# EFFECTS OF PYRROLIDONE-2 AND GAMMA-BUTYROLACTONE ON RATE OF INCORPORATION OF $^{14}$C-LEUCINE INTO PROTEINS OF VARIOUS BRAIN STRUCTURES AND CEREBRAL ARTERIAL TISSUES

S. A. Mirzoyan,* M. G. Zalinyan,
G. A. Gevorkyan, A. V. Topchyan,
and M. G. Balasanyan

UDC 612.825-612.826.4/015.348.014.46:
547.745/.088.6

KEY WORDS: pyrrolidone-2; gamma-butyrolactone; protein synthesis; rat brain.

Gamma-aminobutyric acid (GABA) stimulates incorporation of amino acids into the protein molecule in the ribosomal system of brain tissue of immature rats [2, 6, 7]. The marked cerebrovascular activity of products of cyclic transformation of GABA and of gamma-hydroxybutyric acid (GHBA), namely pyrrolidone-2 and gamma-butyrolactone [1, 5], and also their ability to stimulate the energy metabolism of brain tissue [3] served as the motivation for a study of their action on the rate of incorporation of labeled amino acid into proteins of various structures of the brain and of their arteries.

## EXPERIMENTAL METHOD

Renewal of proteins in the cerebral cortex, hypothalamus, and tissues of the cerebral arteries under the influence of pyrrolidone-2 and gamma-butyrolactone was studied with the aid of $^{14}$C-leucine under normal conditions and during circulatory anoxia of the brain induced by unilateral ligation of the common carotid artery for 20 min. The incorporation process was studied in 28 sexually mature albino rats. The preparations were injected intraperitoneally in doses of 10 and 20 mg/kg. $^{14}$C-leucine in a dose of 50 μCi, with specific radioactivity of 240 mCi/mmole, was injected at the same time. The rats were decapitated 45 min later and weighed samples taken from various tissues (cortex, hypothalamus, blood vessels). After homogenization the proteins were precipitated with a 10% solution of TCA. The proteins thus obtained were solubilized in 0.5 ml of a solution of Protazol (New England Nuclear, USA), and after the residue had completely dissolved, radioactivity was measured on an SL-30 scintillation spectrometer (Intertechnique, France). The counting efficiency of $^{14}$C was 95%. Pyrrolidone-2 was obtained from "Merck" (West Germany) and the gamma-butyrolactone was synthesized in the Department of Natural Sciences, Institute of Inorganic Chemistry, Erevan.

## EXPERIMENTAL RESULTS

$^{14}$C-Leucine, injected into intact animals over a period of 45 min, was incorporated into proteins of the cortex, hypothalamus, and large blood vessels of the brain. As Table 1 shows, pyrrolidone-2 and gamma-butyrolactone had virtually no effect on cerebral cortical protein turnover. However, the preparations caused a quite considerable increase in the degree of incorporation of $^{14}$C-leucine into proteins of the hypothalamus and large cerebral arteries: pyrrolidone-2 increased incorporation of the amino acid into hypothalamic proteins by 43.5%, whereas gamma-butyrolactone increased it by 55.5%. Pyrrolidone-2 and gamma-butyrolactone stimulated incorporation of $^{14}$C-leucine into the protein molecule in tissues of the walls of the cerebral blood vessels by 41.8% and 53.9% respectively.

In the intact animals 20 min after unilateral ligation of the common carotid artery protein renewal in the cortex was reduced on the side of ligation by 55%, whereas on the contralateral side no significant changes were observed. The degree of incorporation of the labeled amino acid into proteins of the hypothalamus and of the cerebral arterial tissues was reduced under these conditions by 40% and 36.3% respectively. Under the influence of gamma-butyrolactone

*Corresponding Member, Academy of Sciences of the Armenian SSR.

Department of Pharmacology, Erevan Medical Institute. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 106, No. 11, pp. 571-572, November, 1988. Original article submitted May 26, 1987.

TABLE 1. Effect of Gamma-Butyrolactone and Pyrrolidone-2 on Degree of Incorporation of $^{14}$C-Leucine (in cpm/g protein of fresh tissue) into Proteins of Various Brain Structures and Tissues of Cerebral Arteries in Normal Rats and after Unilateral Ligation of the Common Carotid Artery (M ± m, n = 28)

| Tissue | Experimental conditions | | | | | | |
|---|---|---|---|---|---|---|---|
| | Normal | | | Reduced blood flow | | | |
| | control | gamma-butyrolactone, 20 mg/kg | pyrrolidone-2, 10 mg/kg | control | ligation for 20 min | ligation for 20 min + gamma-butyrolactone, 20 mg/kg | ligation for 20 min + pyrrolidone-2, 10 mg/kg |
| Cerebral cortex (side of ligation) | 94,2±4,8 | 99,7±5,6 | 98,6±5,2 | 563,0±28,65 | 225,0±12,75 | 305,0±14,0 | 318,0±17,6 |
| Cerebral cortex (opposite side) | 94,2±4,8 | 99,7±5,6 | 98,6±5,2 | 418,0±20,9 | 410,0±20,5 | 511,0±15,55 | 440,0±22,0 |
| Hypothalamus | 22,5±0,5 | 35,0±1,04 | 32,3±0,8 | 25,0±0,75 | 15,0±0,45 | 39,0±1,17 | 72,0±1,4 |
| Cerebral arteries | 330,0±16,0 | 508,0±25,5 | 468,0±20,3 | 334,0±16,7 | 245,0±12,25 | 377,0±18,85 | 393,0±23,6 |

under ischemic conditions protein resynthesis in the cortex of the ligated side was increased by 17.6% and on the opposite side by 24.6%, in tissues of the cerebral arteries it was increased by 53.9%, and in the hypothalamus by more than 2.6 times. Under conditions of a reduced blood flow injection of pyrrolidone-2 stimulated incorporation of labeled leucine into proteins of cerebral arterial tissues by 60.4%, in the cerebral cortex on the ligated side by 41.3% and on the opposite side by 7.3%, whereas in the hypothalamus it was increased by almost 5 times.

It can be concluded from these data that the role discovered previously for endogenous GABA derivatives, namely that cyclic transformation of a linear product strengthens its action on neurocirculatory zones [4], also is observed during a study of the effect of pyrrolidone-2 and of gamma-butyrolactone on the rate of incorporation of $^{14}$C-leucine into brain proteins. Conversion of GHBA into gamma-butyrolactone and of GABA into pyrrolidone-2, which have stronger effects than their linear precursors, takes place with essentially small expenditure of energy—the loss of one molecule of water. Under these circumstances, when the blood supply to the brain is disturbed, pyrrolidone-2 and gamma-butyrolactone exhibit a stronger action on repair processes taking place in the hypothalamus and in tissues of the cerebral arteries.

## LITERATURE CITED


1. S. A. Mirzoyan, M. G. Zalinyan, and A. V. Topchyan, Krovoobrashchenie, 13, No. 6, 1 (1980).
2. S. A. Mirzoyan, A. T. Tatevosyan, and G. A. Gevorkyan, Byull. Éksp. Biol. Med., No. 9, 299 (1980).
3. S. A. Mirzoyan, M. G. Zalinyan, A. V. Topchyan, and M. G. Balasanyan, Pharmacology of Derivatives of Gamma-Aminobutyric Acid [in Russian], Tartu (1983), p. 98.
4. S. A. Mirzoyan, A. V. Topchyan, and M. G. Balasanyan, Problems in Nervous Regulation of the Cerebral Circulation [in Russian], Kishinev (1983), p. 93.
5. S. A. Mirzoyan, M. B. Ordyan, and M. G. Balasanyan, Byull. Éksp. Biol. Med., No. 1, 64 (1987).
6. C. F. Baxter and S. Tewari, International Society of Neurochemistry, Milan (1969), p. 84.
7. C. F. Baxter, GABA in Nervous System Function, New York (1976).