CORRELATION BETWEEN BRAIN TRYPTOPHAN HYDROXYLASE ACTIVITY AND CATALEPSY IN MICE

A. V. Kulikov, N. N. Kudryavtseva, E. Yu. Kozlachkova, and N. K. Popova

UDC 616.8-009.15-092.9-07:616.831-008.931:577.152.3

Key words: tryptophan hydroxylase; catalepsy; striatum.

Catalepsy is immobility combined with plastic muscle tone and is found in fish, amphibians, reptiles, birds, and mammals [1]. It has been suggested that under natural conditions it is linked with fear and manifested as a protective response of complete immobility [13], including during manifestation of submissive behavior in zoosocial contacts [11]. In an excessively strong and inappropriate form catalepsy is a syndrome of pathological behavior characteristic of several forms of schizophrenia. The onset of catalepsy is connected with dopamine insufficiency in the striatum [10], but there is evidence that serotonin may also be involved in its genesis [6]. The writers showed previously [8] that catalepsy in rats is accompanied by a marked increase in activity of tryptophan hydroxylase (TPH), a key enzyme of serotonin biosynthesis, in the striatum. A cataleptoid response of immobility has recently been described in mice, being induced by a series of pinchings of the skin in the neck region, the so-called pinch-induced catalepsy, and significant differences in the intensity of this response have been found in mice of different lines [9]. Meanwhile mice of inbred lines differ significantly in their level of brain TPH activity [5], and serotonin metabolism in the brain of mice exhibiting submissive behavior during intraspecific contacts differs from its metabolism in animals with an aggressive type of behavior [3].

In the investigation described below correlation between activity of this enzyme in the brain and manifestation of pinch-induced catalepsy was studied in mice of different inbred lines and in animals with different types of behavior during zoosocial contact.

EXPERIMENTAL METHOD

Experiments were carried out on mature male mice of six inbred lines: BALB/*c*, CC57Br, DD, AKR, C57BL/6, and CBA. The animals, aged 2-3 months and weighing 20-30 g, were kept under standard conditions. In experiments to study interlinear differences, the animals were kept for 24 h before the experiment in individual cages, in order to abolish the group effect. In the experiments to study the effect of zoosocial status on the intensity of catalepsy and on TPH activity, submissive and aggressive types of behavior were formed in CBA males in a series of consecutive agonistic interactions, using a model of sensory contact [2]. Males in which these types of behavior were not induced served as the control. Catalepsy was induced by pinching the skin of the neck for 5 sec, after which the animal was placed on parallel horizontal bars, arranged at different heights, so that the forelimbs were 23 cm above the bench surface and 3 cm higher than the hind limbs [9]. The test for catalepsy was considered to be positive if the period during which the mouse kept its assigned, unnatural position was not less than 20 sec. The testing time was limited to 120 sec, after which the animal was replaced in the same cage. Each of the next 10 tests was carried out after an interval of 1-2 min. The intensity of catalepsy was estimated as the fraction of cataleptic mice giving a positive test for catalepsy in at least three of the 10 tests. To determine TPH activity, after rapid decapitation of the animals the midbrain, where the bodies of serotonin neurons are concentrated, and the striatum, which plays a key role in the development of catalepsy [12], were isolated in the cold. TPH activity was determined fluorometrically [4] and expressed in picomoles of product (5-hydroxytryptophan), formed during 1 min per milligram of protein, measured by Lowry's method.

Laboratory of Phenogenetics of Behavior, Institute of Cytology and Genetics, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk. (Presented by Academician of the Academy of Medical Sciences of the USSR V. A. Matyukhin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 108, No. 9, pp. 269-271, September, 1989. Original article submitted May 6, 1988.

 0007-4888/89/0009-1222$12.50

TABLE 1. Manifestation of Catalepsy and Brain TPH Activity in Mice of Inbred Lines

Line	Dose of cataleptics	TPH activity, pmoles/mg·min	
		striatum	midbrain
CBA	0,56*	17,8±0,9*	101,9±7,2
BALB/c	0,2	4,1±0,1	46,7±3,1
DD	0,1	11,0±0,9	69,4±1,7
C57BL/6	0,0	10,1±0,6	72,9±3,4
AKR	0,0	13,4±0,5	84,7±3,9
CC57Br	0,0	5,3±0,4	49,8±3,7

Legend. *$p < 0.01$ compared with each of remaining lines.

TABLE 2. Manifestation of Catalepsy and Brain TPH Activity in CBA Mice with Different Types of Behavior during Zoosocial Contact

Type of behavior	Dose of cataleptics	TPH activity, pmoles/mg·min	
		striatum	midbrain
Control	0,56	17,8±0,9	101,9±7,2
Submissive	0,58	16,8±2,0	94,0±2,1
Aggressive	0,0*	12,8±1,8*	85,8±2,9

Legend. *$p < 0.01$ compared with control.

Interlinear differences for the fraction of cataleptics were estimated by the chi-square test after transformation of the fractions into arcsines [7]. Differences in TPH activity were evaluated by Student's test.

EXPERIMENTAL RESULTS

Marked catalepsy was found in mice of only one of the six lines tested (CBA). In 15 of the 27 CBA males studied, a persistent response of immobility developed after only 4-5 tests. Marked catalepsy could not be induced in animals of the other lines. Sometimes a transient and unstable response of immobility developed in individual BALB/c and DD males, but it did not last longer than 30-40 sec. This response did not appear in any of the C57BL/6, AKR, or CC57Br animals (Table 1). Considerable interlinear and, consequently, genotypic differences were found with respect to the fraction of cataleptic mice. The CBA line differed sharply from all the other lines with respect to this feature ($p < 0.01$).

Increased TPH activity in parts of the brain compared with animals of the other noncataleptic lines was found in mice of the only cataleptic line (CBA; Table 1). The differences were most marked in the striatum: TPH activity in this structure of CBA mice was significantly higher than in animals of all other lines studied ($p < 0.01$). These differences were less marked in the midbrain and TPH activity of mice of the cataleptic CBA line did not differ from its activity in animals of the noncataleptic AKR line, although it was higher than in mice of the other lines not exhibiting catalepsy. Thus the same rule was found as previously in rats [8]: a hereditary predisposition to catalepsy is associated with genetically determined raised TPH activity in the striatum.

Besides genotype, the type of zoosocial behavior of the male also was found to have a significant influence on the manifestation of catalepsy in mice. CBA mice, in which as a result of defeats during agonistic conflicts with more aggressive males of the same line a submissive type of behavior had been formed, exhibited well marked catalepsy. However, it was impossible to induce catalepsy (Table 2) in any CBA male in which an aggressive type of behavior had been formed as a result of a series of victories over other males of the same line, irrespective of the duration of manifestation of aggressive behavior. In CBA males with a consolidated submissive type of behavior no changes in TPH activity could be found either in the striatum or in the mid-brain compared with the control (Table 2). Meanwhile TPH activity in the striatum of the aggressive males was much lower than in the control, although with respect to TPH activity in the midbrain they differed significantly from the control and also from mice in which a submissive type of behavior was formed. Consequently, the formation of an

aggressive type of behavior in mice leads to disappearance of the hereditarily consolidated predisposition to manifestation of catalepsy and, at the same time, to a significant reduction of the genetically determined high TPH activity in the striatum.

The onset of catalepsy in mice is thus connected with increased activity of TPH, an enzyme responsible for serotonin biosynthesis. This increase is manifested particularly sharply in the striatum — a structure with which the development of catalepsy in mammals is associated. Increased TPH activity in the striatum is evidently one cause of the development of catalepsy.

LITERATURE CITED

1. I. G. Karmanova, The Evolution of Sleep: Stages in the Formation of the "Waking — Sleep" Cycle in a Series of Vertebrates [in Russian], Leningrad (1977).
2. N. N. Kudryavtseva, Special Features of the Formation of Agonistic Behavior in Mice, Using a Model of Sensory Contact [in Russian], Novosibirsk (1987).
3. N. N. Kudryavtseva and N. K. Popova, Zh. Vyssh. Nerv. Deyat., **35**, 879 (1985).
4. A. V. Kulikov, Vopr. Med. Khim., **29**, 135 (1982).
5. A. V. Kulikov and N. K. Popova, Genetika, **19**, 784 (1983).
6. N. K. Popova, E. V. Naumenk, and V. G. Kolpakov, Serotonin and Behavior [in Russian], Novosibirsk (1978).
7. J. Janko, Mathematical Statistical Tables [Russian translation], Moscow (1961).
8. V. G. Kolpakov, A. V. Kulikov, N. N. Barykina, et al., Biogen. Amines, **2**, 131 (1985).
9. K. Ornstein and S. Amir, J. Comp. Physiol. Psychol., **95**, 827 (1981).
10. C. Pycock, R. Horton, and C. Carter, Dopamine, New York (1978), p. 323.
11. C. P. Richter, Ann. New York Acad. Sci., **56**, 225 (1953).
12. D. Svorad, Paroxyzmalny Utlum, Bratislava (1956).
13. L. B. Wallnau, G. Bordash, and P. Corso, Pharmacol. Biochem. Behav., **14**, 463 (1981).