ROLE OF $GABA_A$- AND $GABA_B$-RECEPTORS IN INHIBITION OF CONTRACTILITY OF THE RABBIT MYOMETRIUM INDUCED BY GABA, AOAA, AND β-PHENYL-GABA

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UDC 618.141-009.1-02:615.31:547.466.3

KEY WORDS: GABA, AOAA, β-phenyl-GABA, GABA receptors of the myometrium

A disturbance of the mechanisms of regulation of the contractile function of the uterus may arise as a result of γ-aminobutyric acid (GABA) deficiency in the central or peripheral stage of regulation. GABA is the leading neurotransmitter or inhibition in the CNS [3] and also at the periphery [7-9]. GABA-positive substances, with an inhibitory type of action, may be used as agents for pathogenetic treatment and prevention of premature termination of pregnancy due to GABA-deficient stages.

It was therefore decided to study the effect of certain GABA-positive substances on myometrial contractility (MC) experimentally and to analyze the peripheral mechanisms of action of GABA.

EXPERIMENTAL METHOD

Experiments were carried out on 122 isolated segments of the uterine cornua from 29 rabbits, ovariectomized or not pregnant, in the diestrus phase, because the uterus of these animals closely resembles in the composition of its receptors that of women. The animals were killed under intravenous amorbarbital anesthesia and the uterus removed. Fuller details of the method were described previously [6].

The effect of GABA, of amino-oxyacetic acid (AOAA), and of β-phenyl-GABA (fenibut) on MC was investigated.

EXPERIMENTAL RESULTS

The study of contractions of the uterine smooth muscle of the rabbits showed that GABA ($9.7 \cdot 10^{-4}$, $1.9 \cdot 10^{-3}$, $3.9 \cdot 10^{-3}$, and $9.7 \cdot 10^{-3}$ M), AOAA ($2 \cdot 10^{-4}$, $3 \cdot 10^{-4}$ M), and β-phenyl-GABA ($4.6 \cdot 10^{-4}$ M) had a stimulating action, whereas in other dilutions GABA ($3.9 \cdot 10^{-2}$ M) AOAA ($8 \cdot 10^{-4}$, $1.6 \cdot 10^{-3}$ M), and β-phenyl-GABA ($1.9 \cdot 10^{-3}$) caused inhibition of contractions. Bicuculline (BCC), a specific antagonist of $GABA_A$ receptors, in a range of concentrations of $1.1 \cdot 10^{-5}$, $2.7 \cdot 10^{-5}$, $5.4 \cdot 10^{-5}$, and $1.1 \cdot 10^{-4}$ M, had a consistintly stimulating effect on the uterus. Picrotoxin (PT), a blocker of the chloride channel of the GABA receptor–ionophore complex, also stimulated myometrial contractions in dilutions of $1.7 \cdot 10^{-5}$, $3.3 \cdot 10^{-5}$, and $6.6 \cdot 10^{-5}$ M.

BCC and PT, in equally effective concentrations, reversed the depressive action of GABA and, to a lesser degree, of AOAA on the uterus. GABA and AOAA, in dilutions depressing the uterus, constantly depressed the stimulating effects of BCC and PT on the uterus. BCC reversed the inhibitory effect of β-phenyl-GABA on the uterus, but not always, whereas PT did so more constantly. β-Phenyl-GABA weakened the stimulating effect of PT on the uterus and abolished the stimulating the effect of BCC on the uterus (Fig. 1).

The results show that GABA, AOAA, and β-phenyl-GABA in low dilutions stimulate, but in higher concentrations inhibit MC. This reversive dose-dependent action on contractions may be evidence that GABA-positive drugs can influence various types of myometrial GABA receptors. We know that the inhibitory effects of GABA are realized through $GABA_A$ receptors ($GABA_AR$) and $GABA_B$ receptors ($GABA_BR$) [2, 5, 7, 8]. AOAA is an inhibitor of GABA-transaminase and increases the concentration of endogenous GABA in synapses of the CNS [3]. β-Phenyl-GAVA is an agonist of $GABA_BR$ [4].

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Department of Pharmacology, Smolensk Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR M. D. Mashkovskii.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 110, No. 11, pp. 503-504, November, 1990. Original article submitted March 16, 1990.

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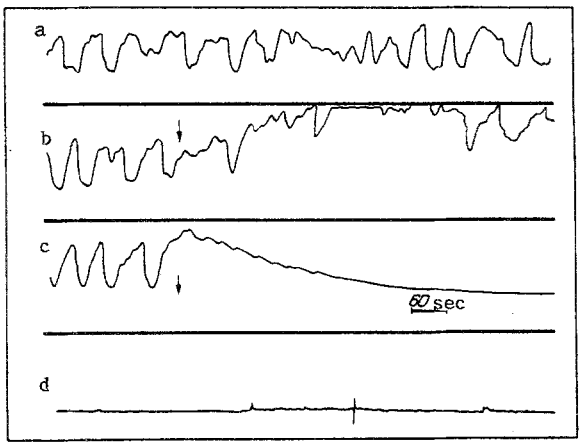

Fig. 1. Inhibition of stimulating effect of bicuculline on the uterus by β-phenyl-GABA: a) initial contractions of isolated segment of uterus from ovariectomized rabbit; b) action of bicuculline ($1.1 \cdot 10^{-5}$ M); c) action of β-phenyl-GABA ($9.3 \cdot 10^{-4}$ M) preceded by bicuculline; d) continuation of action of β-phenyl-GABA (on the same muscle segment).

In our experiments the stimulating action of GABA, AOAA, and β-phenyl-GABA on the uterus in low concentrations is evidently realized through their effect on myometrial $GABA_BR$, and facilitation of presynaptic release of excitatory neurotransmitters. The inhibitory effect of GABA and AOAA in higher concentrations is mediated through specific binding with myometrial $GABA_AR$ and postsynaptic inhibition. This is shown by the antagonistic action of GABA and AOAA, on the one hand, and BCC and PT, on the other hand, on myometrial contractions. The depressing effect of GABA on the uterus in very high concentrations may indicate that in ovariectomized rabbits and also in nonpregnant rabbits in the diestrus phase, peripheral $GABA_AR$ of the myometrium belong to the low-affinity type. Low-affinity $GABA_{A_2}R$ are present in the CNS [2]. Another possibility is that endogenous GABA exhibits low affinity for peripheral $GABA_AR$ in the myometrium. This suggestion is supported by the fact that the depressant activity of AOAA on the uterus was 50-60 times stronger than that of exogenous GABA, and 2 or 3 times stronger than that of β-phenyl-GABA. The uterotropic action of AOAA proves the presence of biosynthesis of the endogenous ligand GABA in the smooth muscle of the rabbit uterus.

The mechanism of the depressant action of β-phenyl-GABA on the uterus is more complex. As a $GABA_BR$ agonist, β-phenyl-GABA in higher dilutions inhibits uterine contractions on account of binding with myometrial $GABA_BR$. In that case β-phenyl-GABA acts as a modulator of presynaptic inhibition of dopamine and acetylcholine release. However, the one-way antagonism with BCC and PT is evidence of binding of β-phenyl-GABA and with myometrial $GABA_AR$. This is in agreement with data in the literature [1] on the action of β-phenyl-GABA not only on BCC-insensitive, but also on BCC-sensitive GABA receptors of the CNS.

Thus the results of pharmacological analysis show that the stimulating effects of GABA, AOAA, and β-phenyl-GABA on the uterus are mediated through myometrial $GABA_B$ receptors. $GABA_A$ receptors are involved in the mechanism of the depressant action of GABA, AOAA, and β-phenyl-GABA on the uterus. This is proved by the antagonistic action of BCC, a specific antagonist of $GABA_A$ receptors, on myometrial contractions, and the reversibility by BCC of the effects of GABA, AOAA, and β-phenyl-GABA. On this basis it can be postulated that the GABA-ergic system is involved in the regulation of the inhibitory function of the rabbit uterus at the peripheral level of the effector itself. The results are evidence of the promising nature of the preclinical study and clinical trials of GABA-positive drugs as potential protective agents for the prevention of threatened abortion associated with pathological uterine hypertonia due to GABA deficiency.

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