INTERHEMISPHERIC ASYMMETRY OF THE NIGROSTRIATAL SYSTEM IN RATS GENETICALLY PREDISPOSED TO CATALEPSY

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There is experimental and clinical evidence of anatomical, neurochemical, and functional asymmetry of the grain in man and animals. Much of the neurochemical data relates to interhemispheric asymmetry of dopamine and its metabolites and receptors, and also asymmetry of structures of the striatopallidal and nigrostriate systems of the brain [1, 15, 16]. A connection has been established between the direction of rotation and spatial preference of movement, on the one hand, and the content of dopamine and its metabolites and receptors and asymmetry in the dopaminergic nigrostriate system, on the other hand [1, 8, 15, 16]. The modulators of this system are evidently acetylcholine and serotonin [9]. The effect of genotype [7] on neurochemical asymmetry has received far less study, and the role of reversal of asymmetry in inherited disturbances of behavior is completely unknown. There has been only one investigation [12] which showed that a genetically linked predisposition to catalepsy is accompanied by predominance of animals in which the content of dopamine, serotonin, and their metabolites is higher in the left hemisphere, although no evidence of locomotor lateralization has been found in them [10].

The aim of this investigation was to continue the study of interhemispheric asymmetry at the neurochemical level and to discover whether anatomical asymmetry in the caudate nucleus, substantia nigra, and nucleus accumbens exists in rats genetically predisposed to catalepsy (GC). These structures have attracted particular attention because the development of catalepsy has been linked with a disturbance of the serotoninergic [3] and dopaminergic [10] innervation in them and, at the same time, their involvement in spatial preference is not disputed.

METHODS

Experiments were carried out on male GC rats aged 2-3 months, weighing 200-250 g, and bred from a noninbred population of Wistar rats. The GC rats exhibited marked predisposition toward the development of catalepsy, and maintained an enforced posture for at least 20 sec [11]. Wistar rats of the same age and sex served as the control. Activity of choline acetyltransferase (CAT) [6] and acetylcholinesterase (ACE) was determined radiometrically [13] and aminopeptidase activity spectrophotometrically [14] in light and heavy synaptosomes from the sensomotor cortex and caudate nucleus of the left and right cerebral hemispheres of the decapitated rats. This last enzyme also was determined histochemically in cryostat sections in the cytoplasm and processes of neurons in layers III and V of the cortex and caudate nucleus by the simultaneous azo-coupling method. Morphological investigations were carried out on paraffin sections 7 μ thick by the method described previously [2] in n. accumbens and s. nigra. The level of asymmetry for all parameters of the GC rats was estimated as the difference between percentages of symmetry for the control and

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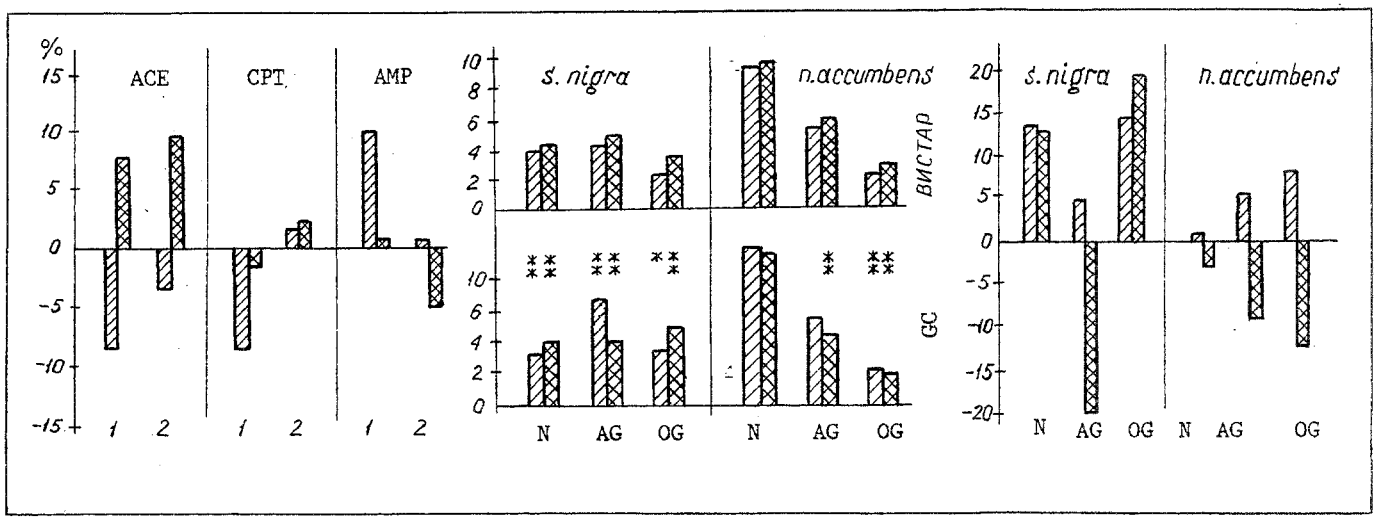

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Skewness for enzyme activity (in %) in caudate nucleus of rats genetically predisposed to catalepsy (GC) and in control Wistar rats. ACE) Acetylcholine; CAT) choline acetyltransferase; AMP) aminopeptidase; 1) light synaptosomes; 2) heavy synaptosomes.

Fig. 2. Number of cells (per unit area of nucleus) in s. nigra and n. accumbens in left and right cerebral hemispheres of rats genetically predisposed to catalepsy (GC) and in control Wistar rats (M $\pm$ m). N) Neurons; AG) astroglia; OG) oligodendroglia. All parameters of right hemisphere differ significantly ($p < 0.05$) from left, except number of neurons in n. accumbens of Wistar rats. Significant (*$p < 0.05$, **$p < 0.001$) from Wistar rats in right and left cerebral hemispheres.

Fig. 3. Skewness of number of neurons and quantity of perineuronal glia (in %) in s. nigra and n. accumbens of rats genetically predisposed to catalepsy (GC) and in control Wistar rats. Legend as to Fig. 2.

experimental animals. The degree of asymmetry of each parameter (A) was calculated by the equation [5]:

RESULTS

Activity of ACE, the enzyme of acetylcholine catabolism, in the light synaptosomes in the caudate nucleus of the right hemisphere was found to be 34.6% higher in GC rats (396.2 $\pm$ 38.1 in the control and 533.1 $\pm$ 42.7 in GC rats, $p < 0.05$). No significant differences in ACE activity could be found between the left and right hemispheres in GC rats, but a tendency was observed toward higher activity of the enzyme on the right side. In the control rats a certain tendency was found toward higher ACE activity on the left side. The level of asymmetry of this parameter in GC rats compared with the control was 15.5% (Fig. 1). No differences in activity of the enzyme of acetylcholine synthesis (CAT) could be found in the caudate nucleus. Activity of both enzymes was identical in the right and left cerebral hemispheres in the sensomotor cortex, in both Wistar and GC rats. Aminopeptidase activity in the control and in GC at the subcellular level was unchanged in both brain structures. Meanwhile, in neurons of the caudate nucleus, higher aminopeptidase activity was found on the left side, more especially in GC rats than in Wistar rats: in GC rats activity of the enzyme was 0.543 $\pm$ 0.003 on the left and 0.371 $\pm$ 0.003 on the right, whereas in Wistar rats it was 0.41 $\pm$ 0.003 on the left and 0.37 $\pm$ 0.002 on the right (in both cases $p < 0.001$). A reflection of the more marked unilateral increase in aminopeptidase activity in the GC rats was a higher level of asymmetry of the GC rats, namely 13.7% (for GC A =- —18.8%, for Wistar rats A = —5.1%, Fig. 1).

Structures of the mesolimbic, dopaminergic system (s. nigra and s. accumbens) in the two groups of rats had a similar cytoarchitectonic structure in the right and left cerebral hemispheres.

In s. nigra of GC and Wistar rats differences were found in the number of neurons and the quantity of oligodendroglia between the left and right hemispheres: in both control and experimental rats, there were one-third more neurons in the right hemisphere, 33.7% more oligodendroglia in Wistar rats, and 46.3% more oligodendroglia in GC rats, also in the right hemisphere (Fig. 2). The unidirectional skewness of these parameters in the control rats and GC rats determines the low level of skewness of GC rats relative to the control (Fig. 3). However, with respect to the number of astrocytes, skewness in GC rats was reversed: there were more astrocytes in Wistar rats in the right hemisphere (by 10%), but in GC rats in the left hemisphere, and in this case significantly so (by 66.8%). As a result, the level of skewness with respect to the number of astrocytes was very high (29.8%, Fig. 3).

Skewness for the amount of perineuronal glia was found in n. accumbens of Wistar rats with predominance on the right, whereas in GC rats this parameter was higher for all types of cells on the left (Fig. 2). Thus, quantitatively speaking, reversal of asymmetry was found in the glial cells in n. accumbens of GC rats, and it was reflected in the higher level of skewness in GC than in the control: 17% for astroglia and 21.4% for oligodendroglia (Fig. 3).

The interhemispheric asymmetry observed in Wistar and, in particular, GC rats for activity of aminopeptidase, an enzyme responsible for hydrolysis of proteins and polypeptides, in neurons of the caudate nucleus with predominance in the left hemisphere, is in agreement with the increase in the number of neurons of the left caudate nucleus, which we found previously in a study of brain morphology in GC rats [2].

Thus, in rats with hereditary predisposition toward catalepsy reversal of interhemispheric asymmetry was found with respect to acetylcholinesterase activity in the caudate nucleus, the quantity of astroglia in s. nigra, and of both types of neuroglia in n. accumbens. Conversely, with respect to aminopeptidase activity in the caudate nucleus and the quantity of oligodendroglia in s. nigra, increased interhemispheric asymmetry was observed in GC rats.

The left-sided increase in the number of all types of cells in GC rats in n. accumbens is in agreement with the increase in the content of dopamine, serotonin, and their metabolites found previously in n. accumbens of the left hemisphere [12]. These results are in good agreement with the fact that, as was shown in a study of the change in the protein spectrum during learning [4], the greatest differences between GC and Wistar rats were found specifically in n. accumbens.

These results are evidence that the mechanism of hereditarily determined pathology of the striatopallidal and mesolimbic dopaminergic systems, controlling motor functions and behavioral and emotional responses, includes reversal of interhemispheric asymmetry.

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