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Effects of Intracranial Injections of 6-OHDA on Food and Water Intakes, Body Temperature and Body Weight Regulation in the Rat

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SINGER, G. AND S. ARMSTRONG. *Effects of intracranial injections of 6-OHDA on food and water intakes, body temperature and body weight regulation in the rat.* PHARMAC. BIOCHEM. BEHAV. 5(3) 309–317, 1976. – 6-Hydroxydopamine was injected either intraventricularly (320 μg in 10 μl) or intrahypothalamically (64 μg in 2 μl) into rats kept under either free feeding or body weight reduced conditions. Intraventricular injections caused a temporary aphagia and hypodipsia in free feeding rats but daily measurements failed to reveal any long term effects; body weight reduced rats did not display the temporary aphagia but were initially hyperphagic. Injections into the more rostral hypothalamic areas of free feeding rats also showed only minimal short term effects; however, some of the body weight reduced group died within several days of injection. Injections made at more posterior loci again showed very little effect in both body weight reduced and free feeding groups; some temporary disruption of feeding occurred from lesions in the proximity of the zona incerta of some free feeding animals.

6-OHDA Eating Drinking Body weight Rectal temperature Far lateral hypothalamus Zona incerta

LESIONS in the lateral hypothalamus have been reported to produce a number of deficits which are known collectively as the lateral hypothalamic (LH) syndrome. These include aphagia, adipsia, anorexia, hypodipsia, hypokinesia, catalepsia, hyperactivity, somnolence, hypothermia, change in regard to sensory qualities of diet and, change in learned aversion of foods. Some of these deficits have been chosen and taken as evidence in support of a number of theoretical positions including interference with a hypothalamic feeding system [1,29], drinking system [13], thermoregulatory system [25], general motivational inertia [14,23], generalized motor impairment or specific motor disfunctions controlling chewing and swallowing [3, 21, 22, 33], sensory neglect [12], a learning deficit [24] and, interference with a central reward system [28].

In recent years, one of the most striking findings reported is that, if a rats body weight is reduced by partial starvation prior to lesioning, then the period of aphagia is either completely eliminated or at least attenuated [20]. The interpretation of this finding made by Powley and Keesey is that the aphagia following LH lesions may lower the set point for body weight regulation. This then, reflects an active long term regulatory process by the animal. Intake of food is withheld until the rat reduces its weight to the new, lower setpoint. Thus, the aphagia of the lesioned, nonstarved rat, is a deliberate form of self-induced deprivation and not just a loss of appetite accompanying neural recovery [20]. The importance of these findings is that they undermine all previous theoretical interpretations of the LH syndrome, for they demonstrate that there is no loss of motivation, no loss of appetite and, that the rat is quite capable of carrying out motor acts, at least in regard to food intake.

A second major approach to the LH syndrome lies in the attempt to explain the variety of behavioral deficits in terms of differing anatomical substrate. In other words, to refine our knowledge of the anatomical location so that individual deficits can be identified and correlated to specific anatomical loci. Early reports by Anand and Brobeck [1] concentrated on the lateral hypothalamus itself, but later reports restricted the location of the most severe effects to the far lateral hypothalamus, globus pallidus and internal capsule [9,15]. Not only is the medial-lateral positioning important, but Balagura *et al.* [4] have shown that variations in the anterior posterior plane must be taken into account. More recently, using the technique of histochemical fluorescence, it has been demonstrated that within the far lateral LH area, there ascends the dopaminergic, nigrostriatal bundle (NSB) [30]. Chemical lesioning of this bundle using 6-hydroxydopamine (6-OHDA) thought to be specific to the depletion of catecholamines at appropriate doses, results in prolonged aphagia, one of the deficits of the LH syndrome [31]. Further, it seems that this system and not the adjacent medial forebrain bundle containing noradrenergic and serotonergic fibres that is responsible for the syndrome [18, 26, 31]. Thus it appears that the fibre system regulating the dopamine content of the neostriatum is responsible for the LH syndrome.

The aim of the present experiments was to examine the role of the far lateral hypothalamus in regard to the Powley-Keesey theory of body weight regulation. The

present communication describes in greater detail work already presented as a preliminary outline [27].

METHOD

Animals

Eighty-nine naive, male Wistar-derived rats, 90–120 days old and weighing approximately 300 g at the time of surgery were used. After surgery, rats were housed individually in wire mesh cages (20 × 23 × 40 cm) in a room with air temperature thermostatically controlled at 22°C. Rats were fed ad lib Mecon rat cubes and supplied with tap water.

Procedure

Surgery. Rats were starved 24 hr prior to surgery, and were anesthetized by a chloralhydrate/nembutal intraperitoneal injection. Stainless steel cannula [6] were either unilaterally implanted in the lateral horn of the third ventricle or, bilaterally implanted in various hypothalamic sites. The following Pellegrino and Cushman [19] coordinates were used for the lateral ventricle loci [10]: AP-0.6 mm, L ± 1.8 mm and, H −3.0 mm, all taken relative to bregma. Intended loci for the hypothalamic implants extended from sites rostral to bregma at AP + 0.8 mm, to posterior to bregma at AP-2.0 mm with lateral and horizontal coordinates of L ± 1.9 mm and H 8.0 mm. Rats were permitted at least a 10 day postoperative recuperation period before being assigned to experimental groups.

Drugs. A 32 μg/μl solution of 2, 4, 5-trihydroxyphenylamine hydrochloride (6-OHDA, Astra) in distilled water containing 2 mg/ml ascorbic acid was prepared immediately prior to injection.

Injections. The injection technique has been described in detail previously [2]. Ventricular implants received 6-OHDA (320 μg in 10 μl) over a 5 min injection period (2 μl per min). The bilateral hypothalamic implants received 6-OHDA (64 μg in 2 μl) into each cannula, at the rate of 1 μl per min. The dose of 6-OHDA injected into the hypothalamus has been shown to produce a nonspecific lesion [7]. Injections were given at approximately 11.00 a.m.

Deprivation. Rats were assigned to one of two groups: body weight reduced or free feeding. Numbers in each group are shown in Table 1. Free feeding rats received Mecon rat chow and tap water ad lib. Body weight reduced rats were between 75 and 80 percent of their predeprivation weight. Body weight reduction of the rostral hypothalamic group was achieved in two ways. Seven rats were reduced slowly over a period of 10 days, while 12 rats were reduced by total food deprivation, with water ad lib for a period of 5 days. A pilot test had previously shown that 5 days total food deprivation reduced rats to the 75–80 percent level. Slow and fast reduction of body weight was carried out in order to control for the severity of the deprivation. Immediately after injection, all rats received fresh food ad lib for the remainder of the experiment.

Except for the ventricular group, no long term studies were carried out. Once it was established that the rats either confirmed or refuted the experimental hypotheses, they were sacrificed. Similarly, in these initial experiments no attempts to overcome aphagia were made by employing special diets. Core temperature was measured every morning at approximately 9 a.m. using a SMEC-10 electronic thermometer.

Histology. Upon completion of experimentation each group of rats was sacrificed by decapitation, the brain removed through the dorsal surface of the skull, and stored in a solution of 10% formal-saline. The brains were blocked in paraffin and sectioned coronally at 20 μ, parallel to the cannula tracts, in the plane of the stereotaxic atlas [19]. Deparaffinized hypothalamic sections were stained in Luxol Fast Blue and Cresyl Violet. Locus of stimulation was determined by placing slides in a photographic projector and adjusting the image to that of the stereotaxic atlas.

RESULTS

The main findings are summarised in Table 1, in terms of aphagia, death and no observable affect. As reported previously [27], ventricular injections of 6-OHDA showed only minimal effects on temperature regulation and food and water intake. The immediate effects of ventricular 6-OHDA injections in free feeding animals was to produce a

TABLE 1

SUMMARY OF EFFECTS OF 6-OHDA ON FEEDING

Injection Site	Condition	
	Free Feeding	Food Deprived
	N = 8	N = 9
Lateral Ventricle	0 - Deaths	0 - Deaths
320 μg in 10 μl	4 - Temporary Aphagia	0 - Aphagia
Unilateral	4 - Unaffected	9 - Unaffected
Rostral Hypo-	N = 12	N = 19
Thalamus 64 μg in	0 - Deaths	12 - Deaths
2 μl Bilateral	1 - Temporary Aphagia	1 - Temporary Aphagia
	11 - Unaffected	6 - Unaffected
Caudal Hypothalamus	N = 20	N = 18
64 μg in 2 μl	0 - Deaths	2 - Deaths
Bilateral	6 - Temporary Aphagia	0 - Aphagia
	14 - Unaffected	16 - Unaffected

temporary anorexia lasting up to 48 hr in some cases. This resulted in a temporary loss in body weight. The temporary anorexia was not displayed by the food deprived group who were hyperphagic, and thus regained weight very quickly. No long-term effects of the drug were observed. However, the two injected groups showed slightly higher body weights than the control group from Day 20 to Day 60. Drug effects on water intake were similar to those on food intake; there was a temporary hypodipsia in the free feeding group. The body weight reduced group were hyperdipsic, but this was very variable. There was no systematic change in body temperature for the free feeding group (Fig. 1); some individuals were hyperthermic 24 hr after the drug injection but these still lay within the range of the predrug baseline measures. The body weight reduced group were hypothermic early in the food deprivation period, but came back to the baseline level within 24 hr of the drug injection. These postdrug temperature changes were transitory and lasted no longer than 48 hr.

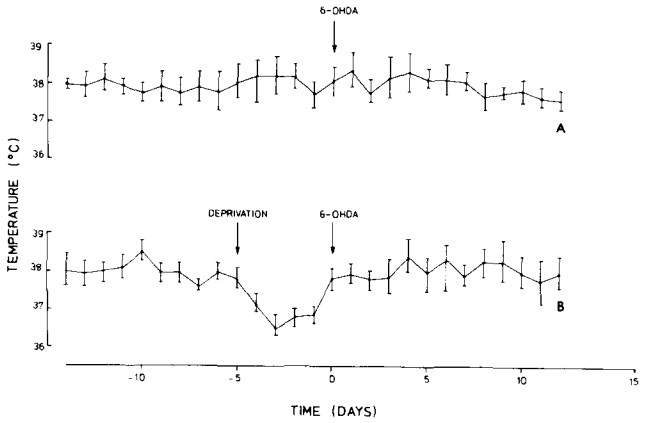

FIG. 1. Effect of intraventricular injection of 6-OHDA on core temperature. A = free feeding group (n = 8) and B = body weight reduced group (n = 9).

Not all rats received the full dose of drug into the ventricles. Lesion sites below the ventricle as shown by histology, indicated that in some animals, much of the drug has passed into subventricular tissue. In other cases, some cortical tissue was destroyed when the drug had retreated back up the cannula tract. The importance of this observation is that it was not possible to predict from the histological evidence, which of the free-feeding rats had previously been behaviorally affected.

The effects of 6-OHDA induced lesions on food and water intakes at particular hypothalamic sites are shown in Figs. 2 and 3. Three rats were excluded because histological analysis subsequent to experimentation showed that some subcranial infection had taken place at some time between surgery and sacrifice. Free feeding rats cannulated in the more rostral hypothalamic areas showed only minimal effects from 6-OHDA injections, as have already been described for the free feeding ventricular rats. Only one rat of the free feeding group in the more rostral sites showed any marked effect, as shown in Fig. 4; because injections were given to nonanesthetized, awake rats, even a one-day feeding reduction must appear significant. However, in the body weight reduced groups, 12 out of 19 rats died within the first 5 days of injection, and one showed a temporary aphagia. Four out of the 5 slow weight reduction rats died, and 8 out of the 12 total food deprivation group died. An example from the latter group is shown in Fig. 5 which illustrates that death was always preceded by a rapid drop in body temperature. It is to be noted that temperature is already slightly disrupted due to food deprivation (See Fig. 5). However, this did not occur in all rats that died, and some rats that did not die also showed the early drop in temperature, and therefore this is not a predictor of the occurrence of death. As approximately the same percentage of rats from both the slow weight reduction and total deprivation groups died, it shows that speed of deprivation is not a contributing factor to early death, and therefore the data for these groups has been pooled. Histological evidence is available for 26 rats with rostral hypothalamic implants. The missing data is due to the rapid occurrence of death, usually overnight, which was not predicted from previous published findings. Figure 6 shows the areas of destruction for the 9 body weight reduced rats that died, and for which histological evidence is available. The loci of injections encroach upon the sub-thalamic structures and along the medial and ventral border of the internal capsule. The fornix, zona incerta, lateral lemniscus, reticular nucleus of the thalamus and entopeduncular nucleus were all damaged in some but not all rats. However, the common anatomical landmark is seen to be the medial border of the internal capsule and the lateral hypothalamus *per se* is not the critical area contributing to the lethal effect. It can also be seen from Fig. 2 and 3 that comparable sites in free feeding rats that overlap with those in body weight reduced rats did not produce lethal effects. Thus, death is due to an interaction between the loci of lesion and the nutritional state of the rat which reflects the degree of energy depletion at the time the lesion is made. In addition, the shape of the lesion may be an important variable. Long thin lesions in the dorsal ventral plane will be less effective than more spherical lesions, if the structure to be lesioned is a fibre tract ascending or descending in the rostral-caudal plane.

In contrast to the rostral sites, rats cannulated at more caudal sites showed only minimal disruption of feeding and drinking (Fig. 7), whether body weight reduced or allowed free access to food. Only two animals from the food deprived group died (Table 1). Figure 8 shows brain loci where 6-OHDA damage caused a very temporary aphagia (approximately 4 days) in free feeding rats. A convenient anatomical landmark for locating this transient effect, is the zona incerta.

DISCUSSION

Although 6-OHDA is supposed to produce specific depletion of catecholamine containing neurons, the doses used in this study have been shown by histochemical fluorescent studies to be non-specific, leading to generalized damage only [7]. For this reason the discussion of the data is in terms of generalized damage which is neurochemically non-specific and may be similar to that produced by electrolytic lesions and the interpretation of the data is not based on the assumption of a specific catecholamine depletion.

The most outstanding findings seem to be the general lack of effect of 6-OHDA in regard to disruption of feeding behavior and the other measurements taken, in spite of the fact that a large number of hypothalamic sites were

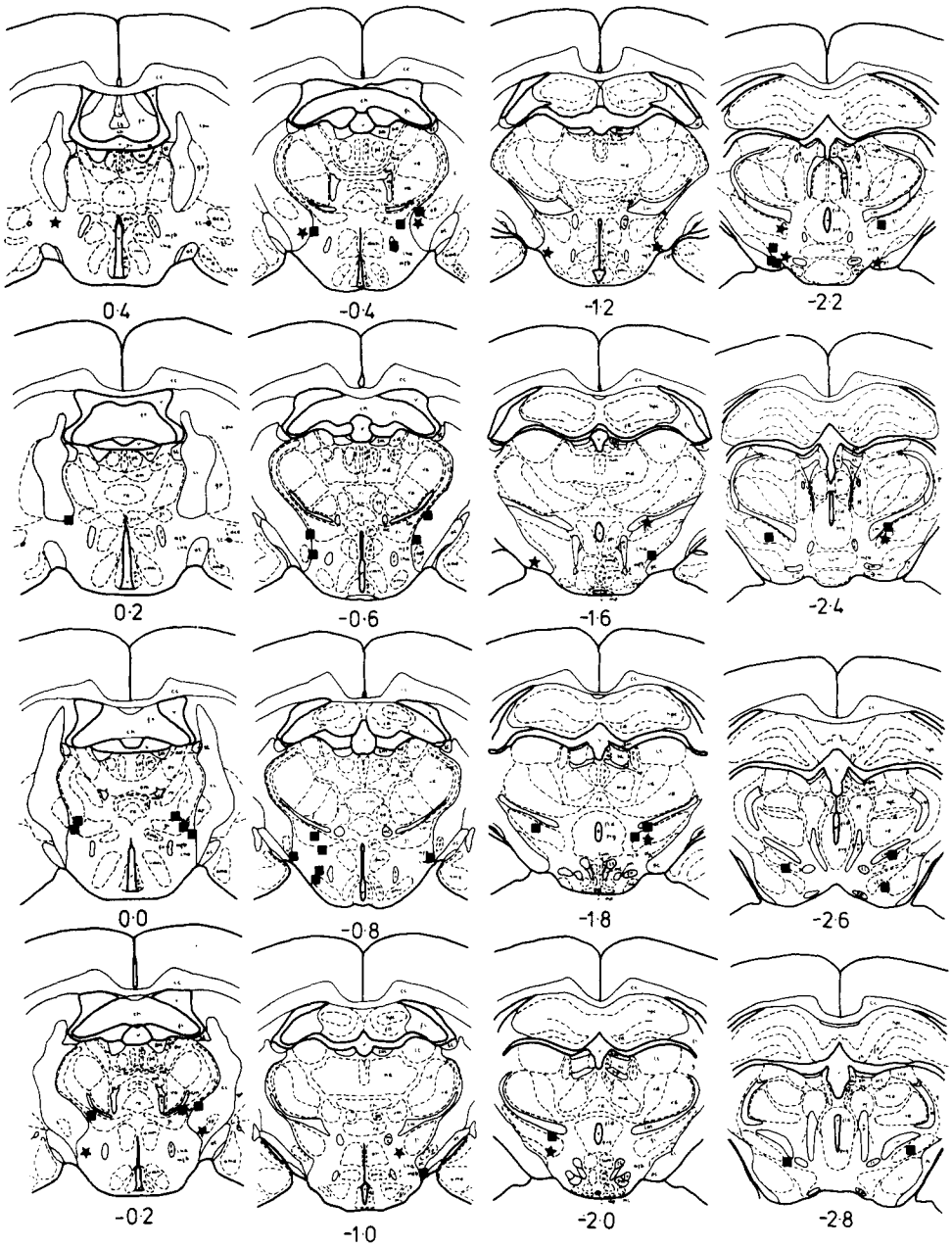

FIG. 2. Reconstruction of loci of tips of cannula from 28 free feeding rats. Plates are modified from the Pellegrino and Cushman rat brain atlas. Symbols for both Fig. 2 and Fig. 3 are: • Death, ★ Temporary aphagia and body weight loss, and ▪ No observable affects. Symbols are placed at the most ventral point in the sections representing the largest extent of damage. Figures 6 and 8, plus map inserts on Fig. 4, 5 and 7 demonstrate more clearly the shape and sizes of individual lesions.

sampled in addition to massive doses of the drug being injected into the ventricles.

The results of the ventricular injections have been discussed in detail elsewhere [27] and are briefly summarised here.

Ventricular injections showed only minimal effects on food and water intake and temperature regulation. Differences in body weight due to food deprivation had no effect on these animals, except that the temporary anorexia of the free feeding group was not seen in the food deprived group. However, because there was no obvious correlation between the anorexia and whether the rats received the full complement of drug into the ventricles, it is quite possible that the temporary anorexia was not due to the interference with lateral hypothalamic mechanisms. Widespread circulation of the drug via the ventricles would cause damage to many brain areas regulating many different biological systems, and thus the anorexia may not have

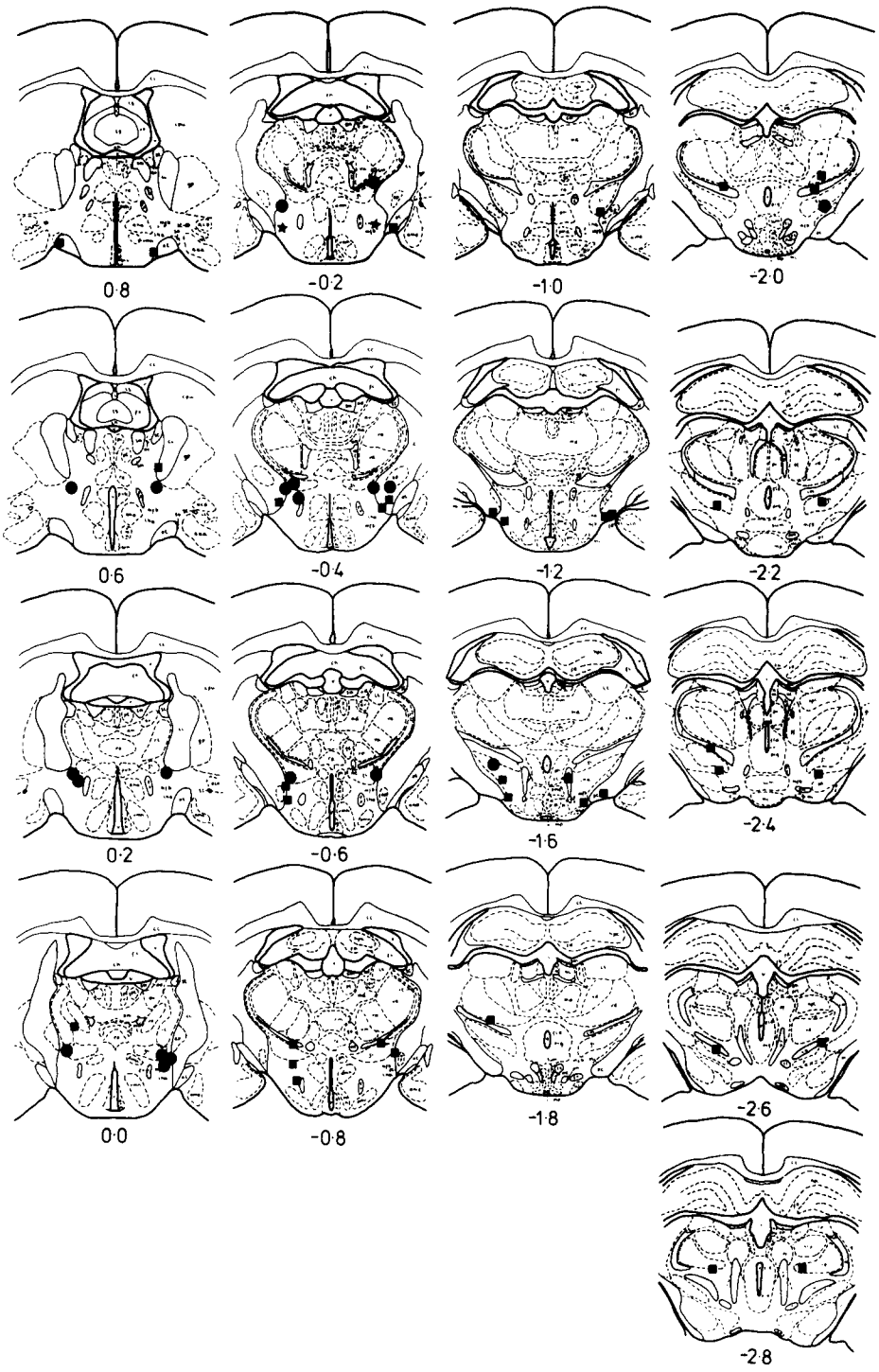

FIG. 3. Reconstruction of loci of cannula tips from 30 body weight reduced rats. Symbols same as for Fig. 2.

been due to interruption of a feeding system *per se*. Ventricular injections as a method for assessing the LH syndrome are therefore questionable.

The lesions in the rostral hypothalamic sites leading to death appear to support the findings of Morgane [14,15] and Gold [9]. These authors have argued that the role of the lateral hypothalamus in the classic lateral hypothalamic syndrome is in fact minimal, and that death is due to the interruption of pathways passing through the subthalamic structures bordering onto the lateral hypothalamus. However, in contrast to previous reports, we find that death only occurs in body weight reduced rats. This may be explicable in terms of the smaller lesions created by 2 μl of 6-OHDA [7] in comparison to larger electrolytic lesions

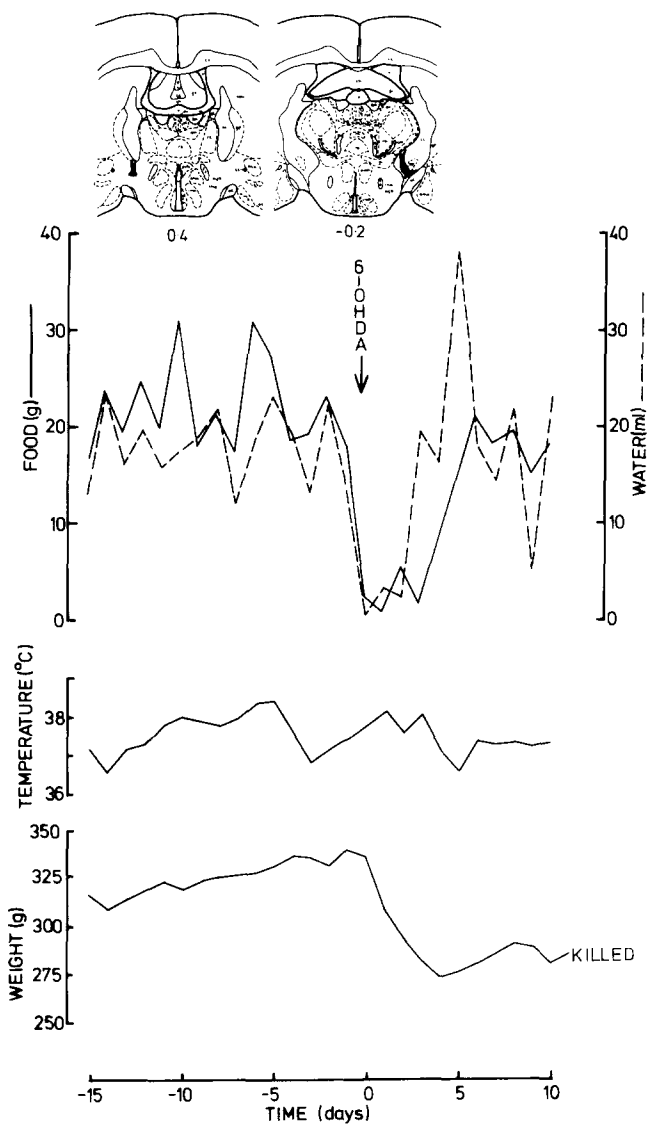

FIG. 4. Effect of 6-OHDA induced lesions on body weight, core temperature and food and water intake in a free-feeding rat cannulated in the more rostral sites. This was the only free-feeding rat of the more rostral placements to show any marked disruption in consummatory behaviour. Day 0 was injection day.

and knife cuts. Small lesions, unless they are bilaterally, perfectly homologous may only destroy part of the system passing through this area, and it may be that it is only in rats already pressed for energy stores by food deprivation that any partial lesion becomes lethal.

In addition, one must also consider the evidence demonstrating changes in the catecholamine uptake mechanisms as a result of deprivational states [8,32]. It is quite conceivable that the state of excitability of neurons in the hypothalamus will affect the uptake of intracranially injected pharmacological compounds, in this particular case, that of 6-OHDA which has been shown to lead to considerable variation in damage patterns, depending on volume, concentration and site of injection [17,27].

Nevertheless, death does not seem to be due to aphagia *per se*, since it occurs very suddenly, and earlier than one

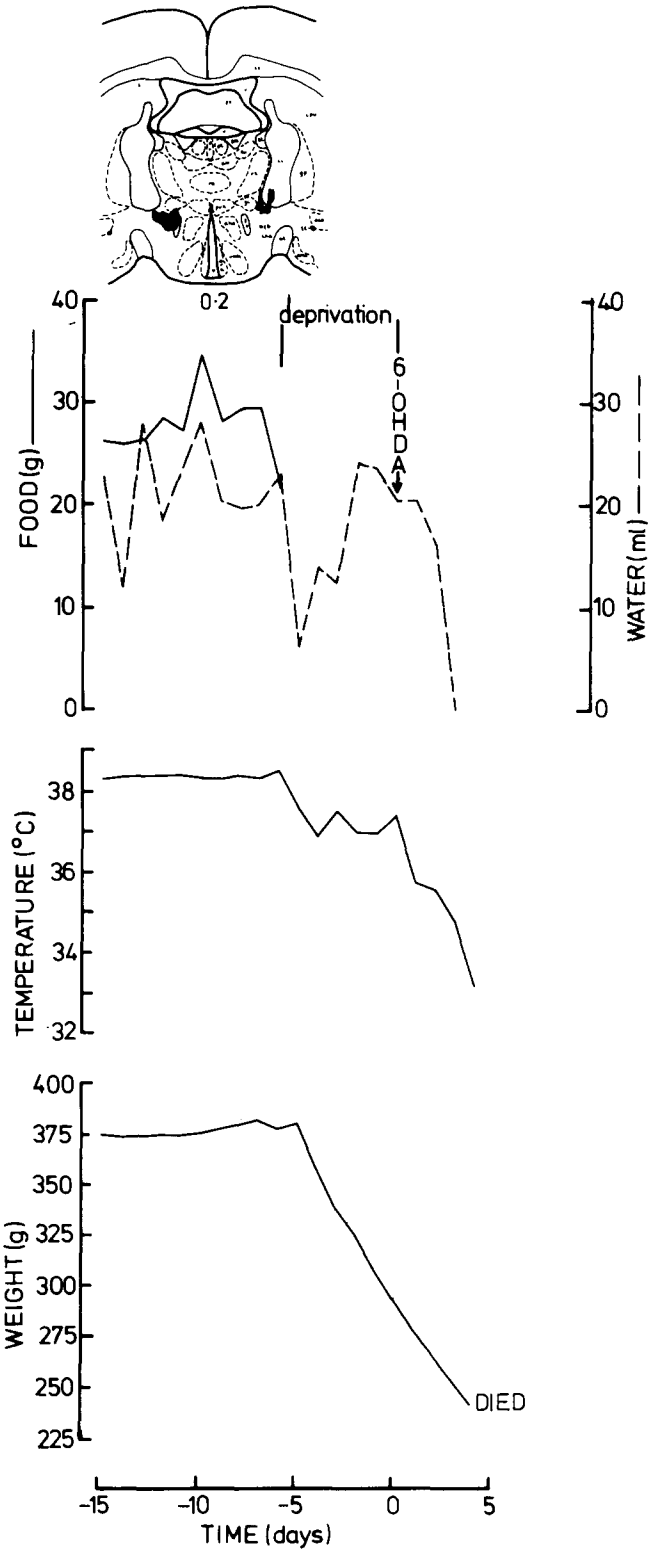

FIG. 5. Effect of 6-OHDA induced lesions on body weight, food intake, water intake and core temperature in a food deprived rat bilaterally cannulated in the more rostral sites. Loci and extent of 6-OHDA damage are shown in inset.

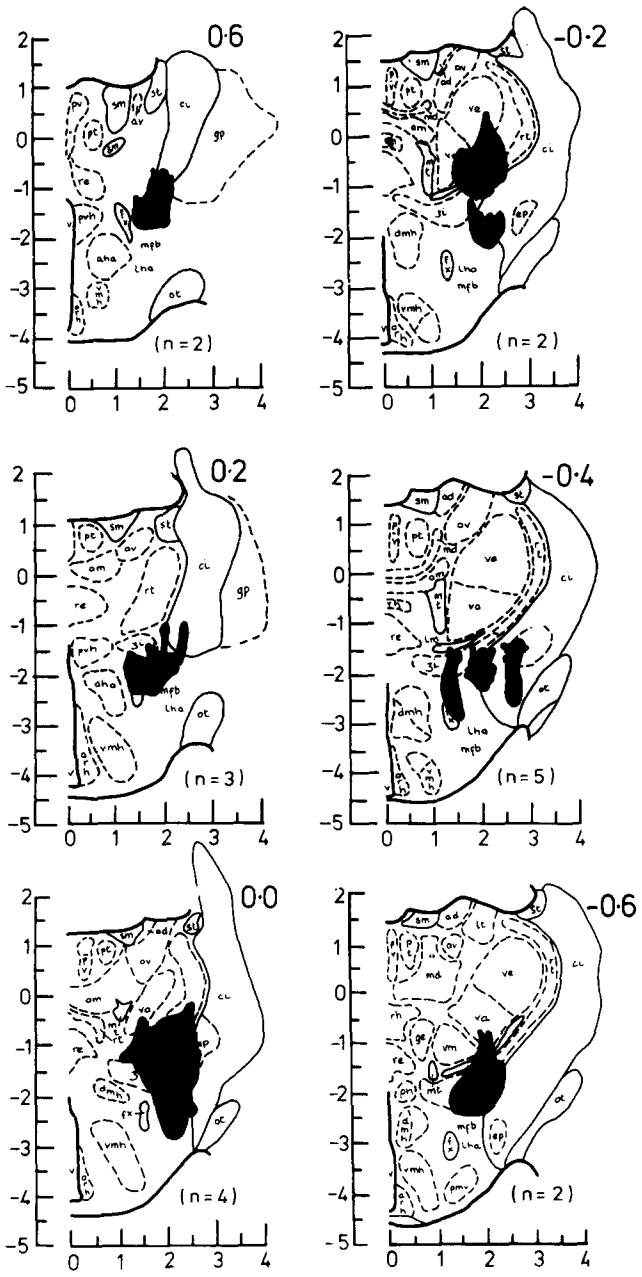

FIG. 6. Eighteen overlapping sites from 9 rats with more rostral placements that died as a result of 6-OHDA induced lesions. Damaged areas are superimposed onto plates derived from the Pellegrino and Cushman stereotaxic atlas.

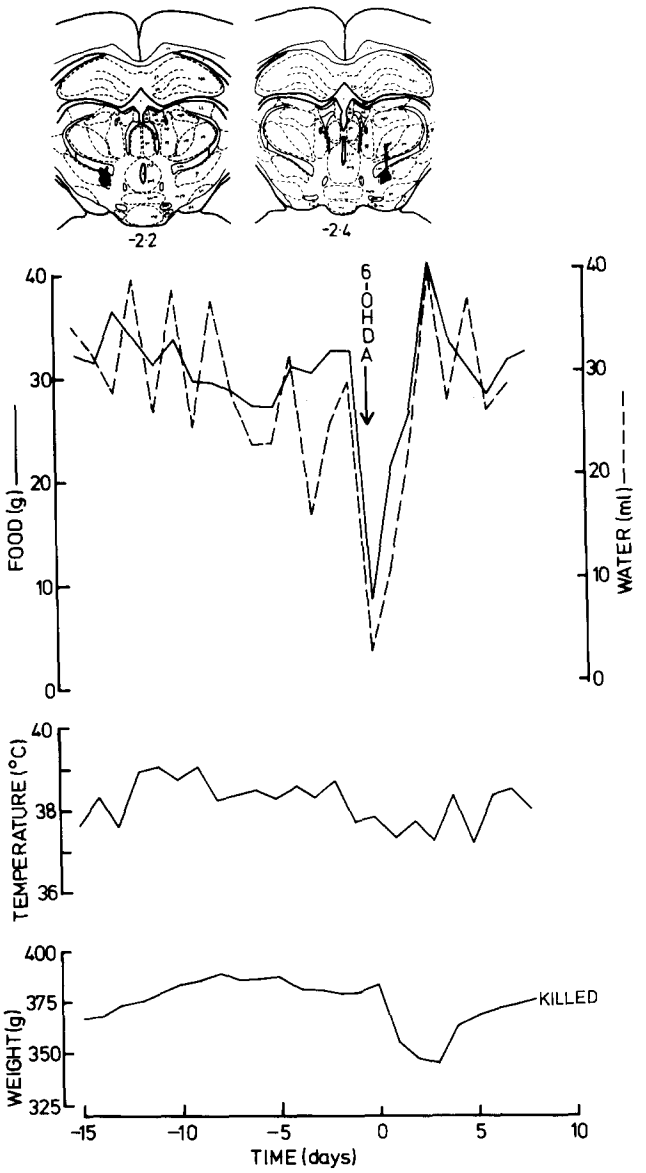

FIG. 7. Effect of 6-OHDA-induced lesions on daily body weight. core temperature and food and water intake in a free-feeding rat cannulated in the more caudal areas. This rat was the most severely affected of the 6 affected in this area.

would expect from food deprivation alone. We have previously starved untreated rats for much longer periods than this and they survive if allowed access to food when body temperature starts to fall.

The lethal effect may be due to an inability to regulate body temperature. It has previously been shown that rats with lateral hypothalamic lesions may fail to maintain their temperature in the cold and that this deficit need not necessarily be accompanied by adipsia and aphagia [25]. This need not be due to the interruption of a temperature control system *per se*, for as some authors have suggested, the LH syndrome may be due to the interruption of motor pathways passing through this area [33]. It is possible that interference with such motor pathways disrupts body activity which in turn leads to an inability to thermo regulate in a rat already depleted of calories by food deprivation. In short, the rat is unable to maintain its normal body temperature even at 22° C.

Medial and ventral lesions involving the ascending ventral and dorsal noradrenergic bundles and the two serotonergic bundles [16] in the lateral hypothalamus itself, did not disrupt consummatory behavior except in one case (Fig. 3, section −0.2 mm). Our results tend to support a dopamine involvement in the LH syndrome as predicted from Ungerstedt's data [31]. Figure 6 shows that in the rostral placements the axonal tracts of the A9, but not the tracts of the A10 seem to be interrupted in the body weight

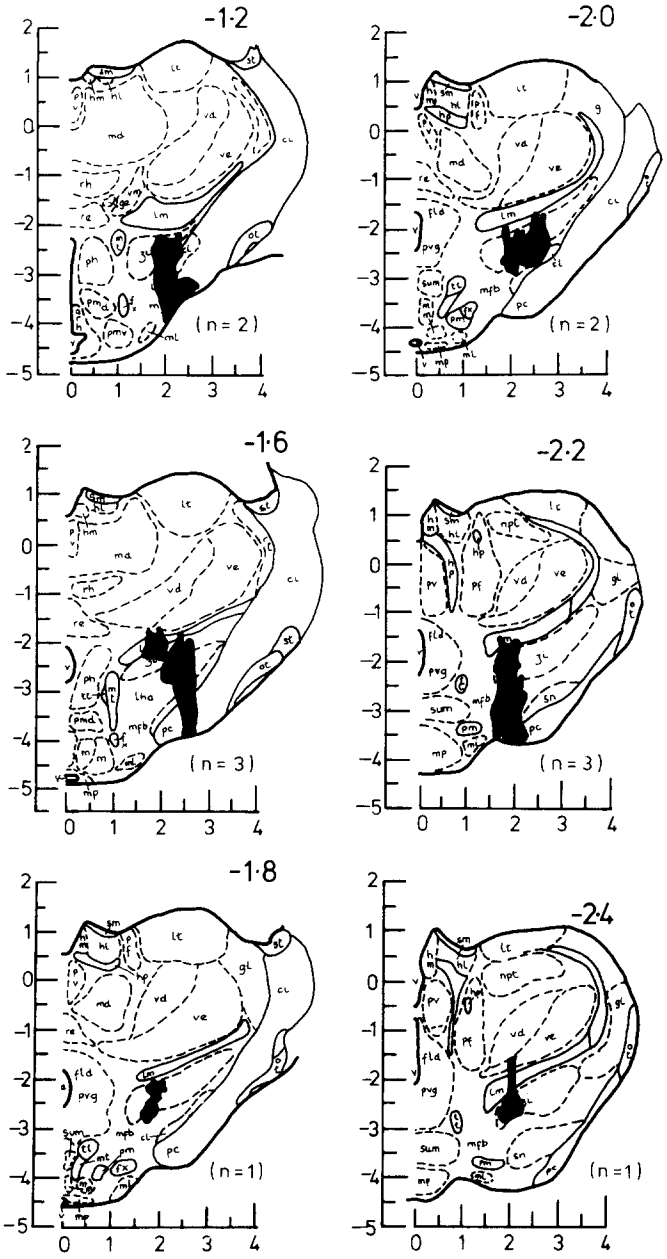

FIG. 8. Twelve overlapping caudal sites from 6 free feeding rats that showed temporary aphagia after 6-OHDA induced lesions. Damaged areas are superimposed onto plates derived from the Pellegrino and Cushman stereotaxic atlas.

reduced rats that died. However, lesions made at more caudal sites which should also have damaged the nigrostriatal bundle appear to be less effective. In fact the affective sites producing temporary aphagia and 2 deaths (see Fig. 8) are essentially too dorsal to interrupt the nigrostriatal bundle. Lesions in the origin of the nigrostriatal bundle itself were not effective (see Fig. 2 and 3). Thus, we must not exclude the possibility that it is the lesioning of some nonmonoaminergic tract that either ascends or descends through the far lateral hypothalamus, which is responsible for the LH syndrome. In this regard Blatt and Lyon [5] reported that a component of an ascending reticular formation pathway which descends into the region of the zona incerta and fields of Forel at caudal hypothalamic levels lead to disruption of feeding. However, disruption of feeding was severe; whereas in the present case the feeding deficit is transitory. Again, this may be due to the difference in the size of the lesions.

The data from the ventricular injections and the caudal hypothalamic injections could be interpreted as support for the Powley-Keesey, body weight set-point theory, in that overall, when lesions did have an effect on consummatory behavior, the temporary aphagia was seen in the free feeding rats, the body weight deprived rats initially being hyperphagic. In contrast, the rostral hypothalamic data is at variance with the body weight set-point theory. Thus, we cannot support nor contradict the set-point theory and further experimentation is needed to clarify the situation. It is quite possible that the Powley-Keesey effective site is far more posterior and slightly more medial than our effective far lateral sites [11], and that at least two separate syndromes are involved under what is generally termed the LH syndrome. Far lateral lesions may interrupt nonfeeding systems such as motor pathways, and thus may affect feeding indirectly whereas lesions in the hypothalamus itself may affect other aspects of the nutritional system such as endocrinological control. The problem can only be clarified by measuring several dependent variables simultaneously, for if only food intake is monitored, then indirect interference with feeding such as via temperature regulation and motor pathways may be interpreted as direct interference with feeding systems *per se*.

Finally, one must consider the general lack of effect of our 6-OHDA lesions from the aspect of some peculiarity involved in the present injection procedure, for it may turn out to be that the state of the organism at the time of injection is important in more than one respect. Slangen has reported that he was: " . . . unable to cause aphagia by injecting 6-OHDA via the cannula 2 weeks postoperatively. However, using the same coordinates, the same volume, and the same amount of 6-OHDA we always caused aphagia in rats when the 6-OHDA was injected via the needle during the stereotaxic operation." Slangen ([26], pp. 404). Our results tend to support this finding. Slangen interprets his results in terms of differential diffusion of the drug under the two conditions. Whilst differential diffusion may exist, it still cannot explain our data; histological analysis shows that with our dose of drug the lesions are quite large enough to destroy the critical zone at the tip of the internal capsule in free feeding rats but that they do not die. Therefore, some other factor must be operating during chemical injection of the anesthetized rat which is not present in the unanesthetized, unrestrained rat. Whilst our results need replication from other laboratories and also need careful elucidation they may still throw some doubt on results obtained from electrolytic lesions carried out on anesthetized preparations, and so add one more puzzle to the enigma of the LH syndrome.

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