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Head Displacement and Bracing in Haloperidol-Treated Rats Compared to Rats With Lateral Hypothalamic Damage

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PELLIS, S. M., Y.-C. CHEN, R. M. CHESIRE AND P. TEITELBAUM. *Head displacement and bracing in haloperidol-treated rats compared to rats with lateral hypothalamic damage.* PHYSIOL BEHAV 35(5) 799–804, 1985.—A characteristic of catecholamine-depletion-induced catalepsy is that such animals resist horizontal displacement, forward, backward or sideward, by bracing, i.e., pushing against the displacing force rather than stepping away as do normal animals [16]. In this report the bracing responses of two cataleptic preparations were compared: (1) intact rats given haloperidol, a dopamine antagonist, and (2) rats with large lesions of the lateral hypothalamus (LH). Although both preparations exhibited exaggerated bracing responses when pushed, the LH rats acted in a non-cataleptic manner when pushed backward by the head; they retreated backward. The backward walking was a head-elicited response, because pushing the body backwards by the shoulders elicited bracing, not walking. Other forms of head displacement elicited body bracing if the body's stability was challenged: as when the head (and thus the body) was pulled forward; or no strong bracing responses if the head was displaced without affecting the body's stability, i.e., when as the head was pushed laterally. Therefore, retreating rather than bracing was elicited by one specific form of head displacement: backward. In contrast, haloperidol-treated rats braced whenever the body's stability was challenged, including when the head was pushed backward.

Bracing Haloperidol Lateral hypothalamic damage Head displacement Body displacement "Retreating backwards" Disconnection of bracing response

CATALEPSY in animal models has been widely used to screen for potentially valuable antipsychotic drugs (e.g., [1, 3, 4]). It is also a symptom often reported in various forms of Parkinson's disease [5, 10, 14]. A diagnostic aspect of catalepsy is the tendency of an animal to remain in awkward postures, but to resist, by an aggregate of allied reflexes, displacement from stable static equilibrium [6, 15, 16, 19]. Cataleptic rats, for example, will actively resist being displaced horizontally or being rolled over, by buttressing against the displacing force, but they do not step in the direction of displacement, as normal animals do [16].

In the present paper it is shown that not all forms of catalepsy are the same. By testing bracing reactions of separate parts of the body, we have found that rats made cataleptic by lateral hypothalamic damage (involving both ascending and descending pathways) differ in one important respect from rats made cataleptic by other means (involving only the ascending pathways).

METHOD

Animals

Fourteen male Long Evans hooded rats, weighing between 300–400 g were used. They were housed individually at a constant room temperature of 21–22°C, under a 12:12 hr light-dark cycle, lights on at 0700. Food and water were available ad lib. Some of the rats did not feed themselves adequately after surgery, and were given wet mash or an intragastrically delivered liquid diet when necessary [17].

Lateral Hypothalamic (LH) Lesions

Surgery was performed using standard stereotaxic procedures. Bilateral lesions were made on six rats, using 1mA for 20 sec (anodal direct current) through stainless steel electrodes (RNE 300 Rhodes Medical Instruments, Inc.). The coordinates, with skull horizontal, were 2.7 mm posterior to bregma, 2.0 mm lateral to the middle of the sinus, and 8.0 mm below the dura. In two rats the electrodes were lowered but no current was passed. Surgery was performed under 0.33 cc/100 g equithesin anesthesia (a mixture of sodium pentobarbital and chloral hydrate). Behavioral testing of the LH rats commenced from 2–5 days after surgery, because it took several days before some rats regained postural support.

At the end of the experiments the rats were given an overdose of Nembutal and perfused through the heart with saline (0.9%) followed by 10% formalin. For analysis of lat-

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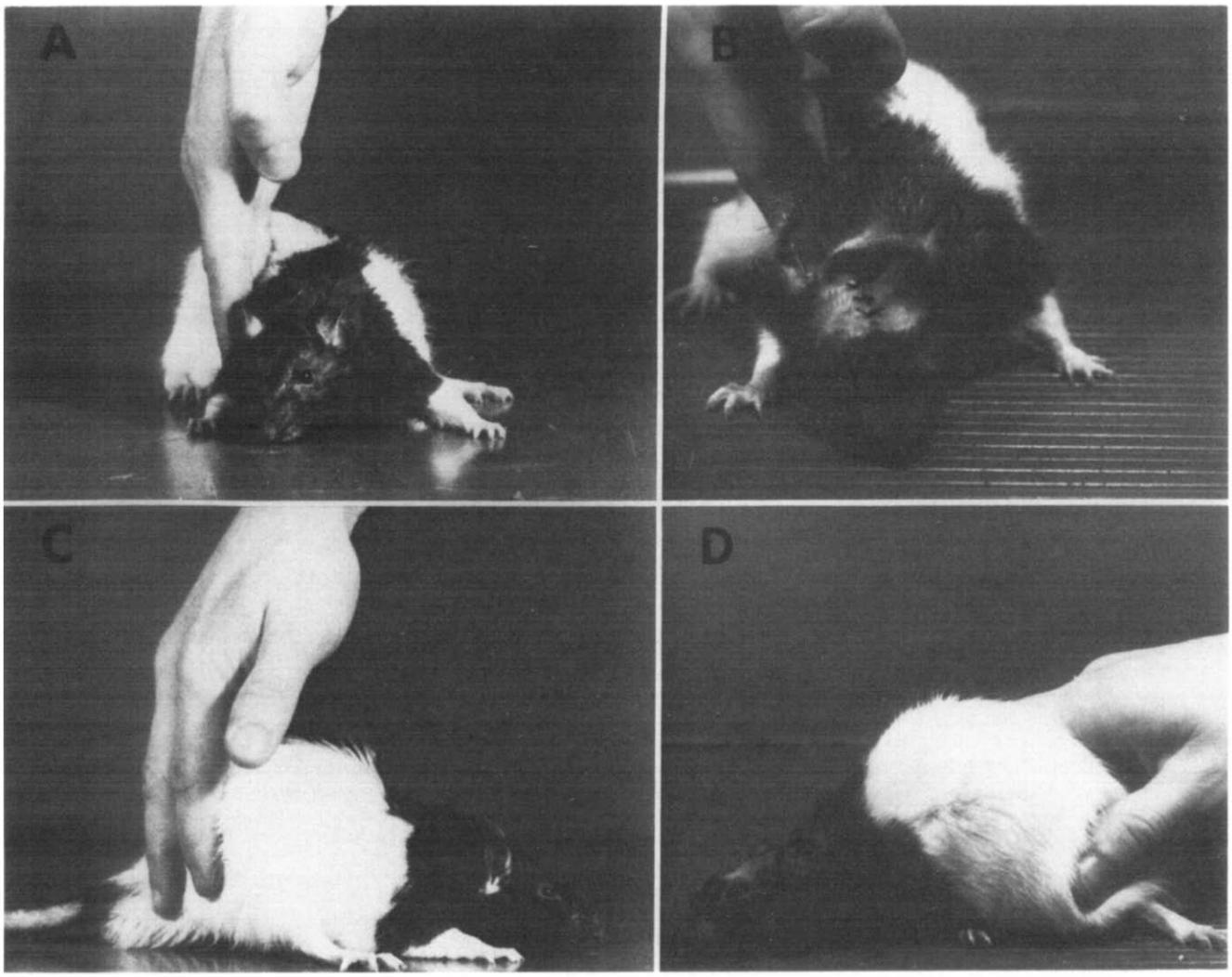

FIG. 1. Bracing responses of haloperidol-treated rats and LH rats when pushed sideward by the flank (A and B, respectively), and when pushed forward by the rump (C and D, respectively). Note the extension of the limbs, shift of the body weight against the displacing force and gripping by the digits, especially of the forepaws. In D the limbs are projecting backwards, showing that they maintained firm paw contact with the ground even though the rat was pushed further forward than could be resisted by forward extension of the limbs. Prior to this the limbs were extended forward as in C.

eral hypothalamic damage, forty-micrometer coronal frozen brain sections were stained with cresyl violet. Tracings of the sections were made with the aid of a Bausch and Lomb projector, and structures were labelled with reference to a brain atlas [11].

Drug Induced Catalepsy

Haloperidol (Haldol, McNeil Laboratories) was used to induce catalepsy in intact rats. Haloperidol was available in 1 ml ampules and was administered intraperitoneally. Six rats were used, 2 were given 1 mg/kg, 2 were given 5.0 mg/kg and 2 were given 7.5 mg/kg haloperidol. Two rats were tested after administration of an equal volume of saline (0.9%), one rat 3 days before haloperidol administration, and the other, 3 days after haloperidol administration.

Behavioral Testing

To test for bracing, the rats were pushed horizontally forward, backward and sideways for up to 1 m at a speed of about 5 cm/sec, and stepping versus maintenance of firm paw contact was assessed (see De Ryck *et al.* [6]; Schallert *et al.* [16]). They were pushed backwards in two ways: (1) by the shoulders, and (2) by the head, leaving the shoulders untouched. Bracing response of the body in response to movements of the head was also tested by pulling the head, and hence body, forward, and by pushing the head laterally while leaving the body untouched. Bracing was tested on a rubber surface to allow the rats to grip the substrate. The bracing responses were recorded on video (Sony Cassette recorder) and on 35 mm still photographs.

RESULTS

When pushed laterally by the flank all the rats resisted being displaced by extending the contralateral limbs against the direction of displacement, by shifting the body weight in

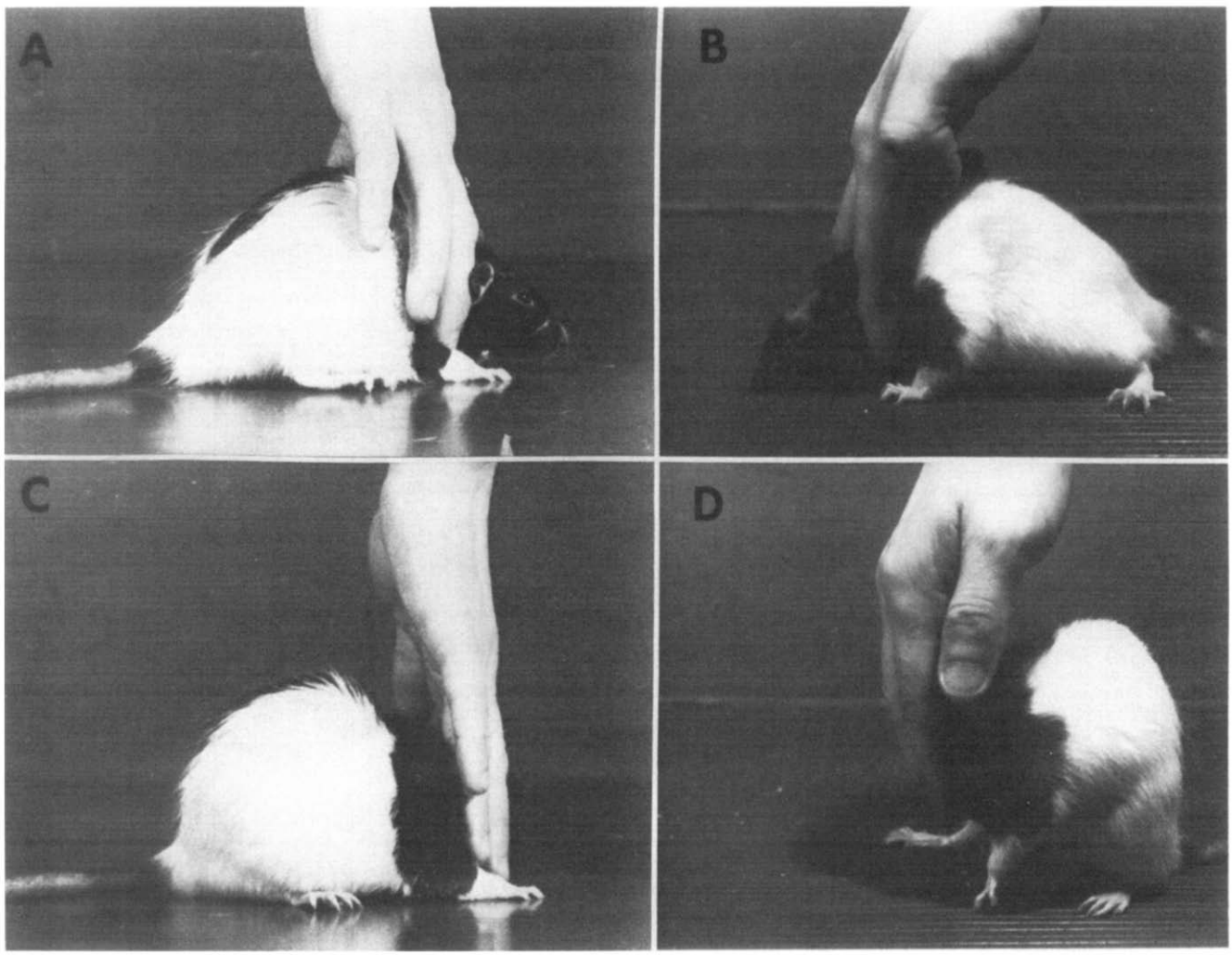

FIG. 2. When pushed backward by the shoulders both haloperidol-treated (A) and LH (B) rats brace against the displacement. When pushed backward by the head the haloperidol-treated rat braces (C), while the LH rat shifts its weight backwards, releasing its grip of the ground with the forepaws (D).

the direction against the displacing force, and by gripping the substrate with the digits (Fig. 1A Haloperidol and B LH). Similarly, when pushed forward by the rump all the rats braced against being displaced forward by extending the limbs forward and pressing on the ground, by pushing the body weight backwards against the displacing force, and by gripping the substrate with the digits (Fig. 1C Haloperidol and D LH).

A difference between haloperidol-treated and LH rats emerged when they were pushed backwards. When pushed backward by the shoulders, both groups of rats resisted being displaced, by gripping with the forepaw digits and pulling the body forward against the displacing force (Fig. 2A Haloperidol and B LH). When pushed backward by the head, the haloperidol-treated rats braced as they did when pushed by the shoulders (Fig. 2A; cf. 2C). In contrast, the LH rats did not brace when pushed backward by the head. Instead, they released their forepaw grip of the ground and shifted their body weight backward, away from the displacing force (Fig. 2D). If they were pushed harder, the LH rats walked backwards, thus shifting their whole body away from the displacing force.

Other forms of imposed head displacements did not result in any differences between haloperidol-treated and LH rats. When the rats were pulled forward by the head, they braced against this by extending their limbs forward and shifting their body weight backward (Fig. 3A Haloperidol and B LH). Pushing the head laterally did not elicit a bracing response (Fig. 4), although some weak resistance by the neck was felt. Therefore, strong bracing responses were only elicited when the body was moved. The two sham operated rats were given 5.0 mg/kg haloperidol 2 days after the operation. They behaved like non-operated haloperidol-treated rats, that is, they braced when pushed in all directions, including when pushed backwards by the head. Therefore, moving backwards rather than bracing in LH rats is not due to

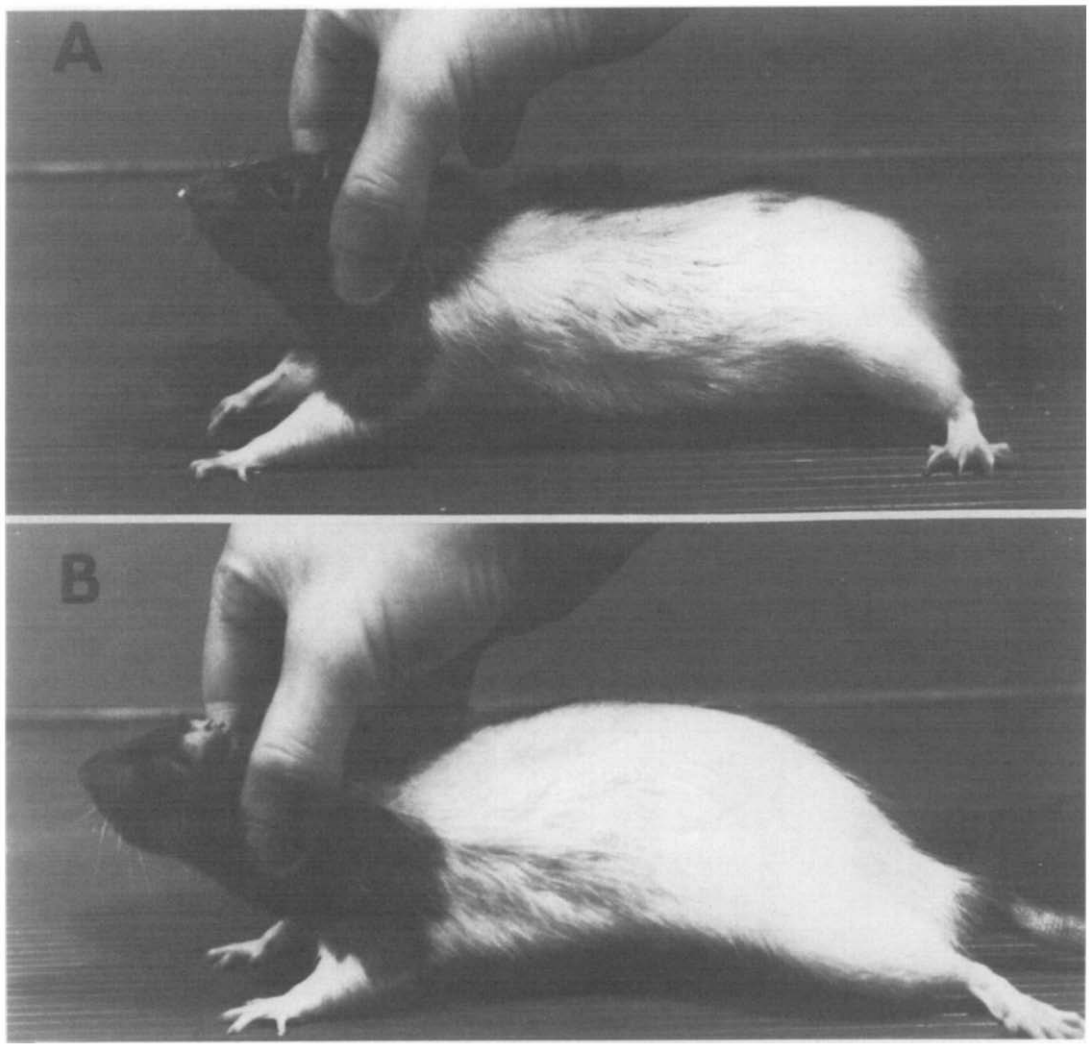

FIG. 3. When pulled forward by the head both haloperidol-treated (A) and LH (B) rats braced against the displacement.

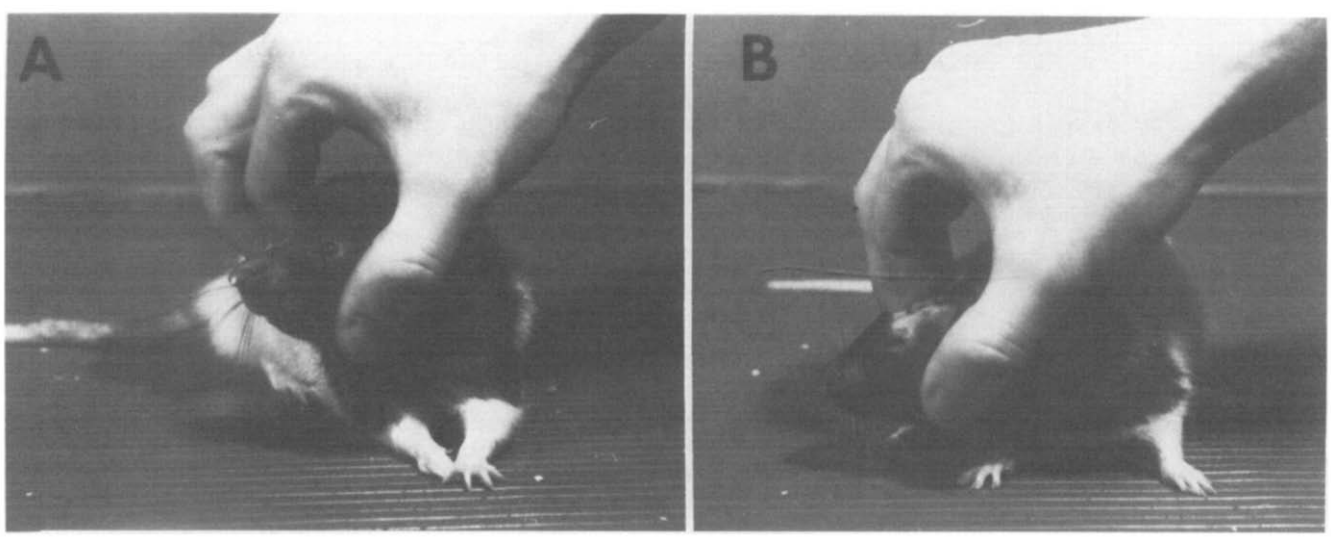

FIG. 4. When the head is pushed sideward it resists a little with the neck muscles, but the head can be bent completely to the opposite side without eliciting a strong bracing response by the body.

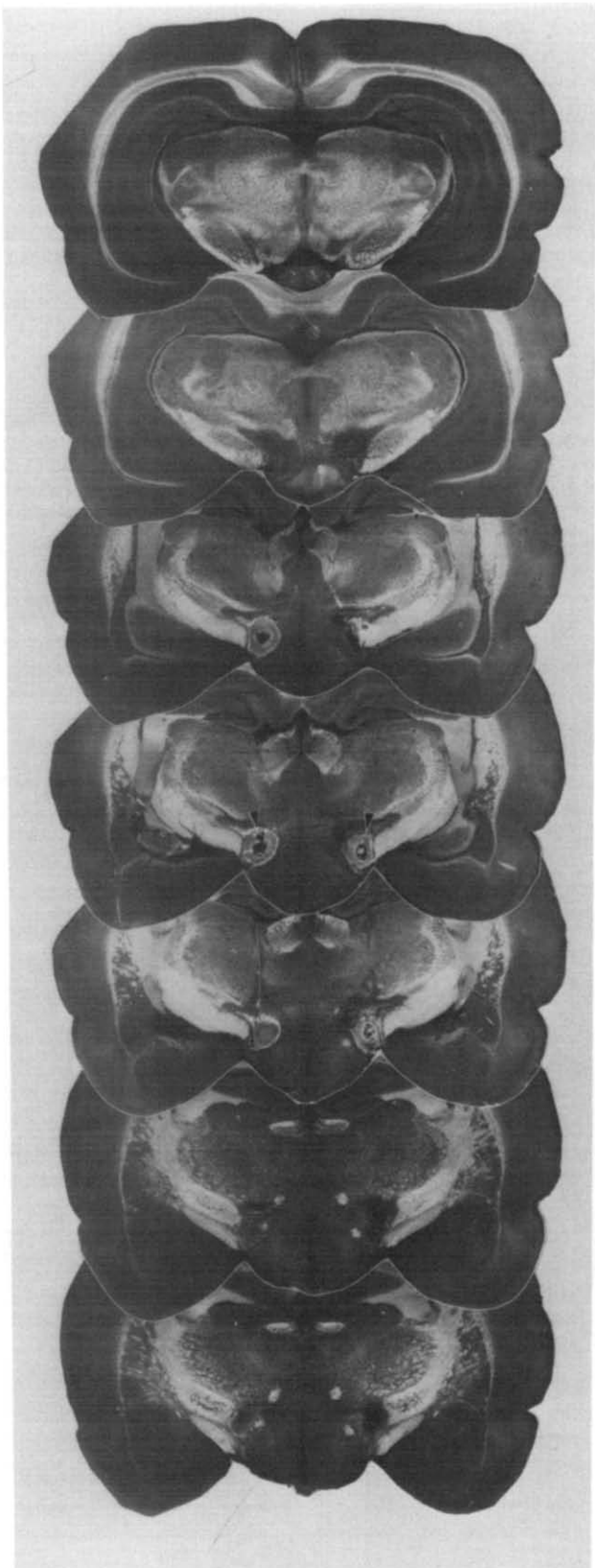

FIG. 5. Successive micrographs showing the damage produced by the LH lesions from anterior (upper photograph) to posterior (bottom photograph) in one rat (No. 414). See text. The width of each original tissue slice was 16 mm.

possible pain induced by pressure on the top of the head in the days immediately following surgery. Similarly, rats with intraventricularly administered 6-OHDA also brace when pushed backwards by the head, even though they have a recent surgical wound on the scalp ([16] and personal observation).

Histological Analysis of LH Lesions

The lesions destroyed the lateral hypothalamus and extended laterally to involve the medial margin of the internal capsule. Most often they encroached upon the zona incerta dorsally and also ventrally toward the dorsal border of the optic tract. Usually the lesions extended as far anteriorly as the supraoptic nucleus and as far posteriorly as the mammillary peduncle and substantia nigra (Fig. 5).

DISCUSSION

When pushed backward by the shoulders, bracing is present in LH rats. When pushed backward by the head, which should be sufficient to elicit the body bracing reflex, and indeed it is in other forms of catalepsy, LH rats retreat backward (Fig. 2D). Therefore, backward pressure on the head clearly triggers a retreating reflex which is incompatible with, and overrides, the bracing that must simultaneously be stimulated.

The difference may be due to the destruction of the descending motor output pathways from the striatum which occurs with large LH lesions, but not with the other forms of dopamine depletion discussed here. For example, apomorphine, a postsynaptic dopamine agonist, releases locomotion in 6-OHDA-treated rats (where only ascending pathways are damaged), but not in rats with LH lesions, where there is also motor outflow destruction [8,9]. Furthermore, some evidence for the release of hindbrain mechanisms by LH partial transection exists. Guzman and Del Pozo [7] showed that decerebration releases a jump reflex in the cat. A similar decerebrate-like jump reflex is released by LH partial transection [18,20]. Methysergide releases different forms of locomotion in akinetic animals, depending on whether the descending pathways have been destroyed. One form of locomotion is released by methysergide in rats made akinetic by intraventricular administration of 6-OHDA, in which the descending pathways are left intact, and another form of locomotion is released by the same drug in rats made akinetic by LH lesions, in which the descending pathways have been destroyed ([2]; Pellis *et al.*, work in progress). Based on these considerations, it would be interesting to know if a decerebrate rat, like a rat with LH partial transection, would also exhibit the head elicited "retreating reflex."

LH rats are shown here to differ from other cataleptic rats in one aspect of bracing. Perhaps other forms of catalepsy differ as well. One should not view bracing as an "act," but as an aggregate of allied reflexes [13]. By testing various parts of the body separately, it should be possible to discover which bracing components are present or absent in particular forms of catalepsy. For example, labyrinthectomized haloperidol-treated rats have weak bracing responses in the forequarters. When pushed sideward by the whole flank, such rats are indistinguishable from intact haloperidol-treated rats. However, when pushed sideward, separately, by the shoulders, and then by the pelvis, the weakened forequarter bracing responses become apparent [12].

Testing the different bodily components of a cataleptic response, such as bracing, may be therefore useful in differential diagnosis of the damage involved in different forms of parkinsonism, as well as in screening the extrapyramidal effects of some antipsychotic drugs.

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