PHYSIOLOGY

Mice Selected for Low Brain Weight Show Heightened Sensitivity to the Convulsive Action of Pentylenetetrazole

N. N. Bogdanov, I. I. Poletaeva, and N. V. Popova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 119, № 5, pp. 460-462, May, 1995
Original article submitted May 30, 1994

Convulsive activity of pentylenetetrazole (25-120 mg/kg) measured in mice selected for large or small brain weight was evaluated, and mice with a smaller brain weight proved to be more susceptible to the damaging action of this compound than those with a larger weight.

Key Words: *convulsive states; pentylenetetrazole; brain weight; selected mice*

Individual variations in the susceptibility to convulsants are of great interest to those doing research on epilepsy. Studies performed with selected and inbred rodent species such as the rat, mouse, and gerbil, have highlighted the considerable promise held by genetic approaches [8]. Highly susceptible to convulsants of various types are DBA/2J mice, which are also prone to develop audiogenic seizures in a certain age interval [9, 10,13]. The brain of DBA/2J mice has been found to weigh much less than that of any of the other 17 mouse strains in which brain weight was measured [12]. Because they have multiple differences in many morphological, biochemical, and physiological characteristics [1-3,6,11,14], inbred mouse strains are of little use in studies designed to shed light on the role of individual factors in the development of convulsions. The body's response to external stimuli, including convulsants, is determined by a large number of variables, and morphological variables (e.g., brain weight and the number of cellular elements and their organization), unlike neurochemical ones, are among those that have been studied least. Of considerable interest, therefore, are stocks of mice selected for large or small brain weight (LB and SB mice, respectively) [4,5].

As found by morphometry, LB mice have a higher absolute surface area of the entire cerebral cortex (mainly because of the larger neocortex) and a higher total number of neural elements than do SB mice [5]. Mice of these two stocks may thus serve as appropriate models for investigating relationships among morphological parameters of the brain and, in particular, between the number of neural elements and the body's responses to various external stimuli.

The aim of the present study was to examine the role of brain weight and the brain weight-associated abundance of neural elements in the genesis of convulsions inducible by pentylenetetrazole (PT).

MATERIALS AND METHODS

The original population used for the selection comprised mice derived by crossing six inbred strains - CBA, DBA/2, C57Bl/6J, C57Br/cd, A/

Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow; Chair of Higher Nervous Activity, Department of Biology, Moscow State University. (Presented by V. S. Rusinov, Member of the Russian Academy of Medical Sciences)

0007-4888/95/0005-0441$12.50

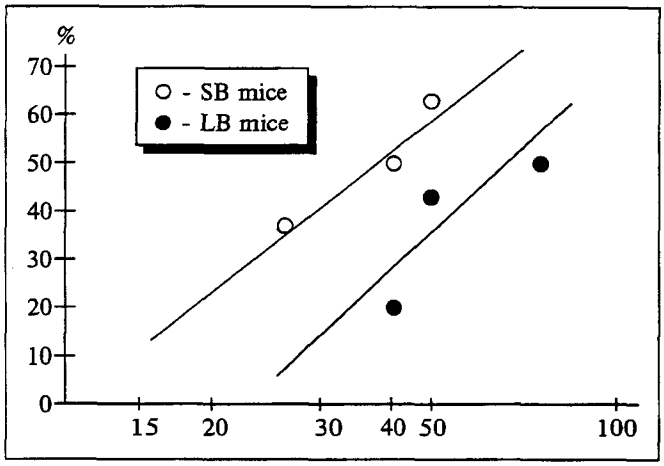

Fig. 1. Convulsive activity of pentylenetetrazole (PT) in LB and SB mice. Ordinate: percent of mice with tonic convulsions.

Sn, and BALB/c [4]. The selection for LB and SB was based on the regression line linking brain weight and body weight. As a result, the two stocks differ considerably in brain weight while the interstock differences in body weight are small in comparison with the range of intrastock variation. Sexually mature males of the eleventh generation from these stocks were used in this study. Separated from females at the age of 5-7 weeks, they were kept in the vivarium under standard conditions, 5-7 animals per cage. The mean difference in brain weight between LB and SB mice of this generation was 75 mg (493.13±2.65 *vs.* 417.09 ± ±2.94). PT was administered subdermally (into the withers) as aqueous solution in doses of 25-120 mg/kg to 30 LB mice weighing 33.39±0.36 g and 28 SB mice weighing 29.82±0.27 g. The latency of tonic convulsions, the number of mice developing convulsions, and the number that died were recorded. Brain weight in the test mice was not measured. The results were evaluated using Biostatistics-III software; characteristic dose-response plots were constructed by Litchfield-Wilcoxon's method.

RESULTS

At two dose levels (50 and 80 mg/kg) used in mice of both stocks, the latency of convulsions was significantly shorter in SB mice ($p<0.05$); after these doses, 37.5% and 66.7% of the SB mice died, respectively, whereas not a single animal died among the LB mice. This indicates that SB mice are more susceptible to the convulsive action of PT (Table 1).

It should be noted that LB mice had a significantly larger ($p<0.01$) body weight than SB mice and so received a higher absolute dose of the compound. The effective dose (ED_{50}) for convulsive activity was 36.84±31.06 mg/kg for SB mice and 74.29± ±53.25 mg/kg for LB mice. Although the differences in the ED_{50} are statistically insignificant, primarily because the slopes of the characteristic dose-response lines are too gentle, these lines meet the criterion of parallelism ($SR<f_{SR}$; $p=0.05$) (Fig. 1).

Although, because of the small sample sizes, it was not possible to obtain a fuller picture of the differences between LB and SB mice in susceptibility to the convulsant used, the results of this study clearly show that SB mice are more susceptible. As the mice of the two stocks had been derived from a genetically heterogeneous population, neurochemical differences, which are strongly marked among mice of individual strains [1-3,6,11,14], are likely to be slight between LB and SB. If so, then the differential susceptibilities of LB and SB mice to the convulsant are most likely to be due to differences in brain weight and in the number of neural elements in the neocortex, or to the more complex spatial organization of neuronal ensembles found in LB mice [5].

Table 1. Susceptibility of Mice Selected for Large or Small Brain Weight (LB and SB Mice) to the Convulsive Action of Pentylenetetrazole (PT)

PT dose, mg/kg	LB mice						SB mice					
	Total №	Mice with convulsions		Latency of convulsions, sec	№ of dead mice		Total №	Mice with convulsions		Latency of convulsions, sec	№ of dead mice	
	n	*n*	%	(*M*±*m*)	*n*	%	*n*	*n*	%	(*M*±*m*)	*n*	%
120	5	5	100	71±15.5	5	100	–	–	–	–	–	–
100	7	7	100	179±19.7	5	71	–	–	–	–	–	–
80	6	3	50	682±79.1	0	0	6	6**	100	378±48.1*	4	66
50	7	3	43	636±52.4	0	0	8	5	63	331±86.6*	3	37.5
40	5	1	20	–	0	0	6	3	50	375±26.6	1	15
25	–	–	–	–	–	–	8	3	37	613±38.4	0	0

Note. Percentages were calculated from the total number of mice. *$p<0.05$ by Student's *t* test, **$p<0.01$ by Fisher's test in comparison with LB mice. Dashes signify "not tested."

Since the advent of behavioral genetics, only a few experiments have been undertaken to select mice for large or small brain weight [7] and, to the best of our knowledge, no studies addressing the differential susceptibilities of such mice to convulsants have been reported. The results of the present study point to an important role played by structural features of the central nervous system in determining the sensitivity or resistance of animals to convulsants.

REFERENCES

1. Yu. A. Blednov, Yu. L. Fedoseev, N. N. Bogdanov, *et al., Byull. Eksp. Biol. Med.*, **102**, № 9, 294-296 (1986).
2. L. I. Serova, A. V. Osadchuk, and E. V. Naumenko, *Genetika*, **25**, № 4, 691-698 (1989).
3. Yu. A. Skrinskaya and E. M. Nikulina, *Genetika*, **24**, № 7, 1321-1324 (1988).
4. N. V. Popova, *Vestn. Moskovskogo Universiteta. Seriya Biologiya*, № 3, 34-40 (1985).
5. N. V. Popova, V. S. Kesarev, I. I. Poletaeva, and L. G. Romanova, *Zh. Vyssh. Nervn. Deyat.*, **33**, № 3, 576-582 (1983).
6. D. K. Ingram and T. P. Corfman, *Neurosci. Biobehav. Rev.*, **4**, № 4, 421-438 (1980).
7. J. L. Fuller, in: *Development and Evolution of Brain Size* (M. E. Hahn *et al.*, eds.), New York (1979), pp. 518-532.
8. W. Loscher, in: *Genetically Defined Animal Models of Neurobehavioral Dysfunctions* (P. Driscoll, ed.), Boston (1992), pp. 111-135.
9. R. J. Marley and J. M. Wehner, *Life Sci.*, **40**, № 23, 2215-2224 (1987).
10. D. J. Nutt and R. G. Lister, *Psychopharmacology*, **94**, № 3, 435-436 (1988).
11. H. A. Robertson, *Europ. J. Pharmacol.*, **56**, № 1-2, 163-166 (1979).
12. T. H. Roderick, R. T. Waimer, C. C. Waimer, *et al., Brain Res.*, **64**, 345-353 (1973).
13. T. W. Seale, T. H. Roderick, and Ph. Skolnick, *Life Sci.*, **40**, № 13, 1267-1276 (1987).
14. D. Wahlsten, in: *Genetics, Environment and Intelligence* (A. Oliverio, ed.), Rotterdam (1977), pp. 93-115.