J. Physiol. (1968), **197**, *pp.* 325–343
With 8 text-figures
Printed in Great Britain

THE RELATIONSHIP OF ENERGY EXPENDITURE AND SPONTANEOUS ACTIVITY TO THE APHAGIA OF RATS WITH LESIONS IN THE LATERAL HYPOTHALAMUS

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(*Received* 12 *December* 1967)

SUMMARY

1. Lesions in the lateral hypothalamus of rats always produced an immediate increase in total energy expenditure. The increase was maintained for 24 hr or longer only in rats that became and remained aphagic. Rats that showed no recovery from the aphagia and were maintained by tube feeding showed a second, larger increase in metabolic rate after about 7 days.

2. The increase in total energy expenditure was associated, initially, with almost continuous motor activity. With continued aphagia an abnormally differentiated pattern of activity appeared at the same time as the second increase in metabolic rate, and the compartment of energy attributable to activity remained high (34 % as compared with 23 % in normal rats). These changes were accompanied by a recovery of an instrumental response for food (lever pressing), of interest in offered foods and of grooming activity.

3. Metabolic abnormality not attributable to activity was indicated by increased creatinine excretion of aphagic but not of hypophagic rats.

4. Rats that recovered spontaneous feeding after aphagia returned towards a normal differentiated pattern of activity, with bursts of activity separated by periods of rest, but showed residual abnormality in creatinine excretion.

5. The intimate association between increase of energy expenditure, abnormality of motor activity and the aphagia produced by lateral hypothalamic lesions is consistent with the hypothesis that motor incoordination or disorganization is a cause of the aphagia.

INTRODUCTION

Bilateral destruction of parts of the lateral hypothalamus of rats can produce aphagia and adipsia or hypophagia and hypodipsia (Anand & Brobeck, 1951; Montemurro & Stevenson, 1957; Morrison & Mayer, 1957). The severity of the acute feeding and drinking response and the recovery of rats so treated are quite variable and are not clearly defined in terms of the location and extent of the lesions within the general lateral area (Morgane, 1961*a*; Morrison, Barrnett & Mayer, 1958). The nature and origin of some of the tracts passing through the lateral hypothalamus and the functions of the neighbouring subthalamic area (Gloor, 1960; Jung & Hassler, 1960; Montanelli & Hassler, 1964) suggest that the functional responses to lateral hypothalamic lesions may involve motor components. Rats with lesions in the lateral hypothalamus which are overtly aphagic orally will press a lever for food and will deliver intragastrically, by lever pressing, a food that they will not ingest orally (Baillie & Morrison, 1963). This was interpreted as indicating a defect in the motor co-ordination or organization of eating and drinking; similar results after amygdalar lesions have been described as an 'eating apraxia' (Brutkowski, Fonberg, Kreiner, Mempel & Sychowa, 1962). This interpretation was rejected by Rodgers, Epstein & Teitelbaum (1965).

These interpretations are, however, indirect. If the presence or absence of motor abnormality could be established the weighing of various possible causes of the aphagia could be given a firmer base. Rats with lesions in the lateral hypothalamus show abnormal posture and movement (Baillie & Morrison, 1963; Teitelbaum & Epstein, 1962) and decrease in spontaneous locomotor activity (Gladfelter & Brobeck, 1962), but these changes were not firmly associated with feeding effects.

If there is, in fact, a component of motor inco-ordination in the functional response to these lesions it seems possible that it would be reflected in an abnormality of the amount and pattern of energy expenditure. Rats with such lesions show a metabolic deterioration, in which rate of body weight loss cannot be arrested by tube feeding (Morgane 1961*a*), and they show an increased 'resting' energy expenditure (Stevenson & Montemurro, 1963).

In the work reported here, rats, in which lesions in the lateral hypothalamus have produced a variety of levels of feeding response, have been examined with respect to the total amount and the pattern of energy expenditure and activity. The results show that energy expenditure and motor activity are greatly increased and their patterns markedly distorted by such lesions, and also that the severity and persistence of these changes are intimately associated with the occurrence of aphagia.

METHODS

The O_2 consumption and CO_2 production of individual male Sprague Dawley rats were recorded continuously for 24 hr periods by methods previously described in detail (Morrison, 1968). The spontaneous activity was recorded and the total energy expenditure and the activity compartment of the total energy expenditure were derived from the 24 hr records as described previously (Morrison, 1968). The sensitivity of the activity recorder was set so that normal respiration was barely detected. The total 24 hr consumption of food and the production of urine, faeces and total evaporated water were also measured. The heat of combustion of food and of faeces was measured by bomb calorimetry. All animal calorimetric measurements were made at 27–29° C. The environmental temperature of the rats at other times was 25–27° C. At all times the rats were maintained on a constant cycle of 11 hr light and 13 hr dark.

For 1–2 weeks before studies were made in the calorimeter all rats were habituated to obtain their food, a liquid milk diet (Morrison, 1968), by pressing a lever. All food supplied in the calorimeter was obtained in this way. The amount of milk delivered by each depression of the lever was about 0·1 ml. with each depression reinforced (i.e. yielding milk). Lever-pressing in the calorimeter was recorded on the records of gaseous exchange and of activity.

Lesions were made in the lateral hypothalamus of the rats with a commercial version of the Stellar–Krause stereotactic instrument (Stellar & Krause, 1954). The rats were anaesthetized with 1 mg/100 g sodium pentobarbitone intraperitoneally and maintained under ether during operation. The exposed tip of a 'Teflon'-covered, 24-gauge 'Nichrome' electrode was placed 1·5–2·0 mm caudad to the bregma, 2 mm lateral to the mid line and 2 mm above the floor of the brain (sphenoid). A direct anodal current of 1·5 mA was passed for 10–20 sec. Partial sham operations were carried up to the point of drilling holes in the skull. About 2–3 hr were allowed after operation before the rat was replaced in the calorimeter.

Each rat was studied in the calorimeter for 1–4 days before operation, so that, in general, comparisons are made with each rat as its own control. (For rat no. 485, the control results of its fellow, no. 486, which died during operation, were used.) Measurements were also made on other normal controls. Six normal rats were studied in the calorimeter for 8–12 days while fed in the same way or deprived of food only for 1 or 2 days. Eleven normal rats were studied during feeding and during total deprivation of food and water for 1 day and 4 during total deprivation of food and water for 2 days. Persistently aphagic rats were tube fed daily from the end of the third day after lesions. Five normal rats were prevented from voluntary intake of food or water for 17 days, and were intubated with water and the liquid diet according to the same schedule as three rats with lesions which never recovered spontaneous feeding. Three of these chronically deprived, tube-fed controls were studied in the calorimeter for periods corresponding to the studies of the chronically aphagic rats.

Daily excretion of creatinine was measured in eight adult male rats (Folin, 1914). These rats were maintained in metabolism cages and food (diet C 21; Millar, White, Brooks & Mider, 1957) and water intakes were also measured daily. Creatinine was measured in urine (*a*) for 5 days in normal rats deprived of food and water on the third and fourth days; (*b*) for the 3 days immediately before and the 3 days immediately after placement of lesions in the lateral hypothalamus of these rats; (*c*) for 6 days, after recovery from the acute effects of the lesions, with deprivation of food and water on the fourth and fifth days. Rats that remained aphagic beyond 3 days were tube fed and were offered liquid diet and mashes until they recovered spontaneous feeding and drinking. Rats that did not show recovery after 10 days of tube feeding were killed.

After termination of each experiment the brain of each rat was dissected out and fixed in neutral formalin and the sites of the lesions were inspected in serial sections stained with haemalum and eosin.

RESULTS

The feeding response to lesions varied from a transient hyperphagia or hypophagia lasting 1–2 days to total aphagia with maintenance by tube feeding for 17 days (Table 1). As a fluid diet was used it is not always possible to distinguish between aphagia and adipsia in the calorimetric experiments. All rats showed some degree of abnormal posture initially and their initial attempts to feed were abnormal. Particularly, they tried to bite the liquid diet off the delivery spout and receiving dish, rather than lapping it as normally.

TABLE 1. Feeding response to lateral hypothalamic lesions and sham operations of rats from which energy exchange data were obtained

Rat no.	Feeding response	Fate	Total days in calorimeter
	Lateral lesions		
21	Hyperphagia, 2 days	Recovered	9
23	Hypophagia, 2 days	Recovered	7
24(*a*)	Hypophagia, 3 days	Recovered	11
24(*b*) repeat	Aphagia, 1 day; hypophagia, 1 day	Recovered	
25	Hypophagia, 2 days	Recovered	9
462(*a*)	Aphagia, 1 day; hypophagia, 1 day	Recovered	11
462(*b*) repeat	Hypophagia, 1 day	Recovered	
463	Aphagia, 1 day; hypophagia, 2 days	Recovered	12
485	Aphagia, 1 day; hypophagia, 3 days	Recovered	6
505	Aphagia, 2 days; hypophagia, 2 days	Recovered	7
506	Aphagia, 1 day	Died	5
507	Aphagia, 17 days, tube-fed	Died	9
508	Aphagia, 15 days, tube-fed	Killed	9
571	Aphagia, 17 days, tube-fed	Killed	7
	Sham operations		
506	No change	Recovered	3
508	Hypophagia, 1 day	Recovered	3
571	Hypophagia, 1 day	Recovered	3
	Prolonged food deprivation—no surgery		
522	Deprived food and water 17 days—tube-fed		9
526	Deprived food and water 17 days—tube-fed		7
571	Deprived food and water 17 days—tube-fed		7

Patterns of energy expenditure and activity

Normal rats show a relatively stable resting energy expenditure (represented in Figs. 1–4 by O_2 consumption) punctuated by well-defined metabolic elevations (Fig. 1). These metabolic elevations are delimited precisely in time by well-defined bursts of activity (Fig. 1; Morrison, 1968). This pattern is described as differentiated activity. The metabolic elevations and associated bursts of activity occur predominantly during the hours of darkness and are infrequent during the hours of light (Morrison, 1968).

After placement of lesions this normal pattern disintegrated for a period varying from a few hours to several days. The immediate post-operative pattern was of almost continuous activity with little or no differentiation of the metabolic record into elevations above a resting base (Fig. 2).

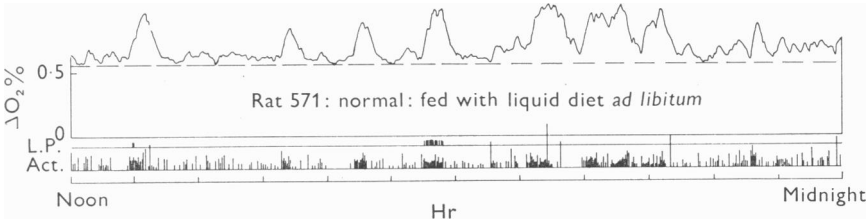

Fig. 1. Oxygen consumption, lever pressing for food (L.P.) and spontaneous activity of normal fed rat during a 12 hr period.

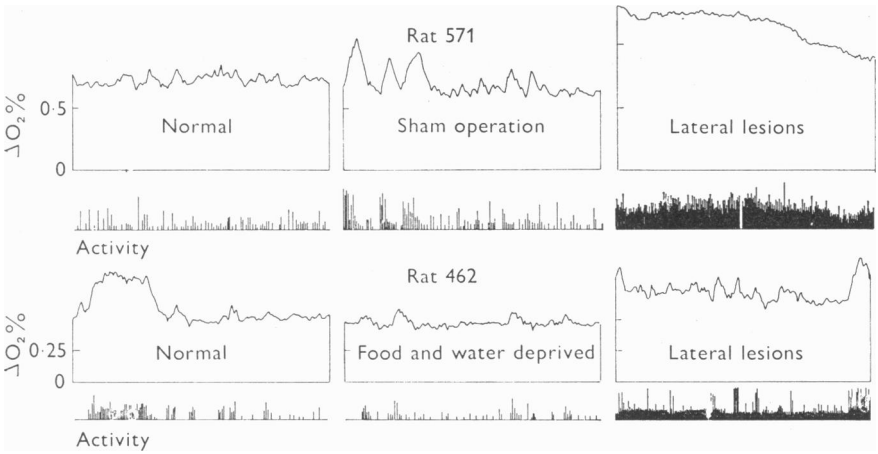

Fig. 2. Oxygen consumption and spontaneous activity of rats for 4 hr (12.00 to 16.00 hr) in normal fed state, deprived of food and water from 10.00 a.m., after sham operation, and after lesions that produced persistent aphagia (571) or produced 1 day of aphagia with recovery (462).

In those rats which showed only a transient hypophagia the period of undifferentiated activity lasted only 3–8 hr and feeding reappeared at the same time as the recovery of differentiation of activity. Those rats which never recovered spontaneous feeding (507, 508, 571) but were maintained by intubation of food, did not recover differentiation of activity until after several days. When differentiated activity did reappear the bursts of activity were distributed over the 24 hr without the normal diurnal variation, and the bursts were separated by briefer than normal periods of inactivity (Fig. 3).

The rats subjected to sham operation continued to show clear differentiation of activity. During the 2–6 hr immediately following sham

operation (Fig. 2) the frequency of bursts of activity resembled the appearance after recovery of differentiated activity in aphagic rats (Fig. 3). Intact rats deprived of food and water and, later, tube fed showed normal differentiation of activity at all times but diurnal distribution eventually became less marked (Fig. 4).

Total expenditure of energy

To decide whether the lesions alter the total energy expenditure of the rat it is necessary to make a comparison between the energy expenditure

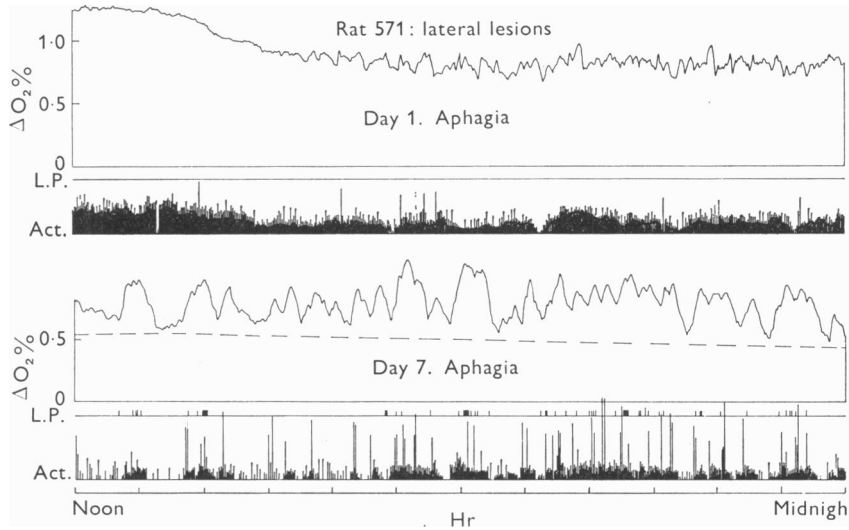

Fig. 3. Oxygen consumption, lever pressing for food (L.P.) and spontaneous activity during 12 hr periods on the first and seventh days after lateral lesions that produced persistent aphagia. Tube feeding started on fourth day after lesions.

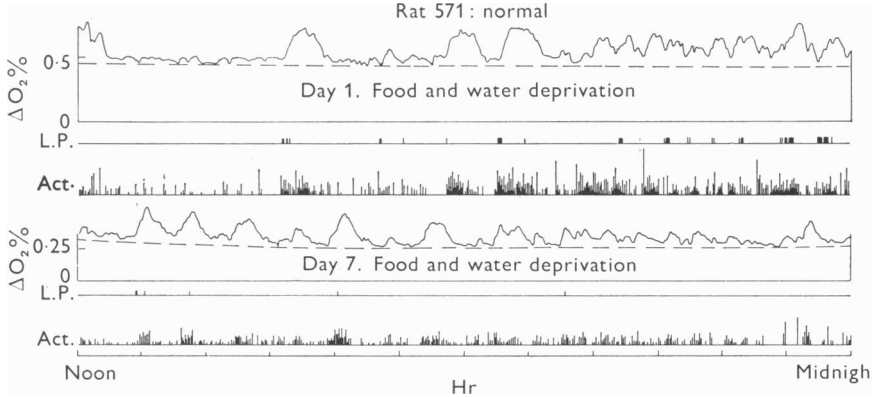

Fig. 4. Oxygen consumption, lever pressing for food (L.P., none delivered) and spontaneous activity during 12 hr periods on the first and seventh days of deprivation of food and water. Tube feeding started on the fourth day of deprivation.

after lesions and the energy which the animal would expend at the same body weight and the same food intake without lesions. All sets of lesions do not produce the same feeding response (Table 1), that is, there can be degrees of hypophagia rather than complete aphagia. Also, food intake itself contributes to the total energy expenditure (e.g. Swift, 1944). The comparison, therefore, must be extended to take account of changes in food intake and not merely absence of food intake.

Control results

Total 24 hr energy expenditure of normal rats fed the liquid diet, including the pre-operative results from the lesioned rats, was related to body size and food intake by the equation

$$E = 23{\cdot}4 + 0{\cdot}059\ (\pm 0{\cdot}012)\ W + 0{\cdot}087\ (\pm 0{\cdot}031)\ F \qquad (1)$$

where E is 24 hr expenditure in kcal, W is mean 24 hr body wt. in g and F is apparent absorbed food energy in kcal (ingested – faeces).

Brief (1 or 2 day) deprivation of food only with water allowed, also conformed to this general relationship as had previously been found (Cumming & Morrison, 1960). The expected energy expenditure of lesioned rats that ate some food was derived from control (pre-operative) expenditures by applying the coefficients of eqn. (1) to the observed changes in body weight and food intake. When the rat is totally deprived of food and water eqn. (1) cannot fully account for the fall in expenditure that occurs. This additional fall is related to the body weight change by the coefficient $+0{\cdot}29$ ($n = 11$). The entire expected change in 24 hr energy expenditure in the particular case of change from the fed state to the food and water deprived state is then derived from eqn. (1) with the coefficient of W altered to $(0{\cdot}06 + 0{\cdot}29) = +0{\cdot}35 \pm 0{\cdot}02$ S.E.

Acute response of energy expenditure to lateral lesions

(*a*) 2–6 *Hr post-operative.* The total energy expenditure of each operated rat for the first 4 hr in the calorimeter after recovery from anaesthetic was compared with the energy expenditure during the corresponding period of the immediately preceding control day (Fig. 2; Table 2). Rats do not usually eat or drink much during the first 4 hr of the 24 hr period (about 10.00 a.m. to 2.00 p.m.). For comparison of treated with fed, control states it was assumed that change in 24 hr food intake or 24 hr deprivation of water would have no effect over this 4 hr period. The adjustment for this comparison was, therefore, made only for change in body weight using the coefficient 0·059 (eqn. 1).

There was a marked increase in energy expenditure by the rats immediately after placement of lesions (Fig. 2). This increase occurred in

TABLE 2. Energy expenditure of rats with lesions in the lateral hypothalamus compared with expected energy expenditure of normal rats at the same body weight and food intake

	Observed fed control			Time after lesions: 0–4 hr (kcal/hr)			0–24 hr (kcal/24 hr)				24–48 hr (kcal/24 hr)			
Rat no.	kcal/hr 0–4 hr	kcal/ 24 hr 0–24 hr	Food AA* (kcal)	Adj. contr.	Obs.†	Obs/AC‡ (%)	Food AA* (kcal)	Adj. contr.	Obs.†	Obs/AC‡ (%)	Food AA* (kcal)	Adj. contr.	Obs.†	Obs/AC‡ (%)
21	1·43	38·0	39	1·41	1·86	132	61	40·1	42·5	106 N.S.	72	41·6	42·7	103 n.s. N.S.
23	1·52	43·8	61	1·53	1·67	109	18	39·6	41·7	105 N.S.	14	38·7	38·7	100 n.s. N.S.
24(*a*)	1·03	30·9	39	1·06	1·45	137	7	27·9	33·5	120	4	27·0	27·7	103 n.s. N.S.
24(*b*)	1·60	46·7	51	1·59	1·99	125	4 (*S*)	36·9	41·7	113	13	37·2	35·7	96 n.s. N.S.
25	1·27	43·1	56	1·25	1·76	141	13	38·5	39·5	103 n.s. N.S.	29	39·7	37·3	94 N.S.
462(*a*)	1·20	35·8	38	1·23	1·71	139	10 (*S*)	30·7	41·0	134	30	33·1	38·3	116
462(*b*)	1·34	36·3	59	1·34	1·55	116	36	34·1	34·8	102 n.s. N.S.	1§	30·2	31·0	103 N.S.
463	1·32	38·2	36	1·33	1·52	114	4 (*S*)	33·6	36·5	109	12	34·0	38·1	112 N.S.
486/485	1·52	43·9	51	1·57	2·24	143	−11	32·8	44·9	137	30	35·4	43·4	123
505	1·65	55·7	71	1·61	2·07	129	−3	38·7	53·0	137	17 (*S*)	31·5	52·7	167
506	1·65	45·6	29	1·64	2·65	162	−2	37·9	39·4	104‖ n.s. N.S.	—	—	—	—
507	1·57	41·0	16	1·54	2·36	153	−1	32·5	45·9	141	0	25·2	37·6	149
508	1·19	31·0	44	1·24	1·65	133	−2	28·3	31·6	117	0	23·2	26·7	115 N.S.
571	1·79	47·6	48	1·80	2·71	151	−12	35·9	50·8	142	−2	28·7	50·6	176

* Apparent absorbed food as kcal ingested less kcal faeces on the same day.

† Observed value after lesions.

‡ Observed value after lesions as % of control adjusted to same body weight (0–4 hr) or to the same body weight and apparent absorbed food (0–48 hr).

§ Feeding lever disconnected. This rat was food deprived but not aphagic.

‖ Rat 506 was moribund and died early in the second day after lesions.

(*S*) After a value for nominal absorbed food intake indicates such large spillage that intake has been taken as zero.

n.s. indicates that difference between observed expenditure and adjusted control expenditure is not significantly greater ($P > 0{\cdot}05$) than the error of the adjustment; N.S. indicates that the difference is not significantly greater ($P > 0{\cdot}05$) than the error of estimate of a single observation.

every case and was, apparently, independent of the acute feeding response (Table 2 and 3). The two rats in which lesions were repeated showed the energetic response to both sets of lesions. A slight increase that occurred in this immediate post-operative period in response to partial sham operations was not statistically significant (Table 3). The intact controls deprived of food and water invariably showed a fall in energy expenditure for the first 4 hr (Table 3).

Rats which had apparently recovered from the feeding effects of lateral lesions and were deprived of food showed the same response as intact deprived controls (Table 3).

TABLE 3. Energy expenditure of rats deprived of food and water or with lesions in the lateral hypothalamus as % of the expenditure of normal fed rats adjusted to the same body weight and food intake

Treatment	First 4 hr		First 24 hr		Second 24 hr	
	n	Mean S.E.	*n*	Mean S.E.	*n*	Mean S.E.
Intact, food and water deprived	11	93 ± 2·0	11	101 ± 1·8	4	104 ± 5·4
Anaesthetic and sham operation	3	110 ± 6·1	3	104 ± 3·1	—	— —
Lesions: Hypophagic	5	127 ± 6·2	5	107 ± 3·3	5	101 ± 1·7
Lesions: Recovered aphagic	—	— —	—	— —	4	112 ± 5·7
Lesions: Aphagic	9	139 ± 5·1	9	126 ± 5·0	4	152 ± 13·4
Food deprived after 'recovery' from lesions	3	90 ± 4·7	3	104 ± 5·6	—	— —

(*b*) 48 *Hr post-operative.* The observed control expenditure of energy for each rat was adjusted to the body weight and food intake observed during the first and second 24 hr intervals after operation. Rats whose nominal food intake was very small and which showed evidence of large spillage and scattering were regarded as aphagic.

Some elevation of total energy expenditure after placement of lesions persisted in most rats for the first 24 hr but was large only in those that were aphagic (Table 2, 3). The elevation persisted during the second 24 hr interval in those rats that continued to be aphagic but declined in those that recovered feeding (Table 2, 3). Over a 24 hr period the rats subjected only to sham operation and rats that were deprived of food after recovery from aphagia showed no elevation in metabolic rate (Table 3).

Chronic response of energy expenditure to lateral lesions

The total energy expenditure of lesioned rats which recovered normal food intake and which were studied 3 or more days after operation was slightly depressed relative to preoperative control levels (93 ± 3·7 % S.E.).

The rats which continued to be aphagic showed persisting and, eventually, further elevation of expenditure relative to controls. The persistently aphagic rats have been compared directly with chronically deprived controls, tube-fed according to the schedule followed with the aphagic rats.

The intact, deprived, tube-fed rats showed a slowly declining energy expenditure with continued prevention from spontaneous feeding (Fig. 5). The rats with persistent aphagia showed, during the first few days, the raised metabolic rate described above (Table 3). At about 7–10 days after lesions all showed a secondary increase in total metabolic rate, to 150–187 % (mean 167 ± 5 % S.E.) of the rate shown by intact rats comparably deprived and tube-fed. They maintained this elevated expenditure until the termination of the experiment (Fig. 5).

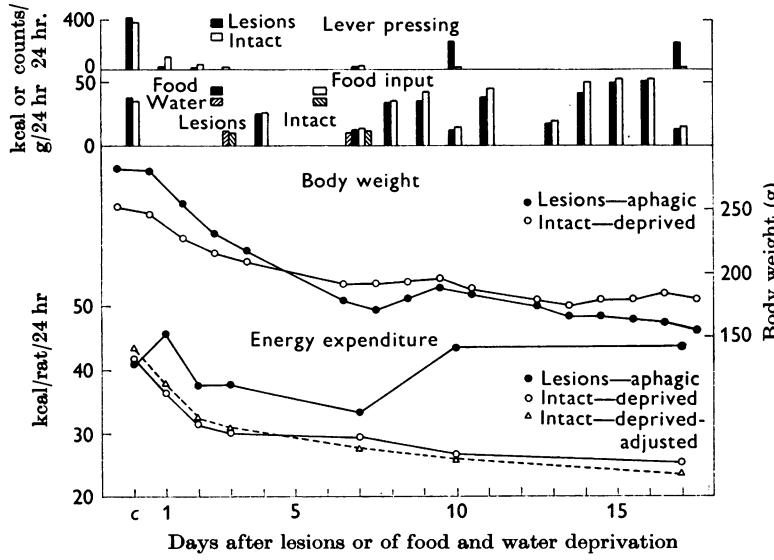

Fig. 5. Total energy expenditure, body weight, lever pressing for food and total food input before and for 17 days after lesions that produced persistent aphagia (rat 507) and before and during 17 days of food and water deprivation of an intact rat (rat 522). Food input during the control period (*C*) was voluntary intake; all food and water inputs thereafter were administered by tube. Intact, deprived, adjusted values for energy expenditure (△) are the values for the deprived control rat adjusted, by eqn. (1), to the body weight and absorbed food input of the aphagic rat on the same day.

Approximately coincident with the development of increased heat production during continued aphagia were (*a*) a change from slight gain of body weight during tube feeding to progressive weight loss even with increased rate of tube feeding (Fig. 5), (*b*) recovery of differentiation of activity (Fig. 3), (*c*) return of lever-pressing activity (Fig. 5) and active interest in foods offered when not in the calorimeter and (*d*) recovery of grooming with particular and damaging attention to the genital area; sustained erection and bleeding of the penis occurred during the initial days of recovery of grooming.

Activity compartment of total energy expenditure

The component of total energy expenditure normally attributable to spontaneous activity in the environmental and feeding conditions used here is about 25 % of the total expenditure (Morrison, 1968). This compartment size was maintained throughout by the deprived intact rats (Fig. 6).

All the lesioned rats were arranged in ascending order of severity of response with respect to each of three criteria: (1) severity of reduction of feeding (Tables 1 and 2), (2) period of total aphagia (Table 1) and (3) period of persistence of raised metabolic rate (Table 2). The rank sums of these give an over-all rank of severity of response.

Block diagrams of the change in relative size of the activity compartment of energy expenditure were arranged in the over-all ranking order (Fig. 6). At the mildest total response the activity compartment after lesions showed no substantial difference from control values or from the values found during food and water deprivation of intact rats (Fig. 6). As the severity of the response increased the size of the activity compartment increased progressively until, with total and sustained aphagia/adipsia, it made up 34 % (range 23·6–43·7 %) of the total energy expenditure compared with 23 % (range 20·1–25·8 %) for the same rats before lesions (Fig. 6). This increased activity compartment was also maintained in a rat (505) that had recovered normal food and water intake and body weight and whose total daily energy expenditure was back within normal limits.

It should be noted that evaluation of the activity compartment of energy expenditure depends on the appearance of differentiated activity with a clearly defined resting level (Morrison, 1968).

For the first 24 hr after lesions some of this increased activity and energy expenditure of aphagic rats was probably produced by panting, as measured by the increase in physiologically evaporated water (total evaporated water corrected for water evaporated from food and faeces). Thereafter, panting was not quantitatively important (Table 4).

Daily excretion of creatinine

The daily excretion of creatinine in the urine of normal rats was only slightly modified by deprivation of food and water (Fig. 7*a*). On the second day after lesions that produced aphagia for 2 days or more there was a marked and statistically significant ($P < 0{\cdot}01$) increase in creatinine excretion (Fig. 7*b*). Rats that showed only a transient hypophagia did not show a significant change (Fig. 7*b*). Rats that had been aphagic but had recovered food and water intake and body weight showed some reappearance

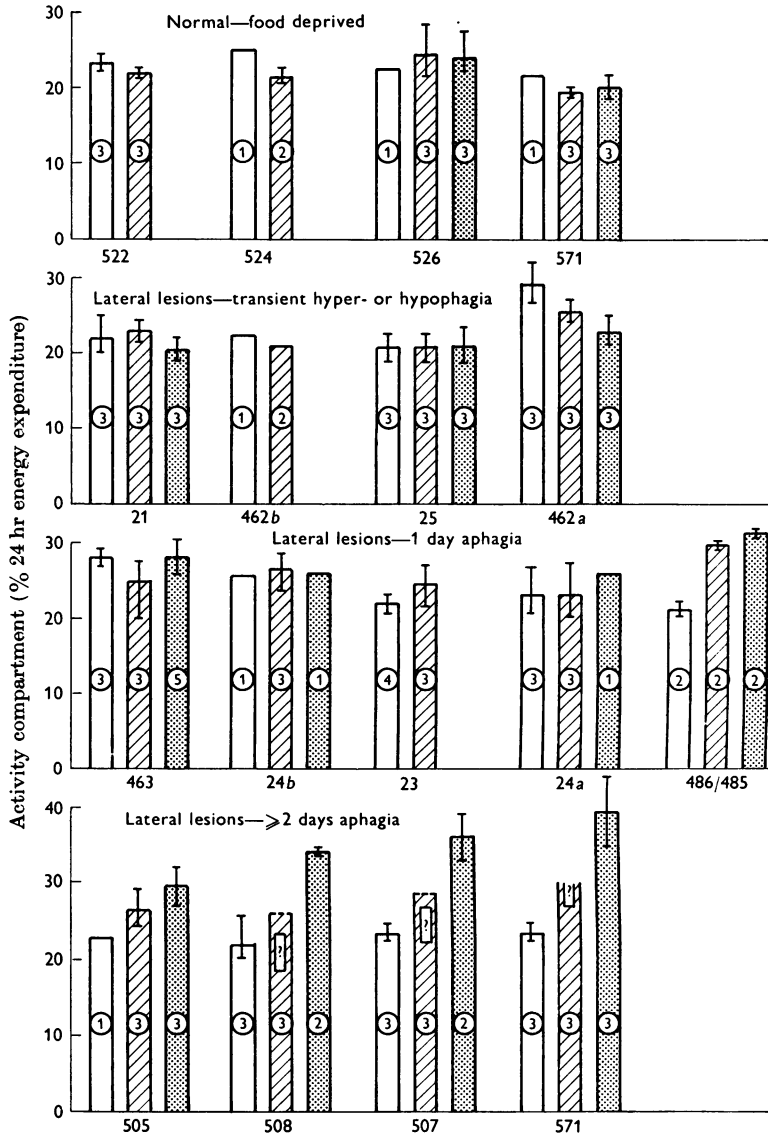

Fig. 6. Mean activity compartment as % of total daily energy expenditure before and after food and water deprivation or lateral lesions. Figures below sets are rat numbers. The sets for lateral lesions are arranged in ascending order of severity of response with respect to feeding and total energy expenditure. Open blocks are control, fed values; hatched blocks are for first 3 days after lesions (or of deprivation); stippled blocks are for >3 days after lesions (or of deprivation). Figures within blocks are number of days on which mean is based. Bars represent range of compartment size. '?' indicates that resting periods were too brief to obtain a reliable estimate of activity.

of this effect ($P < 0{\cdot}001$) when they were deprived of food and water (Fig. 7*c*).

Feeding and food scattering by rats with lateral lesions

All the rats with lesions, while studied in the calorimeter, had access to the liquid diet by lever pressing. When not in the calorimeter and apparently aphagic they had access to the liquid diet, to C21 (Millar *et al.*

TABLE 4. Physiologically evaporated water from rats deprived of food and water, or with lesions in the lateral hypothalamus, as % of evaporation from normal fed rats

Treatment	First 24 hr	Second 24 hr	*n*	S.E.	7–17 days	*n*	S.E.
Intact, food and water deprived	110	95	3	9·2	91	7	8·1
Anaesthetic and sham operation	110	—	3	13·5	—	—	—
Lesions: Hypophagic	111	98	4	10·5	—	—	—
Lesions: Recovered aphagic	139	111	4	12·9	—	—	—
Lesions: Aphagic	156	117	4	7·5	96	6	23·4

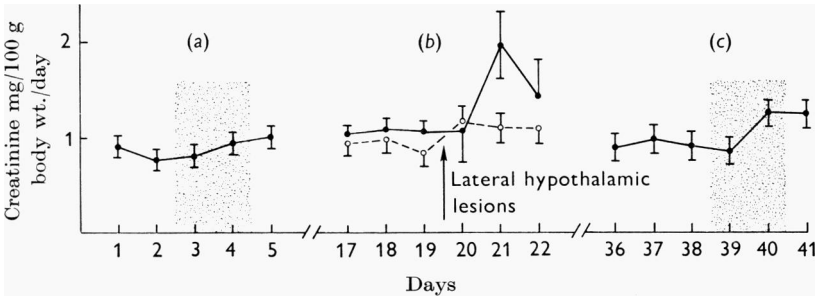

Fig. 7. Mean urinary creatinine/24 hr/100 g body wt. (*a*) of eight intact rats fed and deprived of food and water, (*b*) immediately before and after lateral hypothalamic lesions that produced aphagia ●—● (five rats) or hypophagia ○---○ (three rats), and (*c*) of eight rats after recovery from aphagia, fed and deprived of food and water. The rats in (*c*) include the five aphagic rats shown in (*b*) and three aphagic rats that had lesions made at the same time but had no earlier creatinine measurement. The stippled areas show periods of food and water deprivation. Bars show $\pm 2 \times$ S.E. of mean.

1957) and water and, intermittently, to mashes of Chow or of 'chocolate chip cookies' (Teitelbaum & Epstein, 1962) saturated with water or milk and exposed in open dishes.

When rats 507, 508 and 571 recovered differentiated activity and started lever-pressing again in the calorimeter, they showed interest in the food delivered and gnawed at the delivery spout and receiving dish. They pressed the lever and went immediately to the delivery spout on the opposite side of the cage. Of the food delivered more than 90% could be accounted for as scattered. It cannot be said unequivocally that none of the food delivered by lever-pressing at this time was ingested, but cer-

tainly not enough was ingested to have a detectable effect on loss of body weight.

After recovery of differentiated activity and lever-pressing, these rats also showed active interest in all foods offered when not in the calorimeter (milk, C21, Chow mash and 'chocolate chip cooky' mash). In short-period offerings of mash (0·5–1·0 hr) much of the mash was scattered and body weight changes over these periods showed no evidence of ingestion. Mash dissipated by rat 507 on overnight offerings between days 8 and 14 after lesions was 22, 25, 18, 18 and 50 g without any evidence of arrest of decline of body weight. Milk, sugar-water and water were available but none was ingested. The cup containing fresh C21 always showed tooth marks in the food and smearing of other foods around the edge.

TABLE 5. Recovery of function of rat no. 508

Days after lesions	Recovery of differentiation of activity	Attempts to eat offered foods	Lever pressing counts	Food and liquid ingestion (excl. tube feeding)				
				Mash	C21	Milk	Sugar water	Water
1	No	No	0	—	—	0	—	—
2	No	No	10	—	—	0	—	—
3	No	No	4	—	—	0	—	—
4–6	—	No	—	0	0	0	—	0
7	Yes	Yes	135	0	0	0	—	0
8	Yes	Yes	109	0	0	0	—	0
9	—	Yes	—	+	+	0	—	0
10	—	Yes	—	+	+	0	—	0
11	—	Yes	—	—	+	0	0	0

Rat 508 showed a marginal recovery of eating with recovery of differentiated activity but no recovery of drinking. Of the fully aphagic rats it also showed the least increase in energy expenditure in the 48 hr following lesions (Table 2). The sequence of recovery of food intake and of some features of activity is shown in Table 5. The partial recovery of food intake is assessed on the basis of short-period body weight changes while the foods were being offered and on the amounts of C21 and of fluids apparently consumed. The degree of scattering made weight changes of mashes meaningless.

Location of lesions

All the lesions were in the lateral hypothalamic area with their centres about the level, rostro-caudally, of the caudal part of the ventromedial nucleus and lateral to the descending column of the fornix. Damage from the larger lesions touched the medial edge of the internal capsule and extended medially to involve the fornix. The smaller lesions had, in general, the smaller effects on feeding and on energy and activity patterns (Fig. 8). The prolonged total aphagia was associated with larger lesions and with lesions extending into the subthalamus.

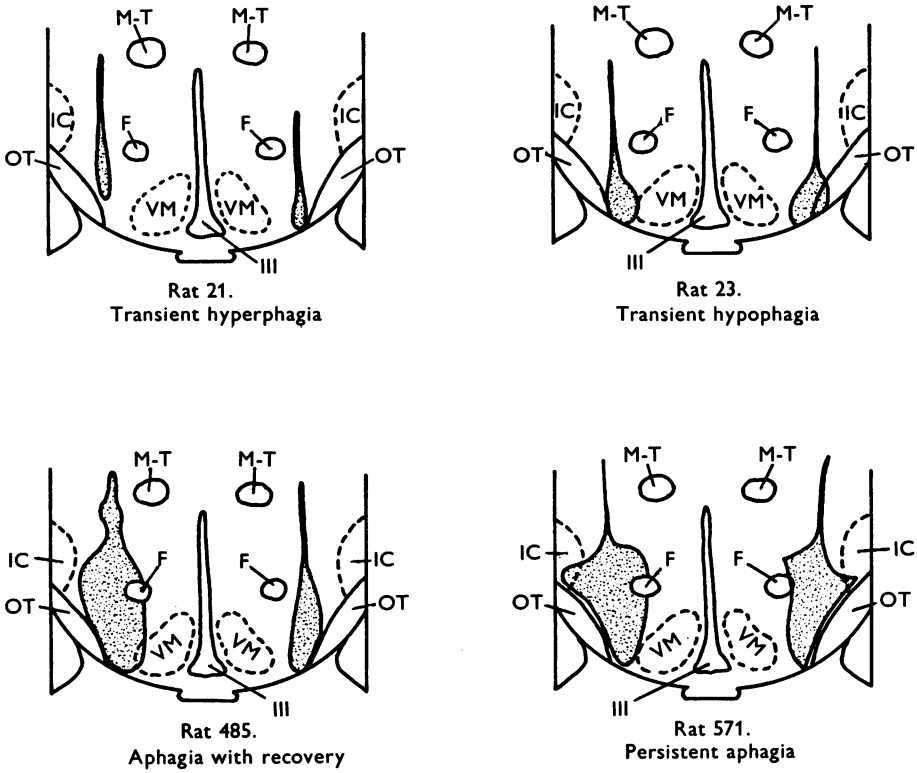

Fig. 8. Spread of destruction in the lateral hypothalamus in the coronal plane of the ventromedial nucleus (5·5 mm rostral to the inter-aural line) of rats showing different degrees of functional response to the lesions. M-T is mammillothalamic tract, F is descending column of fornix, VM is ventromedial hypothalamic nucleus, IC is internal capsule, OT is optic tract and III is third ventricle. Stippled area shows extent of destruction.

DISCUSSION

The results reported here demonstrate that lesions in the lateral hypothalamus produce major changes in energy metabolism, at least part of which is the energetic reflexion of disruption of the normal amount, differentiation and distribution of activity. The immediate post-operative metabolic and activity changes are not specifically tied to a particular form or severity of feeding response to the lesions, but the period for which the changes persist does appear to be related to the severity of the feeding response and the occurrence of spontaneous recovery of feeding.

The acute rise in total energy expenditure after placement of lesions is probably the equivalent of the raised metabolic rate found by Stevenson & Montemurro (1963). They regarded this as a raised resting rate. The

simultaneous activity records show the immediate increase to be largely an effect of the abnormal distribution and lack of differentiation of activity. The effect sustained for 24 hr or more may be the result of a generally increased level of activity. Unfortunately, undifferentiated activity cannot be measured by the methods used here (Morrison, 1968).

The precise metabolic significance of the amount of urinary creatinine is not clear (Keys, Brozek, Henschel, Mickelsen & Taylor, 1950). However, the increased excretion of creatinine on the second day after lesions, in rats made aphagic by lesions, cannot be attributed either to the absence of food (Fig. 7*a*) or to the increase in muscular activity (Shaffer, 1908). The increased excretion may represent a change in resting metabolism or an abnormality of phosphorylation in muscle at this time. This response to lesions leaves a residual effect that can be evoked by food and water deprivation after apparent recovery from the lesions.

The larger elevation in energy expenditure which occurs later in persistent aphagia seems more likely to be the origin of the metabolic deterioration reported by Morgane (1961*a*, *b*). This elevation coincides with the return of differentiated activity and is, consequently, the earliest point at which a reliable quantitative estimate can be made of the size of the activity compartment of total energy expenditure. The activity compartment at this time made up about 35 % of the total energy expenditure and was sustained at that level, compared with the normal size of about 25 % (Morrison, 1968) that was maintained in intact rats comparably deprived and tube-fed. The elevation of total energy expenditure (65 % at constant body weight) is too great to be accounted for solely by the increase in differentiated activity. The increased activity compartment and the increased total energy expenditure suggest an inefficiency of energy utilization, possibly by a biochemical uncoupling.

The abnormal pattern and amount of motor activity after lesions are closely tied to the presence of aphagia. It is not merely a response to food and water deprivation and, except during the immediate post-operative period, does not occur with lateral lesions that do not produce aphagia. The sequence of abnormality is, first, a complete disorganization of activity with, later, a partial recovery of organization allowing the appearance of recognizable, stereotyped behavioural patterns including investigation of food, active but unsuccessful attempts to eat and lever-pressing for food. These findings are consistent with the hypothesis that motor disorganization causes the aphagia.

This hypothesis was originally suggested on the ground that aphagic rats will deliver intra-gastrically, by lever pressing, a food that they will not ingest orally (Baillie & Morrison, 1963). Rodgers *et al.* (1965) rejected this hypothesis because they found that rats would eat small amounts of

some foods 1–9 days before they recovered lever pressing for intra-gastric food. They attributed this preference to palatability of the foods and concluded that 'the rats can eat but do not because they are not hungry'. This conclusion is a consequence of their implicit assumptions rather than of their results. If eating less than maintenance quantities of food is defined as anorexia (Teitelbaum & Epstein, 1962) and anorexia is defined as failure of hunger and exclusive dependence on the sensory qualities of the food (Teitelbaum, 1962) then any failure to eat is, by definition, an absence of hunger. If one defines 'the approach to food as part of the motivational component of feeding' (Epstein & Teitelbaum, 1964) then any failure to approach food is, by definition, a motivational failure.

The experimental evidence presented by Rodgers *et al.* (1965) does not exclude motor disorganization as a component of the syndrome. The amounts of food taken by mouth before recovery of intra-gastric feeding were very small, and the active interest that the rats showed in food indicated the presence rather than the absence of hunger. (Whether their rats actually ingested any of the food that they dissipated is in doubt, for food scattering by such rats is a serious problem.) Motor abnormality has previously been demonstrated after lateral hypothalamic lesions (Gladfelter & Brobeck, 1962; Teitelbaum & Epstein, 1962) and it is shown here that the abnormality is closely tied to the aphagia. When general motor abnormality is severe enough (in the early stage of prolonged aphagia) all highly organized movement, including lever-pressing and, therefore, including intragastric feeding, is interfered with. Characteristics of food affect food intake or attempts to eat and the effects of these appear to be magnified after lateral lesions. Texture of food (Carlson & Hoelzl, 1949; Corbit & Stellar, 1964; Hamilton, 1964) as well as taste or smell is important in this respect. The differences found by Rodgers *et al.* (1965) in apparent intake of different foods were between foods of different consistency. Texture and consistency can be considered as part of the palatability complex but they may also modify the ease of the ingestion process. The latter effect is supported by the difference in energy cost of feeding between different types of food (Morrison, 1968). Differences in attempts to eat or in true intake may reflect differences in ease of organizing the necessary ingestion process rather than differences in palatability. This point requires much more investigation.

There do, however, seem to be sensory characteristics of food that, in the presence of massive hypothalamic damage and in the presence of the associated motor abnormalities, are capable of facilitating or inhibiting attempts to eat or whatever capacity for eating there may be. This is indicated by the greater facility of aphagic rats in intragastric feeding where exteroceptive stimulation is also present (Baillie & Morrison, 1963)

than where exteroceptive stimulation is prevented (Rodgers *et al.* 1965). It is also indicated by the recovery of lever pressing for food although the delivered food is not ingested (this work and Baillie & Morrison, 1963) and, at a later stage of recovery, by the drinking of a liquid diet or sweetened water and the rejection of plain water, or the acceptance of plain water and the rejection of water containing quinine (Teitelbaum & Epstein, 1962).

The motor disorganization that exists in aphagic rats is probably an important cause of the aphagia. It may be severe and general enough to delay the recovery of lever pressing for food. The oral ingestion of some foods, however marginal the amount, may recover earlier if the foods are of the form (e.g. mash or thick liquid) that can be scooped in by a crudely organized feeding movement. However, the total aphagia is probably of mixed causation. Diminished perception of hunger, disruption of subthalamic modulation of sensory input (Lindsley, Zaroodny & Morton, 1967) and inefficient utilization of energy may all contribute to the total syndrome.

I am grateful to Mrs B. Moore and Mr W. Foster for technical assistance.

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