AN EXPERIMENTAL VESTIBULOPATHY PRODUCED BY FORMATION OF A PATHOLOGICALLY ENHANCED EXCITATION GENERATOR IN THE VESTIBULAR NUCLEUS (THE DETERMINANT DISPATCH STATION PHENOMENON)

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The possibility of formation of a pathologically enhanced excitation generator in the vestibular nucleus of the medulla through a disturbance of inhibition in that nucleus was demonstrated and, as a result, the animals developed rotatory movements toward the opposite side. Experimental electrical stimulation or coagulation of the lateral vestibular nucleus showed that the pathologically enhanced excitation generator is based on a system of vestibular neurons which organizes a synchronous volley along the vestibulo-spinal tracts. It is concluded that the pathologically enhanced excitation generator formed in the lateral vestibular nucleus as a result of disturbance of inhibition lies at the basis of the hyperactive determinant dispatch station responsible for the syndrome of vestibulopathy.

KEY WORDS: determinant dispatch station; vestibular system; lateral vestibular nucleus; pathologically enhanced excitation generator; tetanus toxin.

The principle of the determinant dispatch station (DDS) [2, 3] with respect to CNS pathology assumes that pathologically enhanced excitation generators (PEEGs) can be formed in various parts of the nervous system through a disturbance of their inhibitory mechanisms [2, 4, 5, 10]. Hyperactive DDSs based on PEEGs convert a physiological system into pathological and induce the development of corresponding neuropathological syndromes [4, 6, 7, 11].

This paper describes an attempt to create a PEEG in the vestibular nucleus of the medulla and thereby to produce an experimental vestibulopathy.

EXPERIMENTAL METHOD

Experiments were carried out on 200 male albino rats weighing 250-300 g. Tetanus toxin (TT) was used to form a long-term local disturbance of inhibition [9, 12, 15]. Under superficial hexobarbital anesthesia TT (dose 5-10 mouse MLD) was injected into the lateral vestibular nucleus (LVN) corresponding to stereotaxic coordinates P 10, L 2, and H 7 [13]. TT was injected in a dose of $5 \cdot 10^{-4}$ ml by means of a glass micropipet (diameter 50 μ) glued to a Nichrome electrode (diameter 100 μ), insulated except at the tip. The Nichrome electrode was fixed in the animal's brain and was used for electrical stimulation of LVN and for coagulation with subsequent morphological verification of the site of TT injection. The animals' behavior was recorded on motion pictures.

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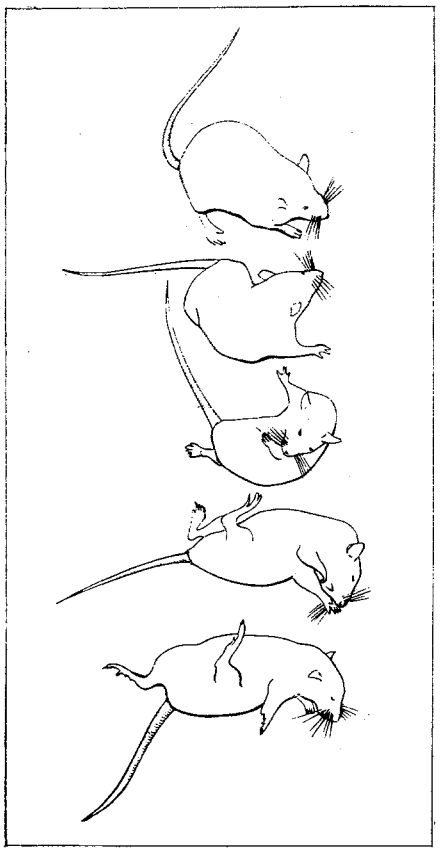

Fig. 1

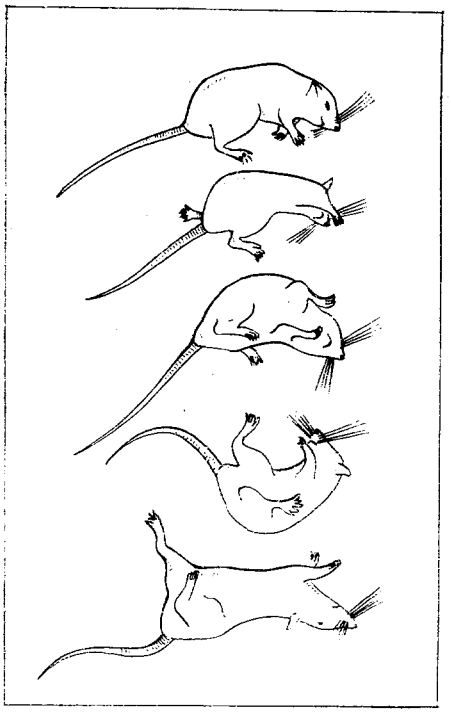

Fig. 2

Fig. 1. Rotatory movement after injection of TT into left LVN. Rotatory movement starts with tic-like motion of animal's head ipsilaterally and upward, and this is followed by rotation of the trunk toward the contralateral side.

Fig. 2. Rolling-over movement after destruction of left LVN. Destruction of LVN evokes a long disturbance of the animal's posture: animal lies on ipsilateral side. Under these conditions locomotion evokes rolling over to the opposite side.

EXPERIMENTAL RESULTS AND DISCUSSION

Injection of TT into LVN. TT was injected into the LVN of 145 animals. The animals developed tic-like movements of the head toward the side of injection and upward 3-4 h after the microinjection. From 5 to 6 h after the tic-like movements, the animal turned completely around the long axis of the trunk in the contralateral direction. The successive phases of the animal's rotatory movement after injection of TT into the left LVN are illustrated in Fig. 1. Initially the rotatory movements were evoked only by specific vestibular stimulation (rotation of the cage, shaking the animal's head, etc.); they were performed slowly, and the animal turned over once or twice during one bout of movement. At this stage, in the period between movements the animal showed no pathological features, its orientation in space was normal, and it moved about freely. In the later stages rotatory movements were evoked by various stimuli, the animal turned over from five to seven times during each bout of movements, and it turned over faster. In the terminal stage the animal performed rotatory movements virtually continuously.

Electrical Stimulation of LVN. Rotatory movements similar to those described above were evoked in 15 intact animals by electrical stimulation of LVN. A single electric pulse applied to LVN evoked a tic-like movement of the animal's head upward and toward the side of stimulation similar to that developing in the first stages of the vestibular syndrome following injection of TT into LVN. Stimulation of LVN by a series of pulses evoked a complete rotatory movement, and the turning speed depended on the frequency and strength of electrical stimulation. Application of a series of pulses (100/sec, 100 μA) to LVN in the course of 1 sec evoked a rotatory movement in the animals like the movement in the late stages of the pathological process after injection of TT into LVN.

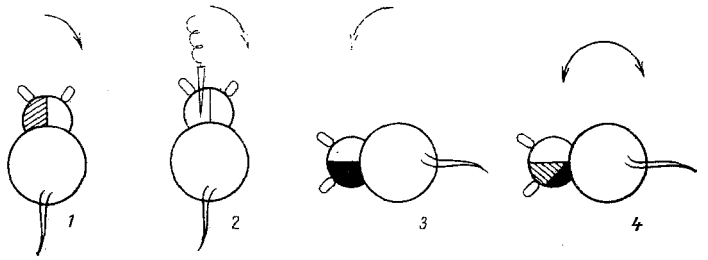

Fig. 3. Direction of rotatory movements under various experimental conditions: 1) rotatory movement after injection of TT into left LVN; 2) rotatory movement evoked by electrical stimulation of left LVN of intact animal; 3) rolling-over movement and disturbance of posture after destruction of left LVN: 4) rolling-over movement, disturbance of posture, and rotatory movement after partial destruction of left LVN into which TT had previously been injected. Arrows indicate direction of rotation of trunk around long axis.

Electrical Stimulation of LVN after Injection of TT into the Nucleus. An electrical stimulation of LVN after the formation of a PEEG in the same nucleus (15 animals) considerably lowered the threshold of electrical stimulation required to evoke rotatory movements. A single pulse, which in the intact animal evoked only a slight movement of the head, produced a full rotatory movement 1.5-2 h after microinjection of TT. During development of the syndrome, progressively weaker single electrical stimulation LVM was required to evoke rotatory movements.

Destruction of LVN. In 25 intact animals LVN was destroyed by the action of the anode of a dc with a strength of 5 mA for 10 sec. The effects of destruction of LVN appeared immediately after injury: The animal lay on the affected side and its head and trunk were turned toward the same side. In the absence of external obstacles, the attempt to move gave rise to continuous movements of rolling over to the ipsilateral side. The successive phases of the rolling-over movement of the animal after destruction of the left LVN are illustrated in Fig. 2. In animals with the vestibulopathy produced by injection of TT into LVN, coagulation of that nucleus evoked the disturbance of posture and rolling-over movement to the ipsilateral side described above, but in this case the rotatory movements to the contralateral side caused by the PEEG in the remaining part of the injured nucleus were preserved. To abolish the rotatory movements completely, considerable destruction of LVN by coagulation with a current of 5 mA acting for 60-80 sec was required.

Injection of TT into LVN thus evoked the appearance of a specific vestibular syndrome. There is reason to suppose that TT disturbs inhibition in LVN in the same way that it does in other parts of the CNS [2, 3, 5-7, 9, 11]. In the system of vestibular nuclei, the target for the action of TT may be several inhibitory systems: the system for contralateral inhibition of vestibular neurons [1, 19, 21], the system of inhibitory connections of the Purkinje cells of the anterior and posterior lobes of the cerebellum with secondary vestibular neurons [14, 18], and the system of inhibitory connections of the interstitial nucleus of Cajal with vestibular neurons [16, 17]. Disturbance of the balance of activity of the vestibular nuclei on the two sides, caused by the formation of a PEEG in one nucleus, probably is responsible for the picture of the experimental vestibulopathy observed. The formation of a PEEG in LVN gives rise to forced paroxysmal rotatory movements toward the contralateral side (Fig. 3, 1). Similar movements could be obtained in the intact animal by electrical stimulation of LVN (Fig. 3, 2). In these experiments the speed, number, and frequency of the rotatory movements depended directly on the intensity of electrical stimulation of LVN. In response to strong electrical stimulation, the animal performed a rotatory movement identical in all respects with the rotatory movement at the height of development of the vestibulopathy evoked by injection of TT into LVN. Comparison of these experimental data indicates that the PEEG in LVN during paroxysmal rotatory movements formed a synchronous volley of impulses traveling along the vestibulo-spinal tracts.

The difference will be noted in the character of the rotatory movements caused by operation of the PEEG in LVN and the character of the rolling-over movements produced by destruction of LVN (Fig. 3, 3). In the first, the movement was paroxysmal and phasic in character and between bouts the animal showed no pathological features. By contrast, after destruction of LVN the disturbance of posture was tonic in character and, as Magnus [8] pointed out, the rolling-over movement after unilateral extirpation of the labyrinths

is a distinctive locomotor act performed against the background of a postural disturbance. Probably after the formation of a PEEG in LVN, the decisive role in the organization of rotatory movements is played by secondary kinetic vestibular neurons [20, 22], whereas the disturbance of posture after destruction of LVN is due to a disturbance of the balance of activity between secondary tonic vestibular neurons. The existence of two largely independent vestibular systems (tonic and kinetic) is illustrated by the experiments with destruction of the LVN in which a PEEG had first been created (Fig. 3, 4). In those animals a postural disturbance and rolling-over movements toward the ipsilateral side evoked by destruction of the nucleus were observed together with rotatory movements toward the contralateral side caused by the activity of the PEEG in the residual part of the vestibular nucleus. Only after considerable destruction of an LVN in which a PEEG had been created were the rotatory movements brought to an end. This fact indicates that for a PEEG to operate in LVN, only a few of the component units of the nucleus are necessary.

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