Neuroscience Letters, 82 (1987) 217–220
Elsevier Scientific Publishers Ireland Ltd.

NSL 04940

'Axial apraxia' in labyrinthectomized lateral hypothalamic-damaged rats

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(Received 29 April 1987; Revised version received 29 June 1987; Accepted 20 July 1987)

Key words: Axial apraxia; Lateral hypothalamus; Labyrinthectomy; Rat

Contact righting, that is, turning from a recumbent position to prone, is abolished for a few days after large electrolytic lesions of the lateral hypothalamus. With recovery, contact righting reappears, but does so in a distinct manner. At first the body is righted by backleg movements, in the absence of any active axial rotation. Later, righting switches from back to front, so that righting begins in the shoulders and then proceeds to the pelvis. Such righting is achieved by axial rotation, that is, the limbs are carried by the torso, rather than vice versa. Labyrinthectomy, when combined with lateral hypothalamic (LH) damage, slows this recovery (now taking as long as 3 weeks), and reveals many intermediate stages of contact-righting. The absence of axial rotation in the early stages of recovery from combined LH damage and labyrinthectomy is compared to the 'axial apraxia' seen in some parkinsonian patients.

In a recent series of reports, Lakke et al. [7–10] have shown that some parkinsonian patients have difficulty initiating righting movements when recumbent. Such patients cannot use axial rotation, but instead use the limbs to push or pull the body over [7]. Lakke [7] argues that because axial rotation in these patients *can* occur under appropriate sensory stimulation, or in times of great stress, this disability reflects inability to 'call up' appropriate motor programs. He therefore calls this deficit 'axial apraxia'. Several animal models of Parkinson's disease, in which the ascending nigrostriatal dopaminergic system is disrupted, do not mimic this deficit [18, 19, 21]. Instead, when placed supine on the ground, dopamine-deficient animals right themselves normally, by cephalocaudal axial rotation [3, 16]. Because simple dopamine deficiency is not sufficient to produce the deficit in righting, it is not surprising that the deficit in axial rotation in patients is not ameliorated by L-DOPA therapy [8]. Therefore, although nigrostriatal dopamine depletion constitutes a major component of Parkinson's disease, [1, 5], additional degeneration of other non-dopaminergic neural systems must be involved, especially in the later phases of the disease. In order to investigate those additional systems it would be useful to provide an animal analogue of parkinsonian axial apraxia.

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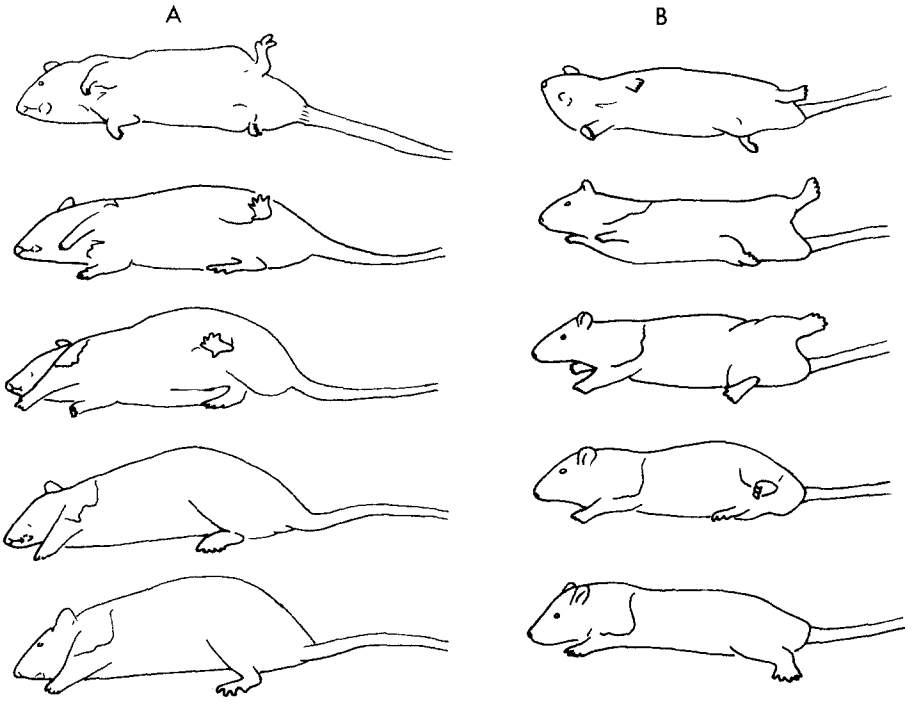

Fig. 1. A: when righting first reappears in the LH-damaged rat, it is caudorostral, not rostrocaudal. The backlegs are used to flip the pelvis to prone. The hindleg on the side that is in contact with the ground flexes and is placed beneath the pelvis. After the sole of the foot contacts the ground, the leg is extended, pushing the pelvis passively to prone, which in turn twists the anterior body to prone. In this form of righting the body is turned to prone without active axial rotation in either the pelvis or the shoulder girdle. B: when fully recovered, the rat rights normally; that is, by first rotating the shoulders to prone, and then rotating the posterior of the body to prone. Note that the body is righted by active axial rotation of both the shoulder girdle and pelvis, the legs merely being carried along. The drawings were traced from a 16-mm movie film exposed at 24 and 32 frames/s, respectively.

In the present paper, a total of 16 animals with electrolytic lesions in the region of the lateral hypothalamus (LH) were used. They sustained damage not only to the ascending dopaminergic systems (e.g. refs. 12, 14, 19), but to other systems as well. The lesions, at their maximum extent, typically extended medially to include the fornix, the lateral border of the ventromedial nucleus, and some of the dorsomedial nucleus; laterally they involved the medial margin of the internal capsule, often encroaching upon the zona incerta dorsally and towards the dorsal border of the optic tract. Usually the damage extended as far anteriorly as the supraoptic nucleus nucleus and as far posteriorly as the mammillary peduncle and the substantia nigra. Further histological details for the rats discussed here will be presented elsewhere [17], and other details regarding location and method have been previously published [2, 15]. In the first 3–4 days after large LH lesions, when placed supine or on their side on the ground rats do not right themselves normally by cephalocaudal axial rotation. Instead, they right themselves by using the hindlegs to push the hind-

quarters over, followed by the forequarters (Fig. 1A). When dropped supine in the air, however, such rats right normally, by cephalocaudal rotation. In other words, the activation provided by falling induces normal righting. Therefore, their loss of axial rotation during righting on the ground appears to be analogous to the axial apraxia observed in some parkinsonian patients [7]. Gradually axial rotation reappears, first in the pelvis, and then later the rat once again rights by cephalocaudal rotation, commencing in the shoulders (Fig. 1B). This deficit in axial rotation, in the early stages of recovery, was found in all of the 8 LH-damaged rats, but not in the 2 sham-operated animals.

Some patients with advanced parkinsonism appear to have central vestibular deficits [13]. They show reduction or absence of compensatory movements when sitting or kneeling on a tilting platform [13]. We therefore either chemically [4, 6] or surgically [2] damaged the labyrinths in 8 LH-damaged rats [2, 15] to see whether this might exaggerate the defects in contact-righting (two rats were first subjected to LH damage and then 2 days later were labyrinthectomized, while the remaining 6 were first labyrinthectomized and then about 5 days later the LH was bilaterally damaged). Whether labyrinthectomy was performed before or after LH damage, recovery of normal contact-righting was greatly slowed down: instead of a mean of 3.5 days (range = 2–9), recovery required a mean of 11.8 days (range = 5–21) (significant at $P < 0.001$ level based on the Mann–Whitney U-test). (Labyrinthectomy without LH damage did not disrupt axial rotation.) The slow recovery in the labyrinthectomized LH-damaged rats revealed several intermediate subcomponent forms of righting involved in the reinstatement of axial rotation. For example, when axial rotation first reappeared in the shoulders, it did so only after the foreleg on the side in contact with the ground made a placing reaction, so that the palm of the paw contacted the ground, apparently triggering the axial rotation. With further recovery, shoulder rotation occurred independently of such forepaw placing, and thus appeared the same as that of intact rats (e.g. as shown in Fig. 1B). These intermediate subcomponents of righting will be described in more detail elsewhere [17]. Furthermore, because contact-righting recovers quickly after LH-damage with labyrinths intact, but with labyrinthectomy such recovery is greatly delayed, it is clear that LH damage produces major deficits in the proprioceptive/tactile control over righting, which are compensated for early in recovery by the vestibular system. Vestibular activation integrates the cephalocaudal gradient of axial rotation in righting on the ground, thus overcoming the deficit in its proprioceptive-tactile activation. These data support the view that the basal ganglia are involved in sensorimotor integration, particularly of somatosensory and vestibular inputs (for review see ref. 11). Finally, our observations indicate that the LH-damaged animal when subjected in addition to labyrinthectomy may mimic some of the later stages of advanced Parkinson's disease*. In particular the labyrinthectomized LH-damaged rat may provide a useful animal analogue for the exploration of the mechanisms underlying parkinsonian axial apraxia.

*Strictly speaking, this animal model, like all others now available, does not mimic the progessive deterioration of Parkinson's disease. Indeed, after damage, recovery occurs. We assume that a sequence opposite to that seen in recovery would be mimicked by progressive deterioration, but ideally this should be tested directly.

We thank Gerri Lennon for typing the manuscript. The work was supported by National Institutes of Health Grant R01 NS11671, a University of Illinois Research Board Award to P.T., and a University of Florida Division of Sponsored Research Award to P.T. and S.P.

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