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ACTION OF GAMMA-AMINOBUTYRIC ACID AND ITS ANALOGS ON SMOOTH MUSCLES OF VEINS

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The role of gamma-aminobutyric acid (GABA) in the metabolism of mammalian nerve tissue has been demonstrated by many investigations [5, 10-12].

GABA is nowadays regarded as the mediator of inhibition, because it satisfies all the criteria required for mediators of the CNS [12].

Besides the existence of central mechanisms of the action of GABA, peripheral effects of this substance were discovered a little later: on the cardiovascular system, respiration, and organs of the gastrointestinal tract [1, 3].

In experiments on the isolated ileum [13, 14], the inhibitory effect of GABA is accepted to be dominant.

There is, however, an important gap in the study of the action of GABA on the smooth muscle of isolated vessels. This is a subject of particular importance because GABA has been shown to have a depressor effect on the systemic blood pressure and on tone of the cerebral vessels [7, 8].

In the investigation described below, the action of GABA and its agonists (phenibut, phenylpyrrolidone, LGPI-29) on the contractile activity of smooth muscle cells of the isolated rat portal vein was studied.

EXPERIMENTAL METHOD

Experiments were carried out on isolated segments of the albino rat portal vein. Contractile activity of a segment of the vessel was recorded on a high-speed automatic writer by means of a mechanical to electrical transducer of the 6MN-1B mechanotron [2]. The original Krebs–Henseleit solution had the following composition (in millimoles/liter distilled water): NaCl 118, KCl 4.7, $MgSO_4$ 1.2, $CaCl_2$ 2.5, KH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11.

Both initial and test solutions were aerated with a gas mixture consisting of 95% O_2 and 5% CO_2. The temperature of the solution during the experiment was 34-35°C. All drugs (GABA and its analogs) were of

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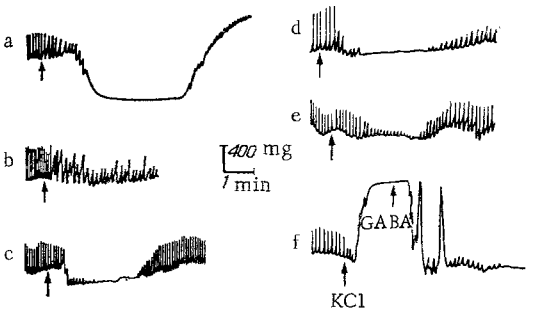

Fig. 1. Effect of GABA in dose of 10 mM (a), phenibut in doses of 10 mM (b) and 20 mM (c), phenylpyrrolidone in a dose of 10 mM (d), and LGPI-29 in a dose of 10 mM (e) on contractile activity of smooth muscles of portal vein, and also effect of GABA in dose of 10 mM against the background of depolarization induced by 50 mM KCl (f). Arrow indicates time of addition of test substance to solution.

Soviet manufacture and were added to the Krebs–Henseleit solution immediately before use. In the course of the investigation, active concentrations of these drugs were determined.

EXPERIMENTAL RESULTS

Experiments on isolated segments of the albino rat portal vein (series I) showed that GABA and its agonists inhibit the function of smooth muscle cells of veins. The effect observed was made up of the negative inotropic, chronotropic, and tonotropic action of GABA and its analogs on contractile activity of the portal vein (Fig. 1). The negative tonotropic effect was more clearly defined in the case of GABA and less so for phenibut; phenylpyrrolidone and LGPI-29 caused virtually no decrease in vascular tone. Phenibut, in a concentration of 10 mM, did not completely arrest the spontaneous phasic contractile activity, but merely slowed the rhythm and reduced the amplitude of the contraction. It was completely blocked by the drug in a concentration of 20 mM. The active concentration of the drugs in these experiments was thus 10-20 mM. Injection of the drugs in these doses inhibited spontaneous contractile activity of the vein during the first few minutes, as shown by a rapid fall in amplitude of the phasic contractions, slowing of their rhythm and, in some cases, a fall in tone. At all times, rinsing out the test solution containing the GABA preparations with Krebs–Henseleit solution led to restoration of regular phasic contractile activity of the portal vein and restoration of the original level of tone.

According to investigations by Godovalova [1], GABA in a dose of 0.01M in experiments in vitro inhibits spontaneous contractions of isolated segments of small intestine recorded by a strain-gauge method. However, according to observations of Morozov [9], GABA, phenibut, and phenylpyrrolidone (in a dilution of $1:10^{-3}$) did not change the tone of isolated segments of the cat femoral artery [4].

The ability of GABA to inhibit phasic and tonic contractions of vascular smooth muscle, studied during this investigation, is in harmony with the well-known clinical observations on the improvement (by means of GABA) and compensation of the cerebral blood flow on account of an increase in the number of functioning capillaries [8]. This fact is evidence of only one thing: the effect of GABA described is evidently mediated through its effect on the smooth muscle components of the precapillary part of the vascular system. Indirect evidence that this is so, although with certain reservations, is given by the present results showing relaxation of the spontaneously functioning vessel, the type of vessel to which the precapillary vessels of the microcirculation indeed belong.

Having found the inhibitory effect of GABA and its agonists on smooth muscle cells of the portal vein, in the experiments of series II we attempted to study the site of application of their action on vascular smooth muscles. It is stated in the literature that GABA has no direct myotropic effect on isolated vessels [9]. In the unanimous view of investigators of GABA, its inhibitory effects on cells are based on the "membrane phenomenon" [6].

The addition of K ions (50 mM KCl) to the solution led to the development of potassium contracture of the smooth muscle cells of the rat portal vein, which was reflected in an increase in tone of the vessel. The study of the action of GABA and its analogs against this background of depolarization of the smooth muscle cell membrane showed that GABA caused disappearance of the potassium contracture after 1-3 min – the phasic contractile activity was restored and the vascular tone gradually returned to its previous level (Fig. 1). In all the experiments of this series, the response of the smooth muscle cells to GABA solution in a concentration of 10-20 mM led to the identical response against the background of blocking of the electrogenic properties of the membrane by means of KCl.

Depolarization of the cell membrane does not prevent the inhibitory effect of GABA and its agonists on contractile activity of the smooth muscle cells of the portal vein.

The results of these investigations thus show that during direct recording of the mechanical properties of the vessels a distinct inhibitory effect of solutions of GABA and its agonists in concentrations of 10-20 mM is observed on the phasic and tonic components of contractile activity of the smooth muscle cells of the rat portal vein. Depolarization of the smooth muscle cells does not prevent GABA from penetrating through their membrane and exhibiting its inhibitory effect. The possibility cannot be ruled out, as Laborit [6] suggests, that GABA is an activator of the universal inhibitory mechanism of cells, by acting on the processes of their energy metabolism.

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