EFFECT OF BUSPIRONE AND DIAZEPAM ON cGMP CONTENT IN THE RAT CEREBELLUM

A. Ya. Korneev, Chan Thi Bin An, and M. I. Faktor

UDC 615.214.22.015.4:612.827/.07

KEY WORDS: buspirone, diazepam, cGMP.

According to the results of experimental investigations and clinical observations, buspirone, a compound of the azaspirodecanedione series, possesses anxiolytic properties equivalent to those of diazepam [4, 7]. At the same time, unlike diazepam, buspirone has no sedative or muscle-relaxing action [4]. The biochemical mechanisms lying at the basis of the pharmacologic effect of buspirone are not yet understood, although there is evidence of its interaction with serotonin and dopamine receptors [4, 5]. Studies of the effect of buspirone on the GABA-benzodiazepine receptor complex have yielded contradictory results [4, 7].

For this reason, in the investigation described below the effect of buspirone on activity of the GABA-ergic system was studied in vivo. The concentration of cyclic GMP (cGMP) in the cerebellum, which falls in response to activation of GABA-ergic mechanisms [1-4], was chosen as the parameter characterizing the activity of this system.

EXPERIMENTAL METHODS

Experiments were carried out on male Wistar rats weighing 120-180 g. Buspirone (Bristol-Myers, USA) was dissolved in physiological saline. Diazepam was used in the form of the solution for injection (Richter, Hungary). The preparations were injected intraperitoneally into the animals in a volume of 5 ml/kg body weight 30 min before decapitation. Control animals received physiological saline. Material for measurement of the cGMP concentration was prepared as described previously [2, 3], with certain modifications. Immediately after decapi-

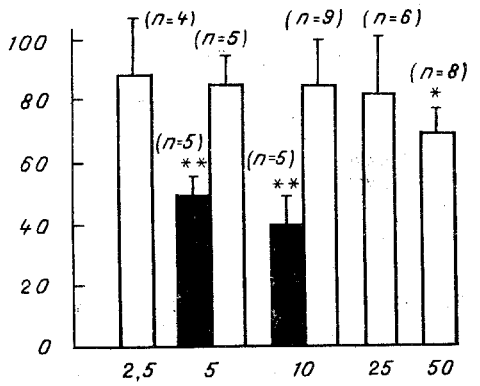

Fig. 1. Effect of buspirone (unshaded columns) and diazepam (black columns) on cGMP level in rat cerebellum. Abscissa, doses of drug (in mg/kg); ordinate, cGMP level (in % of control, taken as 100). n) Number of animals. *P < 0.05, **P < 0.01.

All-Union Mental Health Center, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Snezhnevskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 9, pp. 292-294, September, 1986. Original article submitted October 12, 1985.

 0007-4888/86/0009-1204$12.50

tation the whole cerebellum was removed and weighed, 9 volumes of a mixture of 50 mM Tris-HCl buffer, containing 4 mM EDTA (pH 7.5, 20°C), with ethanol in the ratio 1:1, cooled to −15°C, were added and the cerebellum was homogenized on an "Ultraturrax" homogenizer (30 sec at maximal speed). The time between decapitation of the animal and the beginning of homogenization was 50-65 sec. The homogenate was centrifuged (5000 g, 20 min, 4°C) and the supernatant collected; after dilution three-sixfold, the concentration of cGMP in the supernatant was determined by radioimmunoassy, using a kit from Amersham Corporation (England). When the calibration curve was plotted, allowance was made for the presence of ethanol (4-9%) in the test samples.

EXPERIMENTAL RESULTS

The cGMP concentration in the cerebellum of the control animals, when determined by the method described above, was 590 ± 50 pmoles/mg tissue. The cGMP concentration in the cerebellum of the control animals, according to our own data and results published by other workers [2, 3], when a similar method was used to prepare the samples for analysis, lay within the range of 500-600 pmoles/g tissue, which is much more than the value obtained by the use of microwave treatment of the tissue to ensure rapid arrest of biochemical processes after the animal's death [1, 6]. The reason for this difference is probably an increase in the cGMP concentration in the tissue during the first minute after the animal's death. To test this hypothesis, in a series of experiments the rat's head, immediately after decapitation (in the course of 1 sec) was immersed in liquid nitrogen, after which the cGMP concentration in the cerebellum was determined. For this purpose the cerebellum was placed in 4 volumes of 50 mM Tris-HCl buffer, containing 4 mM EDTA (pH 7.6, 20°C), and was slowly boiled for 5 min; after cooling, the preparation was homogenized and centrifuged as described above and the cGMP concentration determined in the supernatant. In this case a value of 15.5 ± 0.9 pmole/g tissue ($n = 7$) was obtained. This suggests that in the present investigation, as well as in those cited above, it was not the cGMP concentration in the rat's cerebellum that was determined, but the change in this parameter taking place during the first minute after decapitation of the animal.

The cGMP concentration in the cerebellum of animals receiving diazepam in doses of 5 and 10 mg/kg was 50 and 60% lower than in the control respectively (Fig. 1). Administration of buspirone in doses of between 2.5 and 25 mg/kg caused a very small (by not more than 18%; not significant) decrease in the cGMP concentration in the cerebellum. When buspirone was given in a dose of 50 mg/kg the fall of the cGMP concentration in the cerebellum reached 30% ($P < 0.05$). Diazepam caused muscle relaxation and hypodynamic and sedative (in a concentration of 10 mg/kg) effects. Meanwhile, during the action of buspirone only a hypodynamic effect was observed, and this strengthened with an increase in the dose of the drug.

The fall in the cGMP concentration observed in the cerebellum under the influence of diazepam is in good agreement with data in the literature [1-3, 6]. Buspirone, even in a dose of 50 mg/kg, affected the change in the cGMP concentration in the cerebellum by a much lesser degree than diazepam in a dose of 5 mg/kg. Considering data showing the similar effects of buspirone and diazepam in the treatment of anxiety states [4, 7], it can be postulated that GABA-ergic mechanisms do not participate in the realization of the pharmacologic properties of buspirone. This conclusion is in agreement with the hypothesis that buspirone is an anxiolytic with a fundamentally different mechanism of action from the benzodiazepines [7].

LITERATURE CITED

1. G. Biggio, B. B. Brodie, E. Costa, and A. Guidotti, Proc. Natl. Acad. Sci. USA, 74, 3592 (1977).
2. J. C. Blanchard, A. Boireau, and L. Joulou, Pharmacology, 27, Suppl. 2, 59 (1983).
3. A. Boreau, J. M. Stutzmann, C. Garet, et al., Eur. J. Pharmacol., 104, 139 (1984).
4. M. S. Eison and A. S. Eison, Drug Dev. Res., 4, 109 1984).
5. T. Glazer and J. Traber, Eur. J. Pharmacol., 88, 137 (1983).
6. H. Mohler, W. P. Burcard, H. H. Keller, et al., J. Neurochem., 37, 714 (1981).
7. D. P. Taylor, L. E. Allen, J. A. Becker, et al., Drug Dev. Res., 45, 95 (1984).