The investigation thus showed that GABA-INA increases the cerebral circulation and lowers the tone in the two arterial systems of the brain. This effect is more marked in waking cats than in cats under general anesthesia. The compound also lowers the blood pressure. It must also be noted that GABA-INA gives a stronger and more lasting cerebrovascular effect than GABA itself and papaverine [5, 6].

It can be concluded from these results that GABA-INA is a promising drug for clinical use in patients with cerebrovascular disorders.

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EFFECT OF β-ADRENOMIMETICS AND β-ADRENOBLOCKERS ON THE ACTION OF BRADYKININ

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The writer showed previously that the α-adrenoblockers phentolamine and tropaphen reduce the action of bradykinin on extravascular smooth muscles but do not alter the depressor effect of this polypeptide [2]. There is also evidence that the β-adrenoblockers inderal and visken potentiate the depressor effect of bradykinin [1].

The aim of the present investigation was to study the effect of β-adrenomimetics (isoproterenol, orciprenaline, inoline) and also of selective β_1-adrenoblockers (atenolol, practolol) and unselective β_1- and β_2-adrenoblockers (propranolol, pindolol, oxprenolol) on changes in smooth muscle tone, microvascular permeability, and the arterial pressure level caused by bradykinin.

EXPERIMENTAL METHOD

The effect of β-adrenomimetrics (β-AM) and β-adrenoblockers (β-AB) on changes in tone of the extravascular smooth muscle caused by bradykinin was studied on isolated segments of the ileum from guinea pigs weighing 250-350 g. The biphasic response of the intestine to bradykinin (relaxation, giving way to spasm) was recorded under isotonic conditions by means of a balanced pen on the smoked drum of a kymograph.

β-AM and β-AB, dissolved in Krebs' solution, were added in concentrations of between $1 \cdot 10^{-10}$ and $1 \cdot 10^{-5}$ g/ml to the vessel containing the test organ 3 min before bradykinin ($1 \cdot 10^{-8}$ g/ml). The action of each concentration was studied on 5-7 segments of intestine. The experiments results were subjected to statistical analysis.

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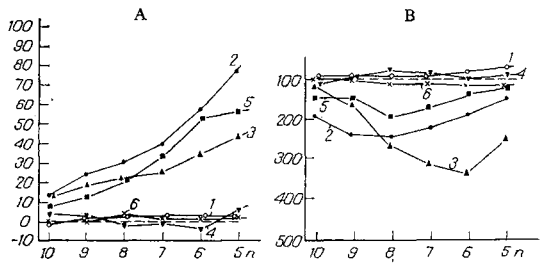

Fig. 1

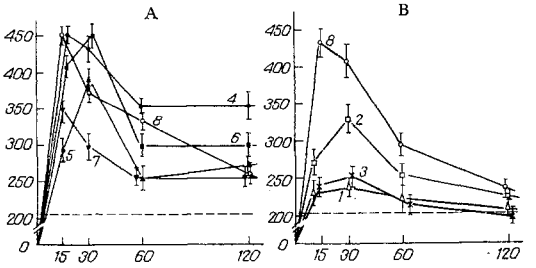

Fig. 2

Fig. 1. Effect of β-AB on spasmogenic (A) and relaxation (B) phases of action of bradykinin on isolated guinea pig ileum. Abscissa, concentration of drugs (in g/ml·10^{-n}); ordinate, change in response to bradykinin (in % of initial responses). 1) D-Propranolol; 2) D,L-propranolol; 3) pindolol; 4) atenolol; 5) oxprenolol; 6) practolol.

Fig. 2. Effect of β-AB (A) and β-AM (B) on dynamics of bradykinin edema of the limb in rats. Abscissa, time (in min); ordinate, change in limb volume (in μl). 1) Isoproterenol (0.1 m g/kg); 2) orciprenaline (0.1 mg/kg); 3) inoline (0.1 mg/kg); 4) D,L-propranolol (1 mg/kg); 5) pindolol (0.5 mg/kg); 6) atenolol (1 mg/kg); 7) oxprenolol (1 mg/kg); 8) control.

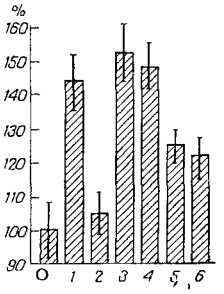

Fig. 3. Effect of β-AB (0.5 mg/kg, intravenously) on depressor effect of bradykinin in rats (in %). O) Original response of BP to bradykinin, taken as 100%; 1,2) propranolol, 3) pindolol, 4) oxprenolol, 5) atenolol, 6) practolol.

The effect of β-AM and β-AB on the course of the edema arising in response to injection of 0.1 ml of a 0.01% solution of bradykinin beneath the plantar aponeurosis of the right hind limb was studied in male rats weighing 130-150 g. The volume of the limb was measured oncometrically before and 15, 30, 60, and 120 min after injection of bradykinin. The drugs in doses inducing a specific effect (0.1 mg/kg for β-AM and 0.1-1.0 mg/kg for β-AB), dissolved in isotonic NaCl solution, were injected intraperitoneally 15 min before the bradykinin. Animals of the control groups were given an intraperitoneal injection of 0.5 ml of isotonic saline. The action of each dose of the drugs was studied on 6-8 animals.

The effect of β-AB on the magnitude and duration of the depressor response to intravenous injection of bradykinin in a dose of 0.1-0.5 μg/kg was studied in male rats weighing 200-250 g anesthetized with urethane (1 ml of the 10% solution/100 g body weight, intraperitoneally). The arterial pressure (BP) was recorded by a mercury manometer in the common carotid artery. Bradykinin and β-AB, dissolved in isotonic saline, were injected through a catheter into the jugular vein in a dose of 0.1-0.3 ml.

The following drugs were used: bradykinin triacetate was from Reanal, Hungary; isoproterenol (novodrin) was from Germed, East Germany; orciprenaline (alupent) was from Zdravlje, Yugoslavia; inoline (tretoquinol) was from Farmakhim, Bulgaria; D- and D,L-propranolol (inderal), pindolol (visken), atenolol, and practolol were all from ICI, England; oxprenolol (trasicor) was from Gedeon Richter, Hungary.

EXPERIMENTAL RESULTS

Unselective β-AB (propranolol, pindolol, and oxprenolol), which affect β_1-receptors of the heart and β_2-receptors of the blood vessels and smooth-muscle organs, starting with a concentration of $1 \cdot 10^{-9}$ g/ml caused a decrease in the spasmogenic phase of the response of the ileum to bradykinin, accompanied by an increase in the relaxation phase (Fig. 1). The effect of the drugs was dose-dependent in character and reached a maximum in the highest concentration tested

($1 \cdot 10^{-5}$ g/ml), in which propranolol reduced the spasmogenic phase of the response to bradykinin by 76 ± 12%, pindolol by 42 ± 9%, and oxprenolol by 56 ± 8%. Cardioselective β-AB (atenolol and practolol) did not affect the myotropic effects of bradykinin in any of the concentrations used. D-propranolol, which has no β-adrenoblocking properties, did not change the action of bradykinin. The reduction in the spasmogenic phase of the action of bradykinin on the intestinal smooth muscle accompanied by a simultaneous increase in the relaxation phase, produced by the unselective β-AB, was thus due to the specific pharmacological properties of these drugs, which block β_2-adrenoreceptors, that are evidently concerned in the mechanism of the myotropic effects of the kinins through a change in the sensitivity of the kinin receptors to the action of the ligand.

β-AM (isoproterenol, orciprenaline, and inoline) had a similar inhibitory action on the spasmogenic effect of bradykinin when given in concentrations of $1 \cdot 10^{-6}$-$1 \cdot 10^{-5}$ g/ml but did not change the relaxation of the intestine produced by bradykinin.

β-AM in a dose of 0.1 mg/kg reduced bradykinin edema of the limb in rats throughout the 2-hour period of observation. The strongest antibradykinin effect was given by isoproterenol and inoline, which reduced the response of the microvessels to bradykinin by 85-90% at the period of its maximal intensity; orciprenaline was less active (Fig. 1).

Depending on the presence or absence of partial agonistic activity, the β-AB had opposite effects on the dynamics of bradykinin edema. Propranolol and atenolol, with no partial agonistic activity, potentiated and prolonged the reactive edema starting from 30 min after injection of bradykinin, whereas pindolol and oxprenolol, with their partial agonistic (isoproterenol-like) action [3], evoked an antibradykinin effect similar to the action of β-AM throughout the period of observation. The results of this series of experiments indicate that the microcirculatory effect of bradykinin are weakened by substances stimulating the β-adrenoreceptors of the microvessels, whereas blocking these receptors potentiates and prolongs the microcirculatory disturbances induced by kinins.

β-AB, starting with a dose of 0.1-0.5 mg/kg (intravenously) potentiated the depressor response evoked in rats by intravenous injections of bradykinin (Fig. 3). Increasing the dose of the drugs to 1 mg/kg had no effect on the bradykinin-potentiating effect of β-AB. The drugs tested did not differ significantly in activity, they increased (when used in the above doses) the response of BP to bradykinin by 20-50%, and their action lasted from 40 to 120-180 min. Besides potentiating the effect of bradykinin, β-AB prolonged the responses of BP to this polypeptide from 10-20 to 40-60 sec. In these experiments, like those *in vitro*, D-propranolol did not change the bradykinin effect.

The data showing potentiation by β-AB of the depressor effect of bradykinin are evidence that β-adrenergic mechanisms participate in the mechanism of the vascular effects of the kinins. Meanwhile prolongation by β-AB of the depressor action of bradykinin may also be linked with their effect on kinin metabolism, for there is evidence of an activating effect of β-AB on kinin formation in rats [4]. The possibility likewise cannot be ruled out that these drugs inhibit activity of kinin-decomposing enzymes.

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