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EFFECT OF GABA AND ITS AGONISTS AND ANTAGONISTS ON UTERINE SMOOTH MUSCLE

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The increase in excitability and contractile activity of the uterus arising as a result of the action of certain etiologic and pathogenetic factors is one cause of abortion [5]. The study of potential physiological antagonists of endogenous factors in uterine hyperactivity may provide a basis for the search for effective antiabortion agents in this case. Hence the importance of a study of endogenous biologically active substances which inhibit the receptor systems of the uterus.

In the last few years reports have been published of the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter of the CNS, and its derivatives on the smooth muscle of peripheral organs, which is realized through a GABA-receptor mechanism [7, 15].

This paper describes the study of the action of GABA and some of its agonists and antagonists on contractile activity of uterine smooth muscle.

EXPERIMENTAL METHOD

Experiments were carried out *in vitro* on 176 segments of the uterine cornua of 24 ovariectomized rabbits (with respect to receptor composition and response to neurotransmitters, sex hormones, and drugs the rabbit uterus closely resembles the human uterus [6]). The animals were killed on the 15th day after ovariectomy. An isolated segment of the uterine cornu, 1.5-2 cm long, was fixed to the floor of a small beaker containing Ringer–Locke or Krebs' nutrient solution. The free end of the segment was tied by a ligature to an Engelmann's lever. The temperature during the experiments was maintained at 38°C by means of a mercury contact thermometer. The nutrient solution was aerated by means of an AÉN-2 microcompressor. Contractions of the uterine segments were recorded by pens of an ink-writing

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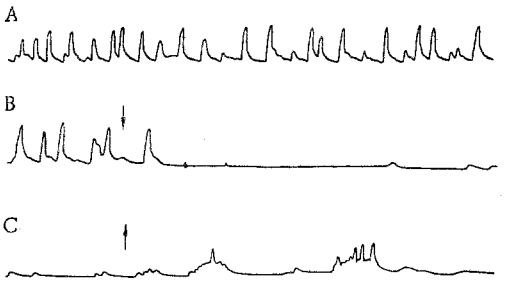

Fig. 1. Action of fenibut on contractions of isolated segment of uterine cornu of ovariectomized rabbit. A) Initial contractions, B) action of fenibut ($4.6 \cdot 10^{-4}$ M), C) contractions after control rinsing (arrow). Here and in Fig. 2: calibration 60 sec.

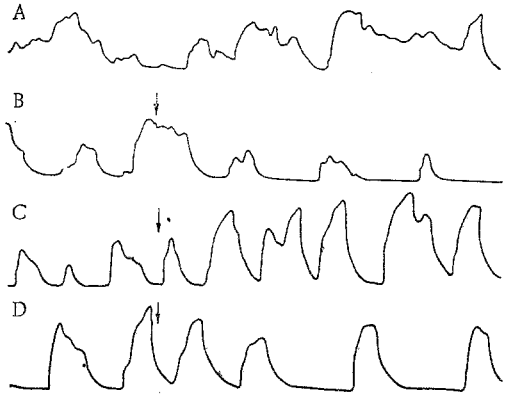

Fig. 2. Antagonistic action of GABA and bicuculline on contractions of isolated segment of uterine cornu of ovariectomized rabbit. A) Initial contractions, B) actions of GABA ($9.7 \cdot 10^{-2}$ M), C) action of bicuculline ($1.1 \cdot 10^{-5}$ M) preceded by GABA, D) action of GABA preceded by bicuculline (on the same segment).

system designed by V. S. Yasnetsov and A. I. Mitrofanov, on electrokymographs with tape winding speed of 0.5-0.7 mm/sec. The substances for testing were added to the beakers when spontaneous contractions of the segment began to appear, and no change in the ionic composition or temperature of the nutrient medium was permitted. Threshold concentrations of the substances at which their inhibitory action began were determined.

EXPERIMENTAL RESULTS

GABA, as an agonist of postsynaptic $GABA_A$-receptors and presynaptic $GABA_B$-receptors of the CNS [2, 13] had an inhibitory action in these experiments on contractions of the myometrium in a concentration of $4 \cdot 10^{-2}$ M. Diazepam, a direct mimetic and agonist of benzodiazepine receptors [12, 13], inhibited contraction of the uterine segments in a concentration as low as $3.5 \cdot 10^{-5}$ M. Sodium valproate (depakine), a GABA-transaminase inhibitor, which selectively increases the GABA concentration in brain tissue [9, 11], also has a relaxing action on the myometrium in a concentration of $2 \cdot 10^{-2}$ M. Fenibut (β-phenyl-GABA), an indirect GABA mimetic and agonist of presynaptic $GABA_B$-receptors [2], had an inhibitory effect in a concentration of $7 \cdot 10^{-4}$ M (Fig. 1). Other GABA derivatives also had a depressant action of contraction of the segments: sodium hydroxybutyrate and nicotinoyl-GABA, both in a concentration of $2 \cdot 10^{-2}$ M.

The GABA antagonist thiosemicarbazide, which selectively lowers its concentration in the brain as a result of inhibition of GABA synthesis [11], on the other hand, had a stimulating action on myometrial contractions in a concentration of $3 \cdot 10^{-3}$ M. Bicuculline, a specific blocker of postsynaptic $GABA_A$-receptors [11], in a concentration of $5 \cdot 10^{-6}$ M, and picrotoxin [12], in a concentration of $5 \cdot 10^{-5}$ M, also has an even stronger excitatory action on contractions.

Against the background of the stimulating action of bicuculline, GABA in equally effective concentrations inhibited myometrial contractions. In turn bicuculline, against the background of the inhibitory effect of GABA, restored contractions (Fig. 2). Against the background of the stimulating action of picrotoxin GABA also caused distinct inhibition of contractions of the segments. Picrotoxin, however, against the background of the relaxing effect of GABA, had a weak and inconstant stimulating action.

The results of these experiments show that GABA and its agonists, acting directly on uterine smooth muscle, have an inhibitory action in the following order of magnitude: diazepam < fenibut < GABA < sodium hydroxybutyrate < sodium valproate < nicotinoyl-GABA. The inhibitory effect of GABA on the uterus is evidently due to its effect on inhibitory postsynaptic $GABA_A$-receptors of the myometrium. According to data in the literature, however, the inhibitory action of GABA in the CNS is also realized indirectly through inhibition of dopaminergic, noradrenergic, serotoninergic, and cholinergic neurotransmitter systems [1, 4, 8]. The mechanism of the depressant action of GABA in this case is realized through presynaptic $GABA_B$-receptors, located on catecholaminergic and cholinergic terminals. Activation of $GABA_B$-receptors reduces the presynaptic release of dopamine, noradrenalin, serotonin, and acetylcholine [1, 13, 14]. In the present experiments fenibut, which plays the role of inhibitory modulator of neurotransmitters, evidently had a similar action. The weaker activity of GABA than of fenibut may perhaps be due to the absence of the hormonal background, with which changes in the composition and sensitivity of receptors of uterine smooth muscle cells are associated [3, 10], in ovariectomized animals.

The data obtained during a study of the action of agonists and antagonists of GABA receptors on myometrial contractions show that the GABA receptor system of the rabbit uterus plays an important role in regulation of the functional inhibition of uterine contractile activity. This provides a basis for the study of GABA derivatives as potential agents for the prevention of abortion in cases of hyperactivity of the uterus and of threatened abortion.

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