result from a more active cell metabolism in the myometrium. "Interference" in the plasma membrane reception of sex steroids during myoma growth characterizes the abnormal sensitivity of tumor cells to regulatory agents.

We have found that the recognition of tropic hormones at the PM level is impaired during tumor growth. Changes in the membrane reception of estrogens and progestins are the most informative criterion of the development of hyperplastic processes in the myometrium. A decrease in the exposure of the progesterone receptors on the cell surface causes a diminution of tissue sensitivity to gestagens.

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Experimental Validation for a Clinical Study of GABA-Positive Substances in Threatened Abortion

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The barouterography method revealed that intravenous phenibut in a dose of 50 mg/kg and phenazepam in a dose of 2.5 mg/kg have a suppressive effect on the contractile isometric (fetus-expelling) activity of the uterus in nonpregnant and pregnant rabbits. Phenibut (150 mg/kg) and phenazepam (3 mg/kg) do not have an adverse effect on fetal development in rats. Clinical trials of phenibut and phenazepam as gravidoprotectors in threatened abortions are recommended.

Key Words: *tocolytics; phenibut; phenazepam*

Spontaneous abortions have a negative impact on female reproductive function and on the health of the progeny, being one of the principal causes of childhood morbidity and mortality [5,8]. There is thus a pressing need to develop effective and safe pregnancy protectors as means of etiopathogenetic therapy.

We searched for potential tocolytics among the agents activating the GABAergic system. Published data on γ-aminobutyric acid (GABA) as the prin-

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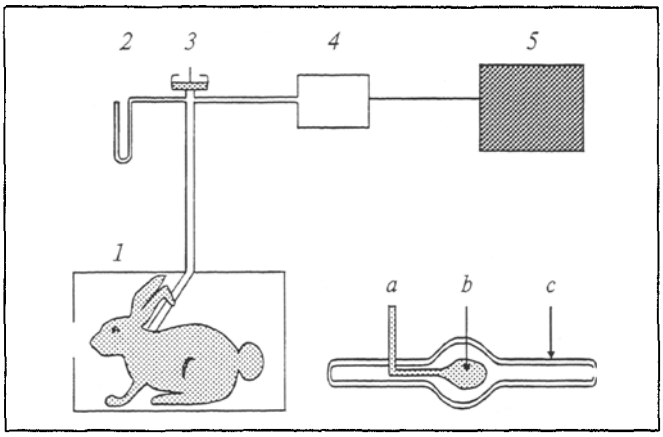

Fig. 1. Scheme of the modified barouterography method. *1*) cage with animal; *2*) water pressure gauge; *3*) capsule for creation of initial pressure in balloon; *4*) barotransformer; *5*) ink–writing device; *a*) tube, *b*) intrauterine balloon, *c*) uterine horn.

cipal neurotransmitter of inhibition [9] and on its contribution to the central regulation of reproductive function [14,15] formed the theoretical basis for our research.

MATERIALS AND METHODS

Two series of experiments were carried out. In the first series, using the internal balloon uterography method [13] modified by us, the uterolytic characteristics of a GABA derivative, phenibut, and the benzodiazepine phenazepam were studied in rabbits. A rubber balloon was surgically implanted in the lumen of the uterine horn of a female rabbit under ether narcosis. The tube was led under the skin and its end brought out on the dorsal surface of the animal. For the measurement of intrauterine pressure (IUP), a water pressure gauge was included in the recording system (Fig. 1). Induced contractile (isometric) activity of the uterine horn involving the longitudinal and circular layers of the myometrium develops in response to balloon dilatation of the horn wall. Synchronous contractions of the horn and IUP fluctuations, the barouterogram, were recorded. Myometrial tone was assessed from the minimal IUP during a pause. The force of uterine contractions was assessed from the maximal IUP at the peak of contractions. The frequency of contractions was recorded. Hence, using barouterography, we created a model for a study of GABAergic agents on the isometric (fetus-expelling) uterine contractility *in vivo* in nonpregnant and pregnant animals. Forty-six nonpregnant (in the diestrus phase) or oophorectomized rabbits and 12 rabbits on gestation days 26-30 were used. A total of 58 experiments were carried out. Phenibut was injected intravenously in doses of 100, 50, and 25 mg/kg, phenazepam in doses of 2.5 and 1 mg/kg. In studies of the combined effect phenibut plus phenazepam was injected in low doses, 25 and 1 mg/kg, respectively. Normal saline was i.v. injected to controls. The experimental and control groups each consisted of 6 to 10 animals.

In the second series the effects of phenibut, phenazepam, and their combinations on fetal growth and development were studied in rats, the agents being administered intragastrically on gestation days 16 to 20. Phenibut in a dose of 150 mg/kg in 2% starch gel, phenazepam in a dose of 3 mg/kg, or a combination of phenibut (150 mg/kg) and phenazepam (3 mg/kg) was injected daily into the stomach of experimental animals, each group consisting of 20 rats. Control pregnant rats were administered a 2% colloid starch solution in the stomach. On gestation day 21 after euthanasia the embryonal material (fetuses and placenta) was analyzed, as were the status of the viscera after Wilson's method modified by A. P. Dyban *et al.* and the bone system after Dawson.

RESULTS

Results of the first series of experiments are summarized in Table 1. Phenibut in a dose of 50 mg/kg induced a reliable decrease of the force of isometric contractions of the uterus 1, 2, and 3 h ($p<0.01$) and a marked reduction of the frequency of contractions 2 and 3 h ($p<0.05$) after injection. Injection of phenibut in a dose of 100 mg/kg resulted in the cessation of uterine contractions. At the same time relaxation of skeletal muscles was observed in the animals. Phenazepam in a dose of 2.5 mg/kg led to a reduction of myometrial tone after 1 h ($p<0.05$), reliably depressed the force of induced uterine contractions during 3 h ($p<0.05$), and noticeably reduced the frequency of contractions 2 h ($p<0.02$) after injection.

Phenibut (50 mg/kg) plus phenazepam (2.5 mg/kg) similarly depressed the laborlike uterine contractions in pregnant rabbits (days 26-30 of gestation) to the point of cessation.

A uterodepressant effect was attained after a combined injection of phenibut and phenazepam in lower doses (25 and 1 mg/kg, respectively).

A study of the effects of the drugs on fetogenesis indicated that phenibut and phenazepam alone and in combined administration to rats during the fetal period of pregnancy did not induce any significant changes in the viscera and bone system of the fetuses. The results agree with published data. Phenazepam administered to rats, guinea pigs, dogs, and mini-pigs in doses from 1 to 50 mg/kg showed

TABLE 1. Effects of Phenibut in a Dose of 50 mg/kg and Phenazepam in a Dose of 2.5 mg/kg on the Contractile Isometric Activity of the Uterus of Nonpregnant Rabbits ($M \pm m$)

Drug	Postinjection period, min	IUP, mm H_2O		Intervals between (frequency of) uterine contractions, sec
		minimal	maximal	
Phenibut	60	85.0±2.35	102.8±3.08*	65.2±3.88
	120	80.7±2.75	97.8±3.70*	68.5±3.27*
	180	77.8±2.59	90.7±3.98*	67.0±3.10*
Phenazepam	60	80.7±1.40*	105.0±2.88*	60.7±3.06
	120	76.4±1.54	96.4±2.55*	68.8±2.57*
	180	72.1±1.09	91.4±2.55*	72.2±3.37
Control	60	87.0±1.95	116.0±2.04	58.5±2.04
	120	82.0±2.38	108.0±2.50	60.1±2.24
	180	76.0±2.69	101.5±3.33	77.3±2.50

Note. Asterisk shows a statistically reliable difference from the control.

no embryotoxic or teratogenic effects [6,12]. Phenibut administered to women with gestoses from gestation weeks 28 to 41 had no detrimental effects on the newborns. The early neonatal period proceeded uneventfully in the majority (98.06%) of the newborns [1,4].

The results of investigations indicate that the GABA-positive agents phenibut, characterized by nootropic and antihypoxic effects [7], and phenazepam, a tranquilizer with a GABAergic mechanism of action [2], are promising pregnancy protectors which have no negative effects on the maternal or fetal organism in experiments. Phenibut and phenazepam are characterized by a physiologic GABAergic mechanism of inhibition of uterine contractility [11].

The present findings and published data give grounds for recommending clinical trials of the Russian-manufactured drugs phenibut and phenazepam as gravidoprotectors. According to our recommendations, the indications for prescribing phenibut and phenazepam are increased excitability and contractility of the uterus in the second and third trimesters of pregnancy, the presence of such risk factors as GABA-deficient states, or hyperproduction of prostaglandins, oxytocin, bradykinin, dopamin, noradrenalin, and serotonin, which exert a direct uteroinducing effect [10]. As sedative agents, phenibut and phenazepam are recommended in threatened miscarriages under conditions of stress. GABA-positive agents may be potentially effective in threatened abortions caused by immunological conflicts between mother and fetus. GABA- and benzodiazepines (phenazepam, diazepam) are characterized by immunosuppressive effects [3].

Phenibut is tentatively recommended to be administered orally in a dose of 0.75 mg/kg every 8 h during the first 2 days, and from day 3 in a dose of 0.5 mg/kg every 8 h for 3-5 days more. An interval of 5 to 7 days is recommended after a course of treatment. Phenibut is indicated for women with a predominant asthenic syndrome. It has a more effective uterodepressant action if used in combination with phenazepam due to a mutual boost of the uterolytic and fetoprotective effect. This is why in more threatening cases and in states of excitation, increased irritability, and anxiety phenibut is recommended in a dose of 0.5 mg/kg together with phenazepam in a dose of 0.001 (1 mg) orally 3 times a day for 5-7 days followed by an interval of 3-5 days. If emergency tocolysis is needed, phenazepam should be injected intramuscularly in a dose of 1-2 ml of a 0.1% ampoule solution.

The studies have demonstrated a suppressive effect of phenibut and phenazepam on the contractile isometric (fetus-expelling) activity of the uterus in nonpregnant and pregnant rabbits. Phenibut and phenazepam alone and in combination have no negative effect on fetal development in rats. The uteroinhibitory activity and safety for the fetus give grounds for recommending clinical trials of phenibut and phenazepam in threatened abortions.

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Radioprotective Action of Lymphokinin, a Composite Preparation of Cytokines

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Lymphokinin injected into mice in a dose of 25,000 U/kg intraperitoneally before or after their single irradiation producing acute radiation sickness is found to prolong their survival. The optimal time for administering Lymphokinin depends on the radiation dose. Its survival-prolonging effect is most marked when it is injected 1 h or 24 h before or 23 h after exposure to a dose of 6.0 Gy.

Key Words: *Lymphokinin (a composite preparation of cytokines); radiation; radiation protection; survival*

One sequela of radiation is damage to the bone marrow with subsequent impairment of hematopoiesis. As a result, various disturbances of the immune status occur and the risk of opportunistic infections and cancer rises considerably, so that the outcome for humans and animals is often fatal.

In recent years, intense efforts have been expended all over the world in the search for radioprotectants-immunostimulants, i.e., medicinal substances that can both enhance the body's resistance to radiation and strengthen the body's natural immune defenses against infection and tumor growth. Therapies relying on the use of cytokines to speed the recovery of bone marrow hematopoiesis and protect against radiation are being developed [3,7,11]. Being natural regulators of the immune and hematopoietic systems, cytokines act as powerful immunostimulants [2-5,9,10].

The purpose of the experiments described here was to evaluate the radioprotective potency of Lymphokinin, a preparation developed at the Center for Cancer Research, Russian Academy of Medical Sciences, and composed of interleukins 1, 2 (its main cytokine), and 6 (IL-1, IL-2, and IL-6) and tumor necrosis factor (TNF).

Center for Cancer Research, Russian Academy of Medical Sciences, Moscow; Research Institute of Military Medicine, Ministry of Defence, St. Petersburg. (Presented by N. N. Trapeznikov, Member of the Russian Academy of Medical Sciences)

MATERIALS AND METHODS

The experiments were carried out on random-bred mice weighing 18-20 g. After all mice had been kept under quarantine surveillance for 7-10 days in

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