12. E. B. Smith and E. M. Staples, Atherosclerosis, 37, 579 (1980).
13. J. B. Smith, L. Smith, E. R. Brown, et al., Proc. Natl. Acad. Sci. USA, 81, 7812 (1984).
14. E. Svensjo, Acta Physiol. Scand., 124, Suppl. 542, 98 (1985).

MECHANISM OF ACTION OF BACLOFEN ON MYOCARDIAL AND VASCULAR CONTRACTILITY

Yu. A. Darinskii, V. Ya. Egorov,
T. A. Smirnova, Yu. D. Ignatov,
and A. V. Dmitriev

UDC 615.217:547.466.3:001.6

KEY WORDS: baclofen; myocardium; vein; artery.

In its effective dose range the γ-aminobutyric acid derivative baclofen (Lioresal), with a muscle-relaxing and analgesic action, has a marked effect on the cardiovascular system [9]. Changes in activity of the cardiovascular system are considered to be due mainly to the central action of the drug, leading to intensification of the flow of sympathetic impulses to adrenoreceptors of the heart and vessels [1, 3-6, 9]. Meanwhile the problem of whether baclofen may have a direct peripheral action on autonomic functions of the body remains open.

The aim of this investigation was to study the effect of baclofen on contractility of cardiomyocytes and smooth-muscle cells (SMC) of blood vessels in vitro.

EXPERIMENTAL METHOD

Experiments were carried out on isolated segments of arteries and veins and the papillary muscle of the left ventricle of the heart of a Wistar albino rat. After decapitation of the animal the papillary muscle, circular segments of the abdominal aorta and iliac artery 2 mm wide, and a longitudinal segment of the portal vein 7 mm long were dissected. The finished preparations were placed in a thermostatted working chamber, perfused with oxygenated Krebs' solution at 32°C, and fixed for recording isometric contractions by means of a 6MKh1S mechanical to electrical transducer. Contractions were recorded on an N-338-2 automatic writer. Contractility of the portal vein (tone, amplitude, and frequency of spontaneous contractions), the abdominal aorta, and iliac artery (tone and amplitude of contractions evoked by electrical stimulation), and the papillary muscle (amplitude, velocity of contraction and relaxation in response to electrical stimulation) were recorded. For electrical stimulation square pulses with a duration of 0.5 msec, frequency of 0.5 Hz, and amplitude of twice the threshold were used for electrical stimulation. Baclofen was added to the perfusion solution after incubation of the preparations in the working chamber for 30 min.

EXPERIMENTAL RESULTS

In low concentrations (up to 10^{-6} M) baclofen caused no significant changes in the parameters recorded. Addition of baclofen to the control solution in a concentration of 10^{-5} M led to an increase in tone of the abdominal aorta and iliac artery of the rats (by 21.7 ± 1.2 and 18.7 ± 1.3% respectively; $n = 27$, $p < 0.05$) and a decrease in amplitude of the phasic contractions (by 15.7 ± 1.4 and 11.9 ± 0.7%; Fig. 1a). The ionotropic effect of the drug lasted 10 min. Baclofen gave none of the effects described above if preceded by α-adrenoreceptor blockade by dihydroergotoxin (10^{-5} M).

Baclofen increased the amplitude of spontaneous phasic contractions of a segment of the rat portal vein (Fig. 1b). Maximal changes in the parameter were recorded after 1 min of the action of baclofen and the inotropic effect lasted 10 min. The frequency of contractions and tone of the vessel showed no significant change. The positive inotropic effect of the drug was preserved after β-adrenoreceptor blockage by propranolol (10^{-5} M), in hypercalcium solution

Department of Anatomy and Physiology of Man and Animals, A. I. Gertsen Leningrad Pedagogic Institute. Department of Pharmacology, Academician I. P. Pavlov First Leningrad Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 106, No. 10, pp. 436-438, October, 1988. Original article submitted February 28, 1988.

 0007-4888/88/0010-1426$12.50

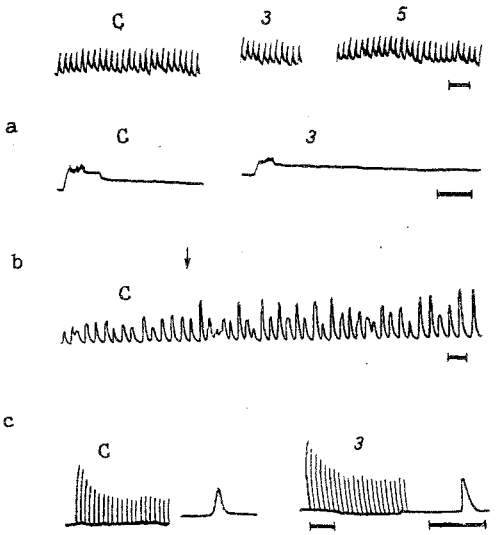

Fig. 1. Effect of baclofen (10^{-5} M) on evoked contractility of iliac artery (a), papillary muscle of left ventricle (b), and spontaneous contractions of rat portal vein (c). C) Control; 3, 5) time (in min) after addition of baclofen; arrow indicates time of addition of baclofen; time marker: a) top traces 30 sec, bottom 1 sec; b) 10 sec; c) 10 and 1 sec respectively.

TABLE 1. Effect of Baclofen (10^{-5} M) on Amplitude of Spontaneous Contractions of Segment of Rat Portal Vein (in % of control, taken as 100)

Series of experiments	Time of addition of baclofen, min		
	1	5	10
Control (n = 10)	+21,2±3,2*	+15,9±1,2*	+10,7±2,9*
After blockade by propanolol (10^{-5} M; n = =10)	+20,0±1,5*	+39,0±6,0*	+54,0±7,9*
After blockade by dihydroergotoxin n=12)	+21,2±2,2*	+13,3±1,4*	—0,1±4,0
In hypercalcium solution (n=12)	+41,0±3,4*	+77,0±9,0*	+37,0±4,8*

Legend. *Significant changes in contractility compared with control ($p < 0.05$).

($[Ca^{2+}]_o$ = 5 mM), and also after α-adrenoreceptor blockade by dihydroergotoxin (10^{-5} M; Table 1). In the last case the inotropic effect of baclofen was short in duration and disappeared by the 10th minute.

Baclofen had a positive inotropic action on contractility of the papillary muscle of the left ventricle (Fig. 1c). An increase in amplitude of evoked contractions (by 21.3 ± 3.9%; n = 12, $p < 0.05$) and in the rate of contraction and relaxation (by 50.6 ± 6.9 and 29.6 ± 1.5%) was observed. On potentiation of the papillary muscle by rest (for 1 min) increased the amplitude of the first contraction in the negative staircase characteristic of the rat myocardium by 20.7 ± 1.4% (Fig. 1c). Against the background of propranolol blockade, these effects of baclofen were completely preserved.

The results are evidence of the marked inotropic action of baclofen on cardiomyocytes and vascular SMC of rats in vitro. The change in the basic parameters of both evoked and

spontaneous contractions of the myocytes reflects the effect of the drug on calcium metabolism in these cells. The increase in tone of the arteries and the increase in the parameters of myocardial contraction and in the amplitude of phasic contractions of the portal vein suggest that a definite role in the hypertensive action of baclofen, observed when the drug is administered systemically, may be played not only by a central, but also by a peripheral mechanism. One of the possible ways whereby this effect may take place is interaction of the drug with adrenoreceptors of the myocytes. Baclofen is regarded not only as a GABA analog, but also as a substance similar in its chemical structure to catecholamines [9]. This may probably explain the abolition of the inotropic effects of the drug on arteries and, to some extent, on the portal vein after α-adrenoreceptor blockade. Preservation of the inotropic effect of baclofen on the myocardium and portal vein after β-adrenoreceptor blockade is evidence that the drug can stimulate contractility of the myocytes, not through adrenergic structures but, for example, by directly affecting membrane permeability and calcium ion transport into the cell. This hypothesis confirms the direct dependence of the positive inotropic effect of baclofen, revealed by these experiments, on the calcium ion concentration in the intercellular medium. The force of the contractions is known to depend on the calcium ion concentration in the sarcoplasm, and the amplitude of the phasic contractions of the portal vein is determined by the inflow of these ions along fast calcium channels of SMC [2, 8]. The effect of baclofen can perhaps be explained also by its ability to stimulate the inflow of calcium ions along voltage-dependent channels into the cell. This same mechanism may also be realized when baclofen acts on the myocardium, for the increase in the rate of contraction and relaxation of the papillary muscle reflects the effect of the drug on the processes of release of calcium ions from and their readmission to the depots [7].

LITERATURE CITED

1. B. V. Andreev, The Neuropsychopharmacology of Analgesics [in Russian], Leningrad (1986), pp. 75-86.
2. M. I. Gurevich and S. A. Bershtein, Physiology of the Circulation [in Russian], Leningrad (1984), pp. 141-176.
3. G. V. Kovalev, Pharmacology and Clinical Aspects of γ-Aminobutyric Acid and Its Analogs [in Russian], Volgograd (1979), pp. 11-25.
4. A. F. Kositsyna, Pharmacology and Clinical Aspects of γ-Aminobutyric Acid and Its Analogs [in Russian], Volgograd (1979), pp. 94-98.
5. E. P. Makarova, The Neuropsychopharmacology of Analgesics [in Russian], Leningrad (1986), pp. 86-90.
6. V. I. Petrov and K. G. Gurbanov, Pharmacology and Clinical Applications of Neuroactive Amino Acids and Their Analogs [in Russian], Volgograd (1985), pp. 21-24.
7. B. I. Tkachenko, Methods of Investigation of the Circulation [in Russian], Leningrad (1976).
8. M. F. Shuba, Fiziol. Zh. SSSR, 27, No. 4, 533 (1981).
9. B. Persson, Acta Physiol. Scand., Suppl. 491, 1 (1980).