EFFECT OF GABA-POSITIVE SUBSTANCES ON STIMULATION OF UTERINE CONTRACTIONS BY EXCITATORY NEUROTRANSMITTERS, PROSTAGLANDIN $F_{2\alpha}$, AND OXYTOCIN

P. I. Sizov

UDC 618.14-009.12-02:[615.357:577.175.82]-085.31:547.466.3].092.4

KEY WORDS: neurotransmitters, GABA, myometrial contractions.

The problem of the premature termination of pregnancy remains one of the most urgent for obstetrics and gynecology [3, 7]. Among the factors involving high risk of spontaneous abortions and premature labor, those of theoretical importance include a significant increase in production of sympathetic mediators by mother and fetus [3].

In this investigation the effect of excitatory transmitters, prostaglandin $F_{2\alpha}$, and oxytocin on contractions of the isolated myometrium and the action of GABA-positive drugs on effects of neurotransmitters, prostaglandin, and oxytocin were studied.

METHODS

Altogether two series of experiments were carried out in vitro on 179 segments of the uterine cornua from 22 ovariectomized rabbits and 10 nonpregnant rats. The animals were killed under ether anesthesia, the uterus was removed, and the experiments were carried out by the method described previously [8]. In series I the effect of dopamine hydrochloride, noradrenalin hydrotartrate, serotonin adipinate, acetylcholine chloride, prostaglandin $F_{2\alpha}$, and oxytocin was investigated and the action of GABA, fenibut (β-phenyl-GABA) and diazepam on contractile activity of the myometrium of the animals also was studied. In series II the effect of GABA-positive substances on the action of neurotransmitters, prostaglandin, and oxytocin was studied.

RESULTS

The experiments of series I showed that dopamine hydrochloride stimulates spontaneous contractions of the isolated segments of the uterus of animals in an optimal concentration of $6.5 \cdot 10^{-6}$ M. The dopamine receptor agonist apomorphine hydrochloride, in a dilution of $3.1 \cdot 10^{-6}$ M, has a similar stimulating action on the uterus. Noradrenalin hydrotartrate has its optimal stimulating action on the uterus in a concentration of $5.9 \cdot 10^{-7}$ M. Serotonin adipinate has a stimulating effect on isotonic contractions of uterine segments in dilutions of between $6.2 \cdot 10^{-5}$ and $1.2 \cdot 10^{-4}$ M. L-Tryptophan in a concentration of $3.4 \cdot 10^{-5}$ M has a similar excitatory action on contraction of the segments. Acetylcholine chloride begins to have a stimulating effect on the uterus in a dilution of $1.1 \cdot 10^{-6}$ M. Prostaglandin $F_{2\alpha}$ stimulates uterine contractions in a concentration of $2.1 \cdot 10^{-7}$ M. Oxytocin was found to have a stimulating action on contractions of the isolated myometrium in a dilution of 1 U/100 ml Ringer—Locke nutrient solution.

The study of the GABA-positive drugs showed that GABA has a depriming action on spontaneous contractions of intact uterine segments of animals in a concentration of $4 \cdot 10^{-2}$ M, probably because of the difficulty with which it passes through biological membranes. Fenibut induces an inhibitory effect on the uterus in a dilution of $1.8 \cdot 10^{-3}$ M. Diazepam inhibits contractions of the isolated myometrium in a concentration of $3.5 \cdot 10^{-5}$ M.

Department of Pharmacology, Smolensk Medical Institute. (Presented by Academician P. V. Sergeev, Academy of Medical Sciences.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 113, No. 4, pp. 387-389, April, 1992. Original article submitted September 17, 1991.

0007-4888/92/0004-0513$12.50

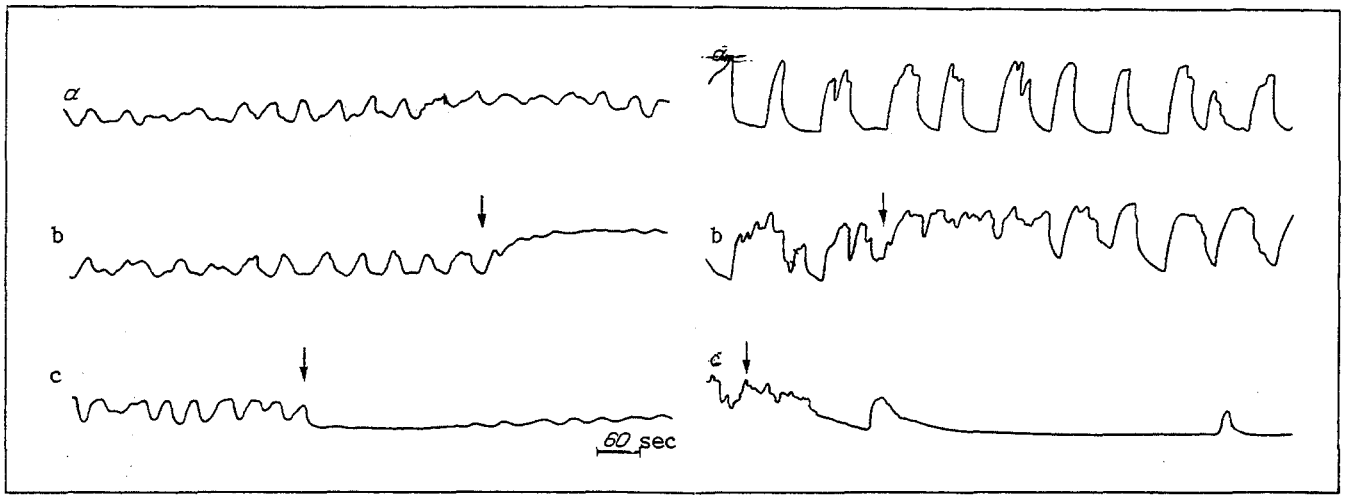

Fig. 1

Fig. 2

Fig. 1. Effect of fenibut on stimulating action of dopamine on the uterus: a) spontaneous contractions of isolated rabbit uterine cornu; b) action of dopamine in a concentration of $6.5 \cdot 10^{-6}$ M; c) action of fenibut in a dilution of $1.8 \cdot 10^{-3}$ M.

Fig. 2. Effect of diazepam on stimulating action of prostaglandin $F_{2\alpha}$ on the uterus: a) spontaneous contractions of intact rabbit uterine cornu; b) action of prostaglandin in a concentration of $2.1 \cdot 10^{-7}$ M; c) effect of diazepam in dilution of $3.5 \cdot 10^{-5}$ M.

In the experiments of series II, against the background of the stimulating action of the neurotransmitters on the uterus, prostaglandin and oxytocin affected the action of GABA-positive agents. GABA was found to have an inhibitory action on the stimulating effects of dopamine, apomorphine, noradrenalin, serotonin, acetylcholine, prostaglandin $F_{2\alpha}$, and oxytocin in the same concentration ($4 \cdot 10^{-2}$ M). Fenibut inhibits the stimulating effects of excitatory neurotransmitters, prostaglandin, and oxytocin on the uterus in a dilution of $1.8 \cdot 10^{-3}$ (Fig. 1). Diazepam inhibits the stimulating action of dopamine, noradrenalin, serotonin, acetylcholine, prostaglandin, and oxytoxin in a concentration of $3.5 \cdot 10^{-5}$ M (Fig. 2).

The experimental results show that the excitatory neurotransmitters dopamine, noradrenalin, serotonin, and acetylcholine, and also prostaglandin $F_{2\alpha}$ and the neuropeptide oxytocin have a stimulating effect on contractions of the isolated myometrium. These findings suggest that the endogenous physiologically active substances listed above can participate in the development of a hyperactive state of the uterus. Hypertonia of the uterus may thus be due not only to a central, but also a peripheral (receptor) mechanism of regulation of myometrial contraction. This conclusion is supported by direct experiments on the isolated myometrium.

The results also are evidence that GABA, fenibut, an agonist of $GABA_B$-receptors [1, 4, 5], and the benzodiazepine receptor agonist diazepam, which has a GABA-ergic mechanism [2, 6], mediate their inhibitory action on the stimulating effects of the endogenous drugs tested on the uterus evidently through the GABA-benzodiazepine receptor systems of the myometrium. This suggests that GABA-positive substances and the GABA-ergic system behave as physiological antagonists of dopamine, noradrenalin, serotinin, acetylcholine, prostaglandin $F_{2\alpha}$, and oxytocin in their action on the uterus.

Our results demonstrate the potential value of a study of GABA-positive drugs and benzodiazepines as protectors of pregnancy in threatened abortion due to increased activity of endogenous physiologically active substances in GABA-deficient states.

LITERATURE CITED

1. L. H. Allikmets, L. K. Rägo, and A. M. Nurk, *Byull. Éksp. Biol. Med.*, No. 5, 64 (1982).

2 A. Ya. Korneev, *Mechanisms of Action of Anxiolytics, Anticonvulsants, and Sedatives* [in Russian], Kiev (1988), p. 27.
3. V. N. Kulakov, T. V. Chervakova, V. M. Sidel'nikova, et al., *Vest. Akad. Med. Nauk SSSR,* No. 5, 3 (1990).
4. K. S. Raveskii and V. P. Georgiev, *Mediator Amino Acids: Neuropharmacological and Neurochemical Aspects* [in Russian], Moscow (1986).
5. L. K. Rägo, A. M. Nurk, A. Ya. Korneev, et al., *Byull. Éksp. Biol. Med.*, No. 11, 58 (1982).
6. P. V. Sergeev and N. L. Shimanovskii, *Receptors of Physiologically Active Substances* [in Russian], Moscow (1987).
7. V. M. Sidel'nikova, *Premature Labor* [in Russian], Moscow (1986).
8. P. I. Sizov and V. S. Yasnetsov, *Byull. Éksp. Biol. Med.*, No. 11, 576 (1985).