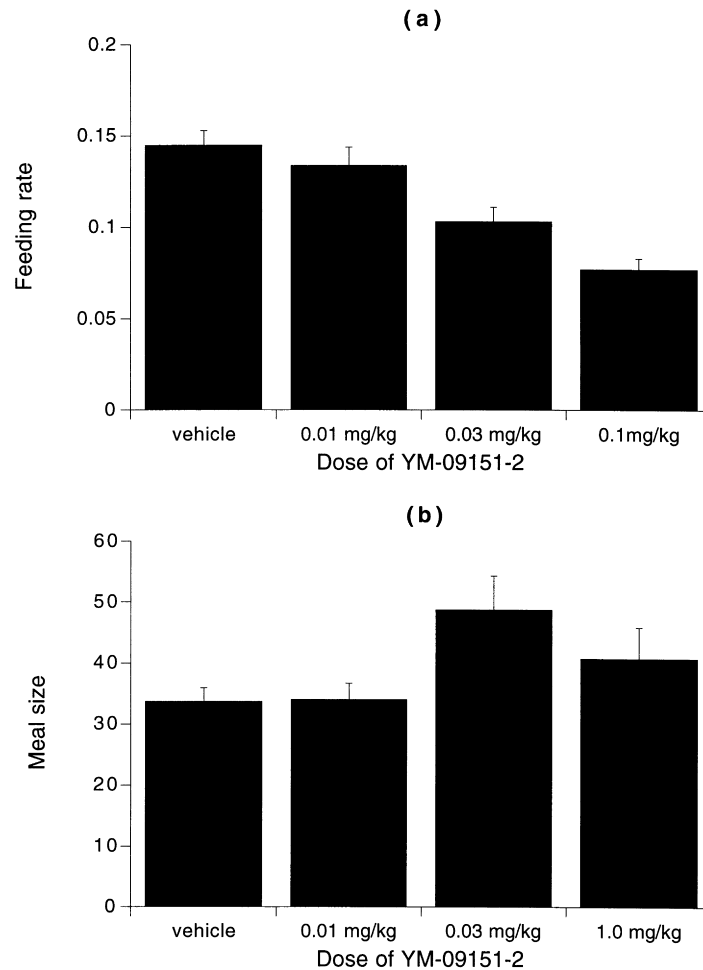


Fig. 6. (a) Within meal feeding rate following YM-09151-2 (0–0.1 mg/kg). (b) Mean meal size following YM-09151-2 (0–0.1 mg/kg). Data originally presented in Ref. [11].

Intriguingly, using a simple intake paradigm following 24 h food deprivation, it has also been shown that 5-HT<sub>1B</sub> receptor knockout mice are insensitive to the hypophagic of DL-fenfluramine [37].

We are now investigating the extent to which mice can be used in meal pattern studies (see Ref. [25] for an independent approach to this problem). Preliminary data [24] have been collected in 5-HT<sub>2C</sub> knockout and wild type mice using meal pattern cages similar to those used for rats. Feeding shows the expected diurnal pattern (high, especially at the beginning and end of the night, low at other times), and ingestion is clustered into meals, although their organisation shows greater variability than in the rat. However, simple technical modifications may overcome this problem; in the rat provision of a sleeping chamber was an important step in this direction [7]. Importantly, following D-fenfluramine challenge (3 mg/kg) the 5-HT<sub>2C</sub> receptor knockout mice again showed the expected insensitivity (Fig. 5a). A log-survivor analysis of meal size (Fig. 5b) suggested that wild type mice showed a reduction in both number

of meals and meal size following fenfluramine, whereas meal number was unaffected by fenfluramine treatment in the 5HT<sub>2C</sub> knockout mice.

The data reviewed in this section indicate that, at the behavioural level, treatments which enhance serotonergic activity have several apparently separate effects on meal patterns. They reduce meal size and enhance the satiety-inducing effect of these smaller meals; in addition feeding rate is suppressed. At a neurochemical level, existing data from the rat is consistent with 5-HT<sub>1B</sub> receptor mediated effects on meal size and 5-HT<sub>2C</sub> receptor mediated effects on feeding rate; in addition we have shown, in studies that are not reviewed here, that there are important CCK/5-HT interactions that influence meal size [13,15]. However, it is important to recall that these conclusions depend on indirect evidence from relatively non-selective compounds. To strengthen or reject these hypotheses, studies using recently developed selective agonists and antagonists are urgently required and it would be very helpful if observations on transgenic animals were able to produce complementary data. The existing studies using transgenic

Table 1

Relative change in meal parameters following lesions of nucleus accumbens or hippocampus (the data are summarised from that presented in Refs. [17,19], apart from the analysis of feed/drink transitions following nucleus accumbens lesions which are presented here for the first time. For these data, the increase in feed/drink transitions was marginally significant,  $F_{1,12} = 4.89$ ,  $P < 0.05$ . Remaining probabilities: \* $p < 0.05$ ; \*\* $p < 0.005$ )

	Hippocampus		Nucleus accumbens	
	Control	Lesion	Control	Lesion
Total intake (45 mg pellets)	415	476 (ns)	429	535 (ns)
Meal size (45 mg pellets)	39.3	18.1**	43.7	26.8*
Meal frequency	12.0	29.1**	10.0	21.6**
Feed/drink transitions	0.05	0.21**	0.03	0.05*

animals already challenge conventional pharmacological studies by suggesting that activation of *both* 5-HT<sub>1B</sub> and 5-HT<sub>2C</sub> receptors is required for the hypophagic action of fenfluramine.

#### 4. Dopaminergic contributions to meal patterning

Blundell and Latham [3] were the first to suggest that dopamine antagonists might have substantial effects on meal patterns of male rats. Subsequently, we [12] demonstrated that the selective dopamine D<sub>2</sub> antagonist YM-09151-2 had two distinct actions on meal patterns. First, feeding rate was reduced, such that the typical inter-pellet interval increased from about 7–10 s at a dose of 0.03 mg/kg YM-09151-2 (Fig. 6a). This effect was produced without any overall change in food consumption. In addition to the reduction in feeding rate, there was a substantial increase in mean meal size at that dose, from 34 to 48 pellets (Fig. 6b). This change was even more striking when the slowed feeding rate was considered; meal duration was more than doubled at the same dose of the antagonist [12]. Comparisons between different dopamine antagonists in this and a subsequent report [17] established that: (a) neither effect was likely to be due to drug action at peripheral dopamine receptors since domperidone, which has minimal central activity following systemic administration, was ineffective; (b) the effect on meal size was characteristic of action at dopamine D<sub>2</sub>-like receptors since the selective dopamine D<sub>1</sub> receptor antagonists SCH23390 and SCH39166 were ineffective. However, both D<sub>1</sub> antagonists induced small reductions in feeding rate and food intake together with a greater reduction in water intake; (c) the actions of dopamine antagonists on feeding rate and meal size were likely to be independent since the magnitudes of the effects did not covary in comparisons between YM-09151-2, raclopride and remoxipride. In a recent study (Clifton and Lee, in preparation) these comparisons have been extended to haloperidol (0.05–0.2 mg/kg), clozapine (1–10 mg/kg) and olanzapine (0.3–3.0 mg/kg). All three drugs reduced feeding rate over the dose ranges that were tested. Haloperidol also produced a strong enhancement of meal size at intermediate doses. Neither of the atypical compounds showed

any tendency in this direction, which was concordant with the relative ineffectiveness of remoxipride in our initial study.

How might these behavioural effects be explained? The slowed feeding rate probably reflects slight motor impairment, but the effect on meal size is more problematic. We initially suggested two possible types of explanation [12]. First, it is known that dopamine may have a ‘satiety-like’ effect at the level of the lateral hypothalamus [39]. Enhanced meal size would be compatible with this hypothesis, but might also predict a substantial increase in total food intake. In fact only raclopride enhanced total intake and the very strong effects of YM-09151-2 on meal size were not accompanied by any overall intake change. An alternative suggestion, which now seems more likely, is that the changes in meal size and frequency result from a more general effect on behavioural switching. It is well known that low doses of dopamine D<sub>2</sub>-like antagonists, across several classes of motivated behaviour, selectively reduce anticipatory/preparatory behaviour; such effects are not prominent after either the administration of D<sub>1</sub>-like antagonists or atypical compounds such as clozapine (feeding [2]; sex [41]). Termination of a meal is likely to be associated with a switch to some other class of behaviour and the timing of such a switch is likely to be influenced both by factors related to the current behaviour and those related to the behaviour which will replace the current one, if one accepts the general hypothesis that motivational systems compete for expression at some final common path [38]. In the present case, the switch is likely to be partly influenced by interoceptive cues arising from food consumption, and a decreased sensitivity to such cues would be interpreted as an ‘anti-satiety’ effect (see above). However, it is equally plausible that the delayed switch from feeding might reflect reductions in the likelihood of appetitive or preparatory responses that lead up to the replacing behaviour. Such a mechanism would be entirely consistent with the literature cited above, and would also fit with the subjective impression that a rat treated with dopamine antagonists feeds with little attention to any extraneous cues within the cage. By contrast, the selective dopamine D<sub>2</sub>-agonist N-0437 reduces meal size, although by increasing meal frequency, it may actually stimulate total food intake at intermediate doses [11].

## 5. Neural substrates of meal patterning

The approach to an explanation of the effects of dopamine antagonists on feeding that has just been outlined focuses attention on the switching mechanisms that determine the bout structure of behaviour. We have examined the effects of two neural manipulations whose effects also seem best interpreted within this framework. The work was guided by the hypothesis, derived from Pennartz et al. [40], that one function of the cortico-striato-thalamo-cortical loop that includes the ventral striatum and mediodorsal thalamus, and receives inputs from limbic structures including hippocampus and amygdala, is to elaborate and control the expression of motivational states such as feeding [47]. We have shown that lesions of nucleus accumbens [16] or hippocampus [19] give rise to a behavioural syndrome in which meals are smaller, but more frequent, than in sham lesioned animals (Table 1). In each case there was no effect on total food intake or the regulation of body weight.

We have also shown that both lesions produce at least some of the typical effects that have already been described in the literature. Animals with accumbens lesions showed no change in intake of either wet mash or palatable salt or sucrose solutions during short test sessions. This suggested that the decrease in meal size did not result from any decrease in hedonic response to food. In the case of hippocampal lesioned animals we were especially concerned that the reduction in meal size and increase in meal frequency might be accounted for by an increase in activity. Indeed measurements of line crossing in an open field showed that these animals were hyperactive, as expected, in a novel environment. [19]. However, measurements of activity in the home cage following a meal, which were provided by satiety sequences, gave no support to the idea that meal size was reduced as a consequence of hyperactivity; the satiety sequences showed the expected progression from feeding through grooming to rest [19] and showed no significant difference from the data for the control animals (see Fig. 4). It also seemed possible, since the hippocampus receives substantial olfactory inputs that the decrease in meal size might have a similar origin to the decrease in meal size produced by anosmia [31]. We therefore tested the animals in a simple olfactory dishabituation task [19]. In this task the rats were allowed to investigate small dishes containing soiled bedding from one of two rat strains. Although animals with hippocampal lesions exhibited reduced levels of investigation of the olfactory stimuli, they showed clear dishabituation to a changed stimulus following three presentations of the same stimulus. Therefore, it seemed unlikely that the increase in meal size and decrease in meal frequency resulted from any impairment of olfactory sensation.

Thus, lesions of both nucleus accumbens and hippocampus resulted in a similar behavioural syndrome which was particularly marked following the hippocampal lesion; this is of particular interest since hippocampal damage in

humans is associated with deficits in the control of meal initiation and termination [43]. The syndrome also resembled part of that described by Kissileff [30] in “recovered lateral” rats (i.e. rats given lateral hypothalamic lesions who had recovered from the initial aphagia and adipsia to normal total intake) but who nevertheless showed a fragmentation of meal patterning. To probe the present hypothesis that the syndrome results from interruptions, at any point, in the so-called “limbic” loop [47], it will be necessary to test the effects of lesions that disrupt the circuit bilaterally, but only lesion a particular structure unilaterally.

In addition to the changes in meal size and frequency, hippocampal or “recovered lateral” rats show substantially increased amounts of drinking during a meal (prandial drinking) [29]; rats with septal lesions also show this change [22]. Hippocampal rats show a much larger number of transitions between feeding and drinking, which implies a similar change (Table 1). However, the changes in meal size and frequency and in prandial drinking are not necessarily linked. In our initial description of the effects of accumbens lesions on the temporal pattern of ingestion, we did not examine prandial drinking, but a reanalysis of the original data files (Table 1) shows only a very small increase in feed/drink transitions which is entirely explained by the increase in meal frequency.

## 6. Concluding remarks

The studies reviewed here show the value of detailed description of unconditioned behaviour that was pioneered by some of the early ethologists (see Ref. [15]). The studies of serotonergic manipulations demonstrate that decreases in food intake depend on reductions of meal size and within-meal feeding rate with no change in meal frequency. It is likely that these represent at least partly independent effects and that they represent an enhancement of endogenous satiety mechanisms. Studies of both dopaminergic manipulations and the contributions of forebrain mechanisms have demonstrated effects on meal patterning that occur in the absence of any effect on total intake. Thus blockade of dopamine D<sub>2</sub> receptors is associated with increased meal size and decreased meal frequency whereas lesions of either nucleus accumbens or hippocampus are associated with increases in meal frequency and decreased meal size. Both types of effect are likely to arise from alterations in the mechanisms that permit switches between feeding and other categories of behaviour.

One important further question concerns the extent to which these effects on the patterning of feeding may be present for other categories of unconditioned behaviour. A fundamental characteristic of motivated behaviours is that they occur in extended bouts; given the discontinuous distribution of most resources in the environment, be they food, water or mates, this makes good functional sense. It may be

that the changes in feeding that we have characterised are also present for other behavioural categories, and reflect interference with general mechanisms that provide the temporal structure in ongoing sequences of behaviour.

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