7. A. Janoff and B. W. Zweifach, Proc. Soc. Exp. Biol. (New York), 114, 695 (1963).
8. E. Mari and E. Rizzatti, cited by H. Selye, The Mast Cells, Butterworths, Washington (1965).
9. H. Selye, The Mast Cells Butterworths, Washington (1965).
10. D. E. Smith and Y. S. Lewis, Proc. Soc. Exp. Biol. (New York), 87, 515 (1954).
11. G. Weissmann and L. J. Thomas, J. Exp. Med., 116, 433 (1962).

COMPARISON OF CONTRALATERAL AND IPSILATERAL ROTATORY RESPONSES TO ELECTRICAL STIMULATION OF THE CAUDATE NUCLEUS IN CATS

É. B. Arushanyan and A. A. Dutov

UDC 612.626.5.014.424

High-frequency stimulation of the caudate nucleus evoked two types of rotatory movements of the head and trunk in freely moving cats: in the contralateral and ipsilateral directions. Contralateral rotations (CR) were evoked from a wider area, mainly from the dorso-medio-central zones of the head of the nucleus. Conversely, ipsilateral rotations were evoked from the ventrolateral zone, they more often contained a tonic component, their amplitude was greater, and their senstivity to L-dopa and chlorpromazine was less. Unilateral injury to the region evoking CR led to ipsilateral asymmetry of posture. When this asymmetry disappeared, injection of L-dopa or apomorphine easily evoked circular movements in the same direction. Removal of zones acting as the source of ipsilateral responses gave the opposite result.

KEY WORDS: caudate nucleus; L-dopa; apomorphine.

According to some workers [6, 9, 10] the striatum may be the primary source of extrapyramidal disorders of the torsion dystonia type. However, attempts to treat such diseases by drugs both potentiating (neuroleptics) and weakening (dopaminomimetics) striatal activity have not given unequivocal results [2, 3, 8], possibly because of the existence of functionally different zones in the caudate nucleus, with different roles in the genesis of rotatory movements and with different sensitivity to the action of drugs.

Electrical stimulation of the caudate nucleus and injection of dopamine into the nucleus in fact evoked two types of rotatory movements. They may be either contralateral or ipsilateral in direction [1, 4, 5].

The object of this investigation was to compare the two responses evoked in cats by stimulation and injury of the caudate nucleus.

EXPERIMENTAL METHOD

Experiments were carried on 34 freely moving cats of both sexes weighing 2-3.6 kg. In the experiments of series I (18 animals) rotatory responses were evoked by electrical stimulation (square pulses, frequency 30 Hz, duration 0.5 msec, duration of stimulation 10 sec) of different zones of the head of the caudate nucleus through previously implanted bipolar nichrome electrodes (thickness of tip 0.1 mm, distance between electrodes 0.5-1 mm). In the experiments of series II (16 cats) electrolytic destruction (dc, 2-4 mA, 3-5 applications for 20 sec each time, at intervals of 1 min, nichrome electrodes 0.3 mm thick) of a definite zone of one of the nuclei was carried out. Rotatory movements in a circle were evoked in these animals by means of dopaminomimetics – apomorphine (1-5 mg/kg) and L-dopa (50 and 100 mg/kg) – injected intraperitoneally 20-30 min before the investigation began. The speed and number of the movements were recorded after 30 min.

In some experiments with electrical stimulation of the caudate nucleus, after control determination of the thresholds of the rotatory responses the animals were given an injection of L-dopa (50 and 100 mg/kg) or chlorpromazine (1 and 5 mg/kg).

Department of Pharmacology, Medical Institute, Chita. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 85, No. 2, pp. 142-145, February, 1978. Original article submitted April 6, 1977.

 0007-4888/78/8502-0132 $07.50

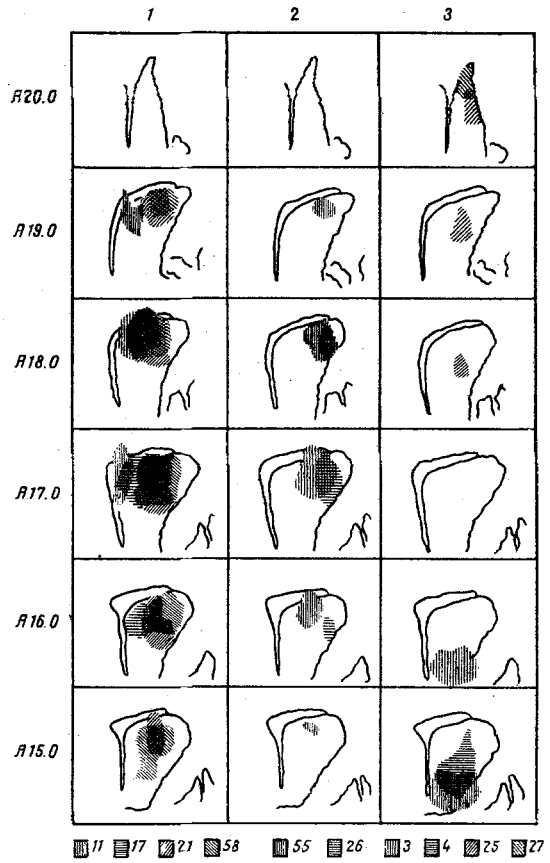

Fig. 1. Effect of injury to different zones of caudate nucleus on direction of spontaneous rotatory movements in the early periods after caudatectomy. Location of zones of brain destruction leading to IR (1), not evoking rotation (2), and evoking CR (3) shown in frontal sections (A 20.0-A 15.0 according to Snider and Niemer's atlas). Numbers below are serial numbers of cats with most characteristic foci of destruction (zone of injury is shaded individually for each animal).

The experiments on each animal lasted from 3 weeks to 1.5 months. After the end of the experiments, the location of the stimulating electrodes and the volume and area of injury were determined in a series of frontal brain sections.

EXPERIMENTAL RESULTS

Effects of Stimulation. In response to high-frequency stimulation of the caudate nucleus two types of rotatory movements developed: rotation of the head and trunk in the direction opposite to stimulation – contralateral rotation (CR) or contraversive movements, to use Hassler's terminology [7] – or rotation in the ipsilateral direction (IR) (ipsiversive movement).

In a previous paper [1] the authors drew attention to differences between the two types of responses. First, their outward appearance is different. The CR usually has the character of a natural motor act; moreover, with an increase in the strength of stimulation, isolated rotation is often replaced by coordinated movements in a circle. In the case of IR tonic rotation of the head and limbs toward the direction of stimulation were most frequently observed, without any transition into stereotyped stepping movements. Second, the two types of rotatory responses were evoked from different zones of the caudate nucleus; CR mainly from the dorso-medio-central and IR from the rostro-ventro-lateral zones. These zones are close, but not absolutely identical, with the regions distinguished by Cools [4] in the caudate nucleus.

TABLE 1. Effect of L-dopa and Chlorpromazine on Thresholds of Different Types of Rotatory Responses

Type of rotation	n	Control	L-dopa, mg/kg		n	Control	Chlorpromazine, mg/kg	
			50	100			1	5
Contralateral	47	3,5±0,1	4,8±0,5	5,8±0,6	38	4±0,12	3,5±0,14	3,5±0 1
Ipsilateral	14	3,2±0,18	2,8±0,2	2,7±0,2	10	2,3±0,12	2,4±0,21*	2,1±0,2*

Legend. n) Number of points of caudate nucleus tested.
*$P < 0.05$ compared with control.

Other differences between the two types of electrically evoked responses were as follows. The CR were the more widespread form of rotatory movements and were easily evoked by stimulation of the greater part of the head and body of the nucleus (CR/IR was 8:1).

On the whole IR were a more generalized and stronger response. They were evoked, for example, by stimulation of lower intensity (mean threshold 2.7 ± 0.11 V, compared with 4 ± 0.06 V for CR). During simultaneous stimulation of two points within the same nucleus, which gave rise to rotation in different directions, only IR were always observed. To abolish IR the strength of stimulation of the competing zone had to be increased by 1.2-1.7 times. Preliminary stimulation of the IR zone inhibited CR for a few minutes, whereas preliminary stimulation of the CR zone had no after-effect.

The rotatory movements in the two different directions also differed in their sensitivity to substances modulating monoaminergic transmission (Table 1). L-dopa, a stimulator of dopaminergic receptors, which in most cases raises the thresholds of CR, at the same time facilitated IR development a little. Under the influence of the adrenolytic and dopaminolytic drug chlorpromazine, the opposite effect was observed. If the changes in the thresholds are compared it will be noted that CR had higher sensitivity to both effects (Table 1).

Effects of Injury. In the early stages (1-2 days after the operation) unilateral injury to the caudate nucleus in most cases (in 14 of 16 animals) led to the development of postural asymmetry. The cat's head, and sometimes its trunk, were turned to one side. When excited for locomotion, the animals began to move in the same direction in a circle. The direction of rotation depended on the location of injury. The predominant type of motor disorder (62% of cases) was ipsilateral asymmetry (rotation to the side of the destroyed nucleus). Histological investigations showed that this asymmetry was mainly connected with destruction of the dorso-medio-central zones of the head, i.e., the region from which CR were easily evoked. Conversely, the less frequent (25% of cases) contralateral asymmetry was the result of destruction of the rostro-ventro-lateral zone – the source of IR. Destruction of the dorso-lateral zones (13%) more often was ineffective (Fig. 1).

Postural asymmetry in most animals (13 to 16) virtually disappeared 7-10 days after the operation. However, it reappeared after injection of the dopaminomimetics L-dopa or apomorphine. Neither drug evoked tonic rotation of the head and trunk in the cats, but neither did they evoke continuous walking in a circle. For several hours of the experiment the direction of movement could change, but nevertheless the preference for one particular direction was evident. It depended on the site of injury and coincided with the direction of spontaneous asymmetry. The results of these observations thus confirm the existence in the caudate nucleus of antagonistic zones, competition between which can take place within one nucleus. On the other hand, as the experiments with unilateral injury to the caudate nucleus show, the direction of rotation is largely determined by intercaudate relationships. This is confirmed by results obtained during stimulation of the caudate nucleus in animals previously undergoing contralateral caudatectomy.

After destruction of the dorso-medio-central zones of the head, the thresholds of CR from the opposite nucleus were considerably reduced. The degree of decrease was proportional to the volume of destruction. The localization of the injury also played a role: In the case of isolated blocking of the CR zone of the other nucleus the shift was clearer than after combined (even allowing for the more extensive volume) blocking of zones responsible for the two types of rotatory responses. Conversely, after injury to the rostro-ventro-lateral zones of the nucleus the thresholds of CR were distinctly increased.

Consequently, not only do zones with opposite function exist in the caudate nucleus, during stimulation of which contraversive and ipsiversive movements arise, but these responses also differ qualitatively from each other. It is reasonable to suppose that regions of the nucleus responsible for rotation in different directions may be differently implicated in the pathological process. This could also be connected with the variability and unequal severity of the symptoms of torsion dystonia, and also differences in its response to pharmacotherapy.

LITERATURE CITED

1. É. B. Arushanyan and A. A. Dutov, Fiziol. Zh. SSSR, 62, 658 (1977).
2. P. V. Mel'nichuk and L. S. Sosnovskaya, Zh. Nevropatol. Psikhiatr., 73, 1495 (1973).
3. A. Barbeau, Cand. Med. Assoc. J., 103, 824 (1970).
4. A. R. Cools, Brain Res., 58, 437 (1973).
5. A. R. Cools and J. M. Van Rossum, Arch. Int. Pharmacodyn., 187, 163 (1970).
6. I. S. Cooper, J. Neurol. Sci., 2, 520 (1965).
7. R. Hassler, Arch. Psychiatr., 194, 456 (1956).
8. S. Mandel, Neurology, 20, 103 (1970).
9. H. Richter, Arch. Psychiatr. Nervenkr., 67, 226 (1923).
10. W. Zeman, Neurology, 20, 79 (1970).

ANALGESIA CAUSED BY AN EXCITATION GENERATOR FORMED IN THE MESENCEPHALON

G. N. Kryzhanovskii* and S. I. Igon'kina

UDC 612.884-06:612.826.4

In experiments on albino rats an excitation generator was formed with tetanus toxin in the dorsal nucleus of the midbrain raphe. The formation of an excitation generator in this nucleus was shown to produce general analgesia manifested against physiological (nociceptive stimulation) and central pathological pain (a pain syndrome of spinal origin). It is concluded that prolonged analgesia arising during activation of certain brain structures is due to the appearance of excitation generators in them, which cause prolonged activation of those structures.

KEY WORDS: dorsal nucleus of the midbrain raphe; excitation generator; pain syndrome of spinal origin; analgesia; tetanus toxin.

Recent investigations have shown that electrical stimulation of the gray matter near the aqueduct, the dorsal nucleus of the midbrain raphe, and certain other brain structures produces analgesia against both nociceptive stimulation and pathological pain [1, 2, 13-16, 19]. The analgesic effect is characterized by gradual development [16] and long persistence (sometimes for several hours) after the end of stimulation [13, 15]. This course of the analgesia sugested [2, 3] that it is due to the formation of an excitation generator in these structures during their electrical stimulation. Model experiments have shown that the pain syndromes of central origin are based on the formation of generators of pathologically enhanced excitation (GPEE) in the corresponding regions of the nociceptive system [3, 5-7]. The pain syndrome of spinal origin has been produced by the formation of a GPEE in the posterior horns of the spinal cord [5], a trigeminal syndrome by its formation in the caudal nucleus of the trigeminal nerve [7], and a thalamic syndrome by its formation in the intralaminar nuclei of the thalamus [6]. On the basis of these investigations the theory of the generator mechanisms of central pain syndromes was formulated [3]. In the investigations mentioned above the GPEE was formed by means of tetanus toxin (TT), which disturbs various types of inhibition [4, 8, 10, 11].

In the present investigation TT also was used to produce a GPEE, this time in the mesencephalic nuclei (the dorsal nucleus raphe), in order to obtain prolonged effects of analgesia against physiological and pathological pain.

EXPERIMENTAL METHOD

Experiments were carried out on 45 albino rats weighing 300 g. To form a GPEE in the dorsal nucleus raphe, purified TT was injected stereotaxically by means of a microinjector, in a volume of $1.5 \cdot 10^{-4}$ ml and a

*Corresponding Member of the Academy of Medical Sciences of the USSR.

Laboratory of General Pathology of the Nervous System, Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow.

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 85, No. 2, pp. 145-148, February, 1977. Original article submitted June 10, 1977.