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Microstructural Analysis of the Involvement of Beta-Receptors in Amphetamine Anorexia

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WILLNER, P. AND A. TOWELL. *Microstructural analysis of the involvement of beta-receptors in amphetamine anorexia.* PHARMAC, BIOCHEM. BEHAV. 17(2) 255–262, 1982.—Rats were trained to take food by pushing the door of the pellet dispenser in an operant chamber. Log survivor analysis of the inter-response time frequency distribution was used to determine whether or not an animal was eating, at any time during a thirty minute session. This information was used to compute eating time, eating rate, and the mean length of bouts of eating and gaps between eating bouts. Video-recordings confirmed that the method discriminated eating from not eating with an accuracy of approximately ninety percent. Amphetamine (0.5 mg/kg) significantly reduced total food intake and eating time, and increased gap length; propranolol (5 mg/kg) significantly increased eating time and bout length. Following propranolol pretreatment, amphetamine significantly reduced eating time and bout length but also significantly increased eating rate; as a result there was no significant decrease in total food intake. The possible mediation of these effects by beta-adrenergic and dopaminergic systems is discussed.

Feeding Microstructural analysis Log survivor analysis Amphetamine Propranolol Catecholamines Rats

AMPHETAMINE has for many years been treated as a reference drug in pharmacological studies of anorexia. However, uncertainty still exists as to the mechanisms which mediate amphetamine anorexia. In common with many other actions of amphetamine the anorexic effect is attenuated by neuroleptic drugs, which are known to be dopamine (DA) receptor blocking agents [1, 6, 13, 15, 16, 19, 20, 33] and by lesions to dopaminergic pathways in the brain [9, 14, 21, 26]. However, it was recently reported that neuroleptics were ineffective in blocking the anorexic effect of a low dose of amphetamine (0.5 mg/kg) [6], suggesting that transmitters other than DA might be involved, particularly at low doses.

Studies employing central drug administration confirm that amphetamine anorexia is not mediated solely by DA. Injection of beta-adrenergic receptor blocking drugs in the region of the perifornical hypothalamus also attenuated the anorexic effect of centrally or peripherally administered amphetamine [18, 19, 20, 22]; this and several other lines of evidence strongly support the concept of a beta-adrenergic satiety system in the perifornical hypothalamus [2, 8, 18, 19, 20, 22, 23, 24, 26]. On the basis of these results, it would be expected that amphetamine anorexia should also be attenuated by peripherally administered beta-blockers. Paradoxically, however, this does not appear to be the case. Preliminary studies in this laboratory failed to demonstrate attenuation of amphetamine anorexia by the beta-blocker propranolol, and with one exception [27] previous investigations have had similar results [13, 15, 17, 28].

The resolution of this paradox may lie in the observation that propranolol impairs the metabolism of amphetamine [29]. This effectively increases the dose of amphetamine, which would tend to mask a partial blockade of the anorexic effect. In the present study, this possibility was investigated using the technique of microstructural analysis [31]. Previous workers have demonstrated that anorexic drugs do not simply reduce total food intake, but also produce characteristic changes in the fine structure of behaviour—for example, amphetamine reduces food inintake primarily by reducing eating time, whilst fenfluramine acts primarily by slowing down the rate of eating [4, 5, 10, 11]. It was reasoned that if the dopaminergic and beta-adrenergic systems control different parameters of feeding, then these might be differentially affected by propranolol. Specifically, if any amphetamine-induced microstructural changes are mediated by beta-receptors, then such changes might be blocked by propranolol whilst at the same time, owing to the increase in amphetamine dose, microstructural changes which are mediated by DA receptors would be enhanced by propranolol.

The sine qua non of microstructural analysis of feeding is knowing at any time whether a subject is eating or not. This is usually achieved by direct observation [4, 5, 10, 11, 12]. However, direct observation is extremely time consuming and labour intensive. We were therefore interested in developing an automated method. Such a method is available in the technique of log survivor analysis [30]: by inspection of

the frequency distribution of inter-response times, it is possible to establish a bout criterion for each subject; this criterion is then applied to decide whether a particular inter-response interval is within or between eating bouts. This method has only previously been used to analyse twenty-four hour feeding patterns, involving thousands of responses [7,30]. Experiment 1 was carried out to determine whether log survivor analysis could also be used to analyse brief (thirty minute) feeding sessions. Experiment 2 describes the application of the technique to the interaction between propranolol and amphetamine.

EXPERIMENT 1

METHOD

Subjects

Twelve male Lister hooded rats (weight 330–400 g) were housed in pairs and maintained on 21-hour food deprivation, with water available ad lib. The animals had had prior experience of continuously reinforced lever pressing for food rewards.

Apparatus

An operant chamber (Campden Instruments Ltd., London), from which the levers had been removed, was programmed to deliver a 45 mg food pellet whenever the perspex food tray door was pressed, subject to the constraint that presses spaced less than one second apart were ineffective. The house light and tray light were illuminated continuously, and the chamber was housed in a sound attenuating box with a smoked perspex viewing window. Each response on the tray door was logged (to the nearest 0.1 sec) by a Cromemco Z2 microcomputer, which displayed the time on a visual display unit (VDU), and subsequently produced a listing of response times and inter-response times (IRTs), an IRT frequency distribution and a log survivor function (see below). Behaviour in the apparatus was also recorded on videotape, using a video camera adapted for low intensity light. By the use of a second camera filming the VDU, and a video-mixer, the occurrence and time of each response on the tray door was also recorded on the film.

Procedure

Following a pretraining period in which 10-min daily sessions were run until all animals achieved asymptotic performance, the animals were given a single 30-min session, which was recorded and filmed as described. The animals were observed to spend long periods eating, directly facing the food tray and only moving to take a further food pellet. From the film, it was possible to identify those inter-response intervals in which behaviours other than eating (rearing, grooming and walking) occured.

Microstructure Analysis

The IRT frequency distribution can be transformed to a survivor function, which shows the number, or the proportion, of IRTs greater than any given IRT (Fig. 1A). A further log transform produces a log survivor function (Fig. 1B). The log survivor function typically falls off steeply, usually in a straight line (indicating an underlying normal distribution), which at the breakpoint changes sharply to a much shallower slope. The assumption underlying log survivor analysis, and tested in the present experiment, is that IRTs shorter than the breakpoint represent responses within a continuous bout of feeding, whilst IRTs longer than the breakpoint represent gaps between feeding bouts.

Following identification of the breakpoint the following parameters of feeding may be calculated: (1) The number of bouts (B) is equal to the number of gaps (i.e. intervals longer than the breakpoint) plus one. (2) Eating time (T) is given by the total of all IRTs smaller than the breakpoint. (3) The length of eating bouts is given by T/B. (4) Since the time taken to eat the final pellet in each bout is neither known nor included in the calculation of eating time, the local eating rate is given by $(N-B)/T$ (where N is the total number of responses), rather than by N/T. An eating rate of 0.1 pellets/s is equivalent to 0.27 g/min.

RESULTS AND DISCUSSION

Subjects consumed a mean of 218 pellets (9.8 g) in the 30-minute session (range: 148–268). Inspection of the log survivor curve for each animal (Fig. 1B) showed breakpoints varying from 12 to 25 sec (mean$\pm$standard error$=16.8\pm0.9$ sec). If the IRT frequency distributions are simply summed across animals, without regard to the differences in breakpoint, the occurrence of behaviours other than eating appears to increase almost linearly for IRTs between 10 and 30 sec (Fig. 2). However, a very different picture is shown by the distribution of IRTs around the breakpoint (Fig. 3). The incidence of behaviours other than eating now shows a marked discontinuity: other behaviours were relatively rare ($5.8\pm0.8\%$ of inter-response intervals) at IRTs shorter than the breakpoint, and highly likely ($88.4\pm2.6\%$ of intervals) at IRTs longer than the breakpoint. It is clear that using the breakpoint to provide an eating criterion for each individual (Fig. 3) affords a far clearer discrimination between eating and not eating than would any arbitrarily chosen criterion (Fig. 2).

Estimates of eating time and local eating rate were calculated by use of the breakpoint, as described above (Table 1). The true values of these parameters were also calculated, by excluding from eating bouts the 5.8% of short inter-response intervals which the film showed to be false positives, and including the 11.6% of long intervals which were false negatives. Compared with these true values, the calculated values under-estimated eating rate by 1.3 (±1.0)%, and over-estimated eating time by 6.5 (±1.7)%. Eating rate appears to be a very robust measure, which is not significantly affected ($t=1.3$, $p>0.1$) by the small proportion of errors. Although eating time is accurate to 6.5%, this figure is actually an over-estimate of the error, since the true eating time makes no allowance for the final pellet of each bout. If it is assumed that these pellets were consumed in the modal time of 4.5 sec (Fig. 2), then a further estimate of true eating time may be made (Table 1). This figure is higher than the calculated value by an insignificant 2.1 (±1.4)% ($t=1.5$, $p>0.1$). Thus as the effects of the two types of error to some extent cancel one another out, the values calculated for both eating time and eating rate are very close to their true values.

Estimates of the number and length of bouts were less accurate, with errors in excess of 40%. However, it is likely that a proportion of the gaps noted on the film were wrongly categorized, since at very short intervals these usually consisted of a single rear or turn, both of which are compatible

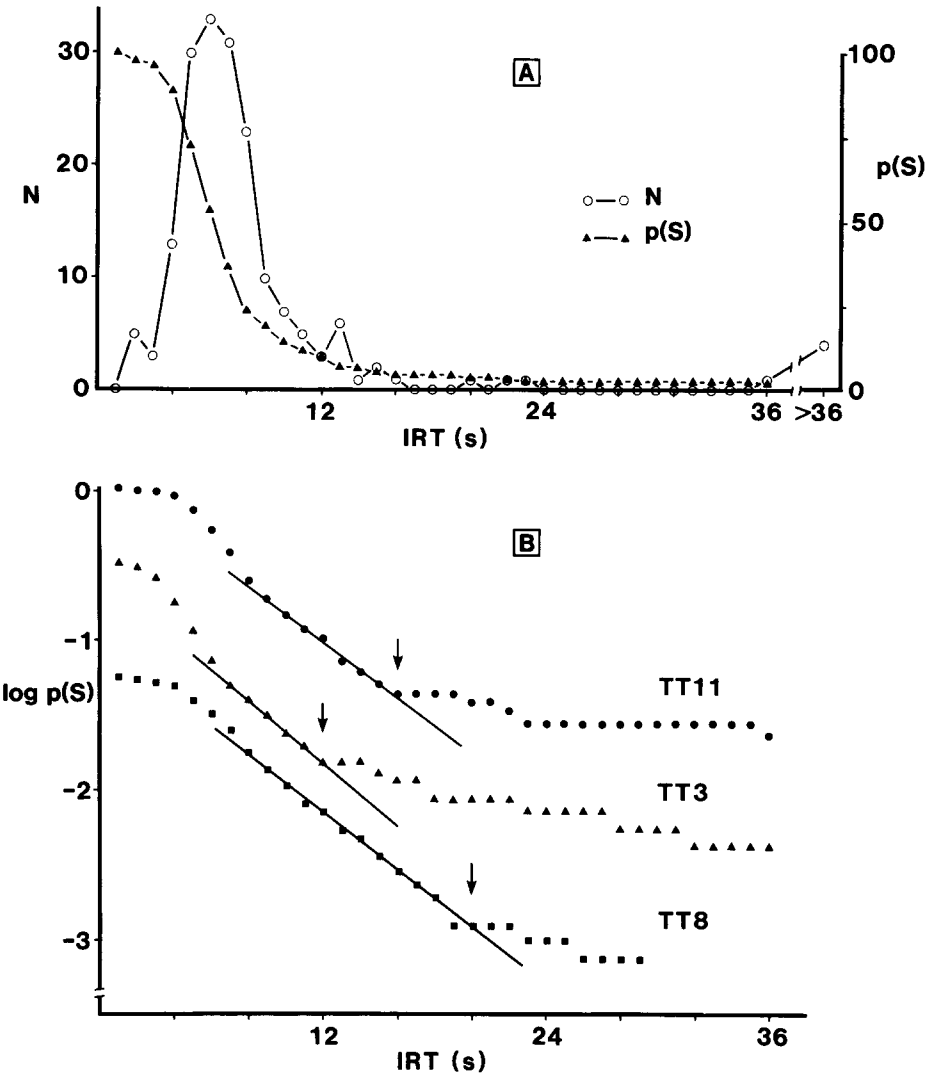

FIG. 1. A: The frequency distribution of inter-response times for a typical subject, and the survivor transform, which shows the proportion of the frequency distribution lying to the right of each point in the frequency distribution. N is the number of responses in each 1s IRT bin and p(S) is the percentage of survivors. B: Three typical log survivor functions. The uppermost curve is the log transform of the survivor function shown in A; for clarity, the other two examples are displaced down by half a log unit. The breakpoint in each curve is marked by an arrow.

with continuous eating; indeed, it was sometimes possible to see that an animal did continue to eat whilst moving away from the food dispenser. If very short gaps (<10 sec) are excluded from the calculation (Table 1), then the discrepancy in the number and length of bouts, though still marked, is considerably reduced (25 and 23% respectively).

In conclusion, the method here described is clearly more successful than the use of arbitrary criteria, for discriminating between eating and not eating. Compared with continuous observation, the method produces very accurate estimates of eating rate and eating time. The method underestimates the number and over-estimates the length of eating bouts, but it does have the advantage that the bout criterion is unambiguous, rather than relying on the often difficult subjective judgement of whether an animal is eating or not. The error arises from the fact that the frequency of responses decreases as IRT increases, which means that there are more responses to the left of the breakpoint than to the right (Fig. 3); the error is therefore relatively constant between subjects. As will be shown below, results obtained using the present method were consistent with those obtained by previous authors using conventional observational methods (Note 1 and Refs. [4, 5, 10, 11, 12]).

EXPERIMENT 2

The doses of amphetamine and propranolol used in the present experiment were chosen on the basis of the following considerations:

(1) We have found that whilst log survivor analysis produces reliable estimates of microstructural parameters

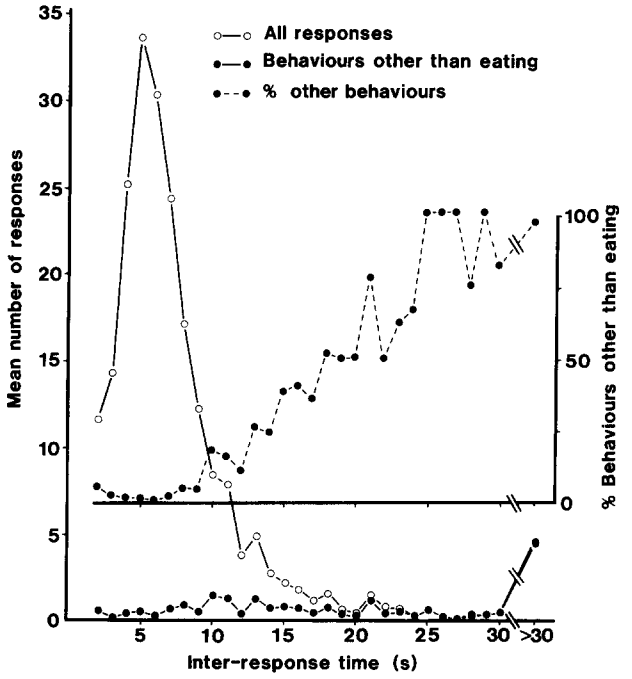

FIG. 2. The frequency distribution of IRTs (mean of all subjects), the distribution of those inter-response intervals in which behaviours other than eating were observed, and the latter as a proportion of the total. For clarity, the percentage scale has been displaced upwards.

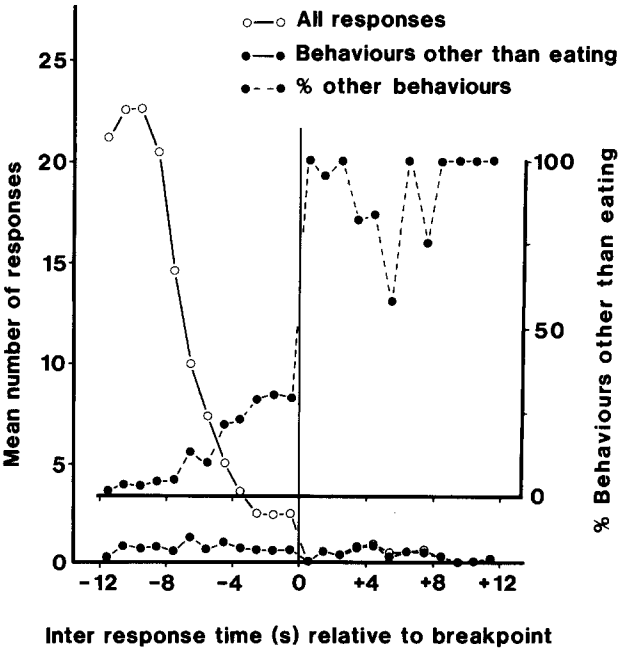

FIG. 3. For each subject, the breakpoint was identified by log survivor analysis (see text), and the frequency distribution of inter-response times plotted for 12 seconds either side of the breakpoint. The figure shows the IRT frequency distribution (mean of all animals), the distribution of those inter-response intervals in which behaviours other than eating were observed, and the latter as a proportion of the total. For clarity, the percentage scale has been displaced upwards.

TABLE 1

COMPARISON OF MICROSTRUCTURAL PARAMETERS DERIVED FROM DIRECT OBSERVATION AND FROM LOG SURVIVOR ANALYSIS

	Eating Rate (pellets/sec)	Eating Time (sec)	Number of Bouts	Bout Length (sec)
Calculated	0.162 (±0.007)	1289 (±70)	12.3 (±1.3)	128 (±21)
True	0.164 (±0.007)	1205 (±55)	23.1 (±1.8)	62 (±6)
Error %	−1.3 (±1.0)	6.5 (±1.7)	−43.7 (±6.3)	41.0 (±7.4)
Adjusted		1308 (±55)	16.9 (±1.3)	83 (±7)
Error %		−2.1 (±1.4)	−25.0 (±6.6)	22.9 (±7.7)

Microstructural parameters were calculated using the bout criterion derived from log survivor analysis (see text). True values were obtained by direct observation. The adjusted values add 4.5 sec per bout to true eating time, and exclude gaps of less than 10 sec when counting the number of bouts. The percentage error terms refer to calculated values in relation to true/adjusted values. All values are means (±SE).

when animals are making hundreds of responses, it becomes difficult to identify the breakpoint when the number of responses is small. It is therefore necessary to use a low dose of amphetamine which produces a relatively small anorectic effect; we chose a dose of 0.5 mg/kg, which in a previous study [32] produced an anorectic effect of roughly 30%.

(2) The dose of propranolol should be as high as possible, but should not itself produce an anorectic effect, since that would unduly complicate interpretation of the results. In preliminary studies, we found that a small (20%) but significant anorectic effect was produced by 10 mg/kg propranolol; a dose of 5 mg/kg was therefore chosen for the present study.

METHOD

Twenty-four male Lister hooded rats (weight 360–430 g) were trained to feed by pressing the door of the pellet dispenser in one of three identical operant chambers, as described above. Ten-minute daily sessions were run until all animals attained asymptotic performance. On experimental days, the animals received two intraperitoneal injections: propranolol HCl (5 mg/kg) (Sigma) was administered 60 min before the start of the session and d-amphetamine sulphate (0.5 mg/kg) (Smith, Kline and French) 30 min before. Control injections in both cases were distilled water (1 ml/kg). During experimental sessions, which were 30 min long, a computer recorded each response on the tray door, as described above. Each animal received all four treatment combinations in a counterbalanced order, at two-day intervals. On the intervening days, a 10-min session was run, with no drug treatments. Analysis of microstructural parameters of feeding was carried out as described above. Results were analysed by analysis of variance, supplemented by tests of simple main effects. The mean breakpoint in the four conditions varied between 16.8 and 18.3 sec; the differences were not significant (all F-ratios <1).

RESULTS

Amphetamine caused a small (13%) but highly significant ($p<0.001$) decrease in food intake (Fig. 4A), which was apparently blocked by propranolol pretreatment (interaction: $F(1,23)=3.2$, $0.05<p<0.1$). However, this conclusion would be seriously misleading. Total food intake may be broken down into eating rate and eating time (Figs. 4B and C), and propranolol actually increased the amphetamine-induced changes in both these parameters: eating rate was only very slightly increased by amphetamine alone, but a substantial increase was seen following propranolol pretreatment; eating time was decreased by amphetamine, and this effect was also somewhat greater following propranolol pretreatment. It is the combination of decreased eating time and increased eating rate, following propranolol pretreatment, which results in no significant net change in total intake.

A description of the distribution of behaviour within the session is given by the mean length of feeding bouts, the mean length of gaps between bouts, and the initial latency; these three parameters determine the total feeding time. Amphetamine did not significantly decrease bout length (Fig. 4D), but did significantly increase the length of gaps (Fig. 4E). Propranolol treatment blocked this effect (Fig. 4E). There were smaller, but insignificant effects on latency (Fig. 4F) (see Note 1).

Propranolol significantly increased bout length (Fig. 4D); this effect led to an increase in eating time (Fig. 4C), and is reflected in an increase in bout size (Fig. 4G), and a decrease in the number of bouts (Fig. 4H). As was the case for eating rate, propranolol increased the effect of amphetamine on bout length (Fig. 4D), bout size (Fig. 4G) and the number of bouts (Fig. 4H): on each of these measures, significant effects of amphetamine were seen following propranolol pretreatment, but amphetamine alone produced small and insignificant effects.

In both pretreatment conditions, the effect of amphetamine on eating time was significantly correlated with the change in total food intake; after propranolol pretreatment, there was also a significant negative correlation between the decrease in food intake and the increase in eating rate (Table 2). In both conditions, a significant correlation

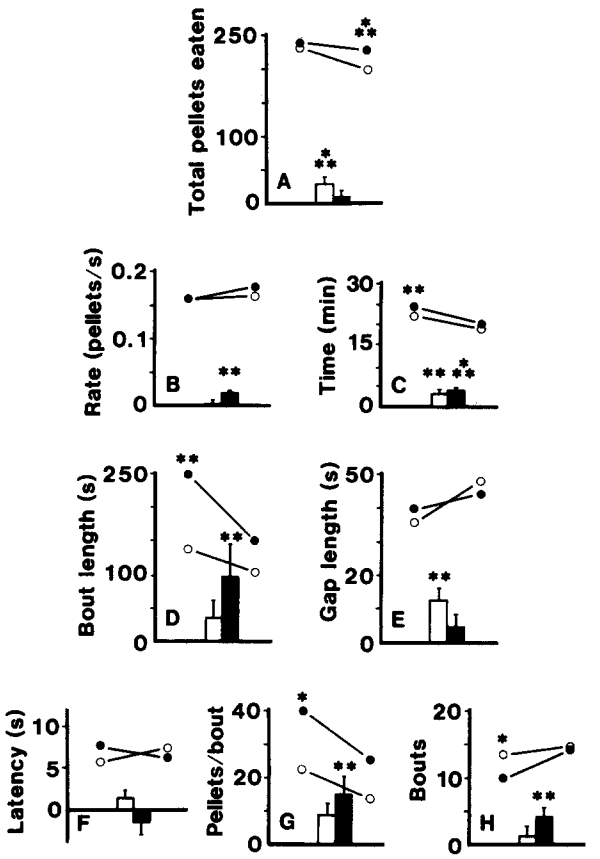

FIG. 4. Effect of amphetamine and propranolol on microstructural parameters. A: Total food intake; B: Local eating rate; C: Eating time; D: Bout length; E: Gap length; F: Latency; G: Bout size; H: Number of bouts. Circles show the scores in each condition: Left—control, right—amphetamine; white—control, black—propranolol. Bars show the difference brought about by amphetamine (mean + standard error): white—control, black—propranolol pretreatment. One star—$p<0.05$; two stars—$p<0.01$; three stars—$p<0.001$.

was seen between the increase in eating rate and the decrease in bout length (even though in the control condition there was no significant net change in either). However, changes in these parameters were uncorrelated (in one case, there was a significant negative correlation) with increases in gap length. In the control condition only, changes in gap length were significantly correlated with changes in total food intake.

GENERAL DISCUSSION

The apparent outcome of Experiment 2 was an attenuation of amphetamine anorexia by propranolol. However, it is clear from the microstructural analysis that this result is largely fortuitous, since propranolol, amphetamine and the propranolol-amphetamine combination each produced a different pattern of behavioural changes. The results reveal the wealth of information which is lost by restricting studies of feeding to measures of total food intake. The generality of the following discussion must obviously be qualified by the fact that only a single dose of each drug was tested. However, in view of the complexity of the behavioural data, it

TABLE 2

INTERCORRELATIONS BETWEEN AMPHETAMINE-INDUCED CHANGES IN MICROSTRUCTURAL PARAMETERS

	Total ↓	Rate ↑	*Time* ↓	Bout Length ↓	*Gap Length* ↑
Total ↓		−.28	.46*	.24	.47*
Rate ↑	−.45*		.63†	.45*	−.08
Time ↓	.50†	.46*		.80†	.12
Bout length ↓	.35*	.40*	.81†		
Gap length ↑	.09	−.18	−.12	−.44*	

The table shows correlations (Spearman rank-order correlation coefficients) between the changes induced by amphetamine in different microstructural parameters. *$p<0.05$; †$p<0.01$. The upper part of the table shows values obtained in control conditions; and the lower part shows values obtained following propranolol pretreatment. Arrows show the direction of change; italicized parameters were those in which significant net changes were seen.

might be noted in passing that a similar criticism could be levelled at the more standard design, in which a range of drug doses are tested against the single dependent variable, total food intake.

Propranolol did not affect eating rate, but increased bout length, and consequently, bout size and eating time. Whilst these effects did not cause a significant increase in food intake, it is clear that appropriate testing circumstances might reveal hyperphagia, and this has, in fact, been observed (see Note 2). This result is consistent with the finding that hyperphagia was caused by lesions to adrenergic systems innervating the perifornical hypothalamus [2, 20, 21], and with the concept of a beta-adrenergic satiety system.

It has been previously reported that the anorexic effect of a low dose of amphetamine (0.25 mg/kg) was caused by a selective effect on eating time with no change in eating rate [11]. The present study confirmed this observation; it was also found that the decrease in eating time was brought about primarily by an increase in the length of gaps, with no significant change in the length of eating bouts.

In contrast to the effect of amphetamine alone, after propranolol pretreatment, gap length was the only parameter (other than latency) which was not significantly altered by amphetamine. The animals showed, on the one hand, a different hypophagic effect (decreased bout length), and on the other, a hyperphagic effect (increased eating rate). As a result, there was no significant net change in food intake. Since the interaction of propranolol with amphetamine produces such contradictory effects, it is clear that, depending on the dose and specific experimental conditions, the outcome might be a decrease in the efficacy of amphetamine (the present study and ref. [27]), no change [13, 15, 17], or even an increase [13, 15, 28]. It is important, however, not to lose sight of the fact that in the present study, propranolol did block the effect underlying amphetamine anorexia, and also blocked the correlation between changes in gap length and changes in total food intake.

The starting point for the interpretation of these results is the observation that propranolol interferes with the metabolism of amphetamine [29]. To what extent may the effects of propranolol be understood as simply an increase in the dose of amphetamine? In this study, only a single dose of amphetamine, 0.5 mg/kg was tested. However, it is well established that amphetamine at 1 mg/kg significantly increases eating rate and decreases eating time [3, 4, 5, 11, 12]. It has also been reported (or it is possible to calculate from published figures) that bout length and bout size were decreased by amphetamine [4,5]. Data on the length of gaps have not previously been reported, but from published figures it is possible to calculate that amphetamine caused a substantial increase in gap length (see Note 3). The effects of propranolol are therefore consistent with a functional increase in the dose of amphetamine, with one exception: gap length. Propranolol blocked the effect of amphetamine on gap length, where an increase would be predicted from an increase in dose.

Not only was gap length the only parameter which was significantly altered by amphetamine alone, but also, this was the one parameter which was not significantly intercorrelated with all the others. The results therefore suggest the involvement of two separate mediating systems. At low doses, amphetamine induces anorexia by increasing gap length (i.e. reducing the tendency to begin eating), and at higher doses (assumed to result from propranolol pretreatment), a number of other mechanisms come into play. The anorexic effect of the low dose appears to be mediated by beta-receptors, since the increase in gap length was blocked by propranolol. The other effects appear to be dopaminergically mediated, since it has been reported that the changes in eating rate, bout length and bout size are antagonized by DA receptor blocking drugs [5,11]. It is of great relevance to the present argument that gap length was the one feeding parameter which was unaffected by the DA receptor blocker pimozide (see Note 3).

The relationship of the observed effects to the physiological control mechanisms for food intake is uncertain. The putative beta-receptor mediated effects of amphetamine and propranolol (decreases in the likelihood of starting and stopping eating, respectively), may represent direct effects on hunger and satiety mechanisms; the present methods are appropriate for further investigation of this problem. However, the putative DA-mediated effect appears less likely to

be a direct satiety effect. A general theory of stimulant drug action has proposed that the effects of amphetamine may be described as an increase in the intensity of ongoing behaviour combined with an increased tendency to change behaviour [25]. This model is strongly suggested by the correlations observed in the present study between the amphetamine-induced increase in eating rate and shortening of bouts: increases in eating rate were significantly correlated with decreases in bout length, both in the control condition and also following propranolol pretreatment (Table 2). Thus, it may be that amphetamine has two anorexic effects, one genuine and the other an artefact of the stimulant effect, mediated respectively by beta-adrenergic and dopaminergic systems.

NOTES

Note 1

In general, the microstructural parameters reported in this study are comparable to those of other workers. The exception is eating latency; values reported here are some 10–25% of those in previous reports [4, 5, 10, 11, 12]. This difference might reflect the salience of the food dispenser in the present study, and also the subjects' long experience of the testing procedure. The short initial latency suggests a high degree of stimulus control by the food dispenser, which would tend to reduce disruptive drug effects.

Note 2

In most studies, propranolol reduces food intake at higher doses, probably by a non-specific sedative effect. In one study [13], however, a significant increase in food intake was observed at a dose of 4 mg/kg ($t(11)=3.2, p<0.01$, calculated from published figures).

Note 3

From values of latency, eating time and number of bouts, published by Blundell and Latham [5], it is possible to calculate the following figures for mean gap length: saline—76 sec; amphetamine—142 sec; pimozide—49 sec; pimozide + amphetamine—144 sec. In the present discussion, it is assumed that bout length and gap length are the primary variables, the values of which determine the number of bouts: the animal decides when to start eating and when to stop, but cannot control the number of bouts, even if it wanted to, since it does not know how long the session will last.

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REFERENCES

1. Abdallah, A. H., D. M. Roby, W. H. Boeckler and C. C. Riley. Role of DA in the stimulant effect of DITA in mice: comparisons with d-amphetamine. *Eur. J. Pharmac.* **35:** 29–34, 1976.
2. Ahlskog, J. E. Food intake and amphetamine anorexia after selective forebrain norepinephrine loss. *Brain Res.* **82:** 211–240, 1974.
3. Antelman, S. M., A. R. Caggiula, C. A. Black and D. J. Edwards. Stress reverses the anorexia induced by amphetamine and methylphenidate but not fenfluramine. *Brain Res.* **143:** 580–585, 1978.
4. Blundell, J. E. and C. J. Latham. Pharmacological manipulation of feeding behaviour: possible influences of serotonin and dopamine on food intake. In: *Central Mechanisms of Anorectic Drugs,* edited by S. Garattini and R. Samanin. New York: Raven Press, 1978, pp. 83–109.
5. Blundell, J. E. and C. J. Latham. Characterization of adjustments to the structure of feeding behaviour following pharmacological treatment: effects of amphetamine and fenfluramine and the antagonism produced by pimozide and methergoline. *Pharmac. Biochem. Behav.* **12:** 717–720, 1980.
6. Burridge, S. L. and J. E. Blundell. Amphetamine anorexia: antagonism by typical but not atypical neuroleptics. *Neuropharmacology* **18:** 453–457, 1979.
7. Burton, M. J., S. J. Cooper and D. A. Popplewell. The effect of fenfluramine on the microstructure of feeding and drinking in the rat. *Br. J. Pharmac.* **72:** 621–633, 1981.
8. Carey, R. J. Effects of selective forebrain depletions of norepinephrine and serotonin on the activity and food intake effects of amphetamine and fenfluramine. *Pharmac. Biochem. Behav.* **5:** 519–523, 1976.
9. Carey, R. J. and E. B. Goodall. Attenuation of amphetamine anorexia by unilateral nigrostriatal lesions. *Neuropharmacology* **14:** 827–834, 1975.
10. Cooper, S. J. and R. L. Francis. Feeding parameters with two food textures after chlordiazepoxide administration, alone or in combination with d-amphetamine or fenfluramine. *Psychopharmacology* **62:** 253–259, 1979.
11. Cooper, S. J. and R. L. Francis. Interactions of chlordiazepoxide and anorectic agents on rate and duration parameters of feeding in the rat. *Psychopharmacology* **69:** 261–265, 1980.
12. Cooper, S. J. and K. F. Sweeney. Effects of spiperone alone and in combination with anorectic agents on feeding parameters in the rat. *Neuropharmacology* **19:** 997–1003, 1980.
13. Dobrzanski, S. and N. S. Doggett. The effect of propranolol, phentolamine and pimozide on drug-induced anorexia in the mouse. *Psychopharmacology* **66:** 297–300, 1979.
14. Fibiger, H. C., A. P. Zis and E. G. McGeer. Feeding and drinking deficits after 6-hydroxydopamine administration in the rat: similarities to the lateral hypothalamic syndrome. *Brain Res.* **55:** 135–148, 1973.
15. Frey, H. and S. Schulz. On the central mediation of anorexic drug effects. *Biochem. Pharmac.* **22:** 3041–3049, 1973.
16. Heffner, T. G., M. J. Zigmond and E. M. Stricker. Effects of dopamine agonists and antagonists on feeding in intact rats and 6-OHDA-treated rats. *J. Pharmac. exp. Ther.* **20:** 386–399, 1977.
17. Lehr, D. and W. Goldman. Continued pharmacological analysis of cosummatory behaviour in the albino rat. *Eur. J. Pharmac.* **23:** 197–210, 1973.
18. Leibowitz, S. F. Catecholaminergic mechanisms of the lateral hypothalamus: their role in the mediation of amphetamine anorexia. *Brain Res.* **98:** 529–545, 1975.
19. Leibowitz, S. F. Identification of catecholamine receptor mechanisms in the perifornical lateral hypothalamus and their role in mediating amphetamine and l-DOPA anorexia. In: *Central Mechanisms of Anorectic Drugs,* edited by S. Garattini and R. Samanin. New York: Raven Press, 1978, pp. 39–82.
20. Leibowitz, S. F. and L. L. Brown. Histochemical and pharmacological projections to the perifornical hypothalamus in relation to feeding inhibition. *Brain Res.* **201:** 315–345, 1980.
21. Leibowitz, S. F., N. J. Hammer and L. L. Brown. Analysis of behavioural deficits produced by lesions in the dorsal and ventral midbrain tegmentum. *Physiol. Behav.* **25:** 829–843, 1980.

22. Leibowitz, S. F. and C. Rossakis. Analysis of feeding suppression produced by perifornical hypothalamic injection of catecholamines amphetamines and mazindol. *Eur. J. Pharmac.* **53:** 69–81, 1978.
23. Leibowitz, S. F. and C. Rossakis. Pharmacological characterisation of perifornical hypothalamic β-adrenergic receptors mediating feeding inhibition in the rat. *Neuropharmacology* **17:** 691–702, 1978.
24. Leibowitz, S. F. and C. Rossakis. Mapping study of brain dopamine- and epinephrine-sensitive sites which cause feeding suppression in the rat. *Brain Res.* **172:** 101–113, 1979.
25. Lyon, M. and T. W. Robbins. The action of central nervous stimulant drugs: a general theory concerning amphetamine effects. In: *Current Developments in Psychopharmacology,* vol. 2, edited by W. B. Essman and L. Valzelli. New York: Spectrum, 1975, pp. 79–164.
26. Samanin, R., C. Bendotti, S. Bernasconi, E. Borroni and S. Garattini. Role of brain monomines in the anorectic activity of mazindol and d-amphetamine in the rat. *Eur. J. Pharmac.* **43:** 117–124, 1977.
27. Sanghvi, I. S., G. Singer, E. Friedman and S. Gershon. Anorexigenic effects of d-amphetamine and l-DOPA in the rat. *Pharmac. Biochem. Behav.* **3:** 81–86, 1975.
28. Schmitt, H. Influence d'agents interférant avec les catécholamines et la 5-hydroxytryptamine sur les effets anorexigènes de l'amphétamine et de la fenfluramine. *J. Pharmac.* **4:** 285–294, 1973.
29. Shoeman, D. W., C. R. Sirtori and D. L. Azarnoff. Inhibition of amphetamine tolerance and metabolism by propranolol. *J. Pharmac. exp. Ther.* **191:** 68–71, 1974.
30. Slater, P. J. B. The temporal pattern of feeding in the zebra finch. *Anim. Behav.* **22:** 506–515, 1974.
31. Wiepkema, P. R. Behavioural factors in the regulation of food intake. *Proc. Nutr. Soc.* **30:** 142–149, 1971.
32. Willner, P. and T. Montgomery. Attenuation of amphetamine anorexia in rats following subchronic treatment with tricyclic antidepressant. *Communs Psychopharmac.* **4:** 101–106, 1980.
33. Zis, A. P. and A. P. Fibiger. Neuroleptic-induced deficits in food and water regulation: similarities to the lateral hypothalamic syndrome. *Psychopharmacology* **43:** 63–68, 1975.