ANTAGONISTIC PROPERTIES OF A TETRASUBSTITUTED VASOPRESSIN ANALOG WITH SELECTIVE ANTIDIURETIC ACTION

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An important role in the regulation of many processes taking place in man and animals is played by the neurohypophyseal hormones (NHH) vasopressin and oxytocin. However, the broad spectrum of pharmacologic action of NHH (vasopressor, oxytocic, antidiuretic, and other activities) limits their use in medicine. An intensive search is therefore in progress for synthetic analogs of vasopressin and oxytocin, possessing selectivity of action. Meanwhile, the creation of effective antagonists of vasopressin and oxytocin is of great importance for the treatment of pathological states associated with raised NHH blood levels (coronary insufficiency, renal hypertension, etc.) and also for the study of the mechanisms of hormone—receptor interaction.

This paper gives the results of a study of the biological activity of a new tetrasubstituted analog of vasopressin (compound I), synthesized in the Laboratory of Peptide Chemistry, Institute of Organic Synthesis, Latvian Academy of Sciences.

EXPERIMENTAL METHOD

The effect of the substances on arterial blood pressure (BP) was studied in experiments on male and female albino rats weighing 180-200 g, anesthetized intraperitoneally with 25% urethane solution (0.5 ml/100 g body weight). BP was recorded in the common carotid artery by means of a "Bentley Trantic Physiological Pressure Transducer" on a two-channel "Gemini" automatic writer (Ugo Basile, Italy). The substances were injected into the femoral vein in a volume of 0.1 ml/200 g body weight, in doses of 0.05 to 500 μg/kg. To compare the effect of compound I on the vasopressor effect of arginine-vasopressin (in a dose of 0.025 μg/kg), synthesized at the Experimental Factory of the Institute of Organic Synthesis of the Latvian Academy of Sciences (vasopressor activity 248 ± 28 IU/mg) we used compound II [1-(β-mercapto-β,β'-cyclopentamethylenepropionic acid], 2-0-methyltyrosine, and 8-arginine-vasopressin (H-5350, from Budendorf, Switzerland). The two compounds were injected in different doses 3 min before injection of arginine-vasopressin and the effect of the latter was evaluated in the absence and in the presence of compounds I and II. Inhibitory effects of the substances was expressed by the value of ID_{50} (the dose inducing 50% inhibition of the effect of arginine-vasopressin).

Oxytocic activity of compound I was studied within the concentration zone from 10^{-9} to 10^{-5} M in experiments on the isolated uterus of rats weighing 180-200 g by the method in [2]. The preparations were incubated in Jalon's solution at 32°C, aerated with air, and with a load of 1 g. Contractions were recorded under isometric conditions by a TB-611T transducer connected to an RM-6000 polygraph (Nihon Kohden, Japan). The action of compound I on the myotropic effect of arginine-vasopressin was assessed by comparison with that of compound II. Preliminary exposure of the compounds with the antagonists continued for 3 min. The inhibitory action of the substances was assessed as the difference (Δ, %) between the myotropic effects of arginine-vasopressin in the absence and in the presence of antagonists. The value of pA_2 was calculated from curves showing the inhibitory effect of the test substances as a function of their concentration [2].

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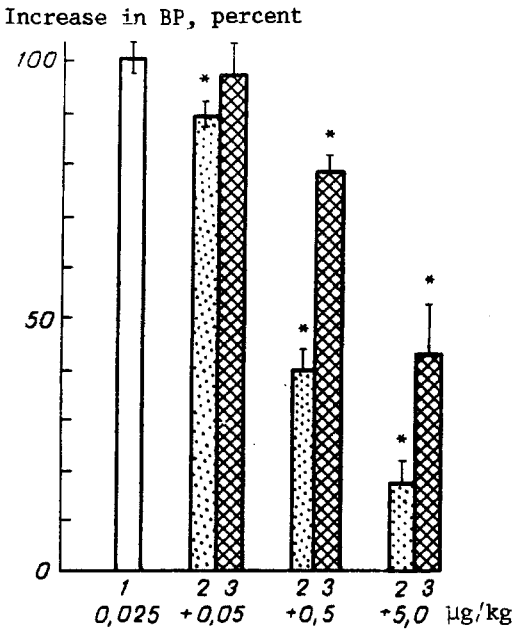

Fig. 1. Effect of compounds I (1) and II (2) on vasopressor effect of arginine-vasopressin (3) in experiments on anesthetized rats. *p ≤ 0.05. compared with arginine-vasopressin.

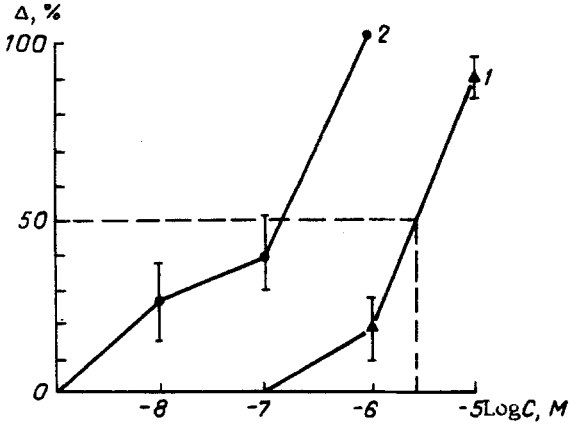

Fig. 2. Concentration–inhibitory effect curves of compound I (1) and II (2) on myotropic effect of arginine-vasopressin in experiments on isolated rat uterus.

The antidiuretic activity of compound I was compared with that of adiuretin (DDAVP) [1-(β-mercaptopropionic acid), 8-arginine-vasopressin; from Spofa, Czechoslovakia] by the method in [1, 3] in the modification [4]. Activity was assessed in experiments on male rats weighing 150-250 g by comparing the mean half-periods of diuresis ($T_{1/2}$, time in min, taken to collect urine in a volume equal to half of the water intake), obtained after injecting the test substances in different doses into the rats.

During statistical analysis of the results each value was determined as the arithmetic mean of 6 experiments ± the mean square error of the arithmetic mean (σ).

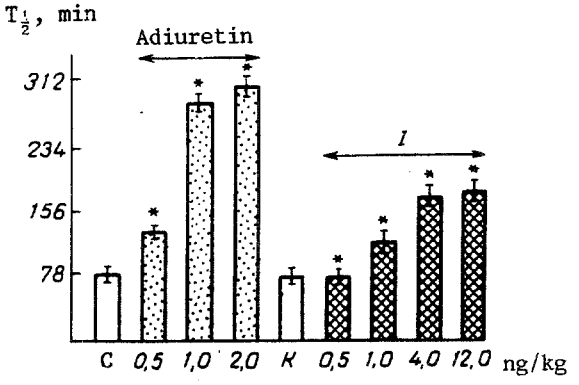

Fig. 3. Antidiuretic effect of adiuretin and compound I as a function of dose. C) Control (0.1 ml physiological saline/100 g body weight). *p ≤ 0.05 compared with control.

EXPERIMENTAL RESULTS

Experiments on anesthetized rats showed that compound I in doses of 0.05 to 500 μg/kg had no effect on BP, whereas it caused marked dose-dependent inhibition of the pressor effect of arginine-vasopressin (Fig. 1). The inhibitory effect of compound I was somewhat weaker than that of compound II (ID_{50} was 3.7 and 0.29 μg/kg respectively).

Experiments on the isolated rat uterus showed that within the concentration range from 10^{-9} M to 10^{-5} M compound I has no effect on the uterine smooth muscle, but it inhibits the myotropic effect of arginine-vasopressin (pA_2 = 5.68 ± 0.08). As Fig. 2 shows, the inhibitory effect of compound II, as in the experiments in vivo, was an order of magnitude greater (pA_2 = 6.78 ± 0.11).

The study of the antidiuretic effect of compound I showed that compared with adiuretin, which possesses marked dose dependence, the antidiuretic activity of compound I is weaker (Fig. 3). Thus the effect of compound I in a dose of 1 ng/kg is comparable with the effect of adiuretin in a dose of 0.5 ng/kg, whereas the maximal effect of compound I in a dose of 4 ng/kg is 60% of the effect of adiuretin. In the case of preliminary administration (24 h beforehand) of compound I in a dose of 4 ng/kg, the delay to excretion of urine induced by arginine-vasopressin (500 ng/kg) was reduced by half (from 4 to 2 h). This indicates that compound I not only has an antidiuretic effect, but can also exhibit an anti-antidiuretic effect, which is characteristic of partial agonists.

The investigation thus showed that compound I does not possess vasopressor or oxytocic activity, but exhibits a selective antidiuretic effect, somewhat weaker than that of adiuretin. A characteristic feature of the pharmacologic action of compound I is inhibition of the vasopressor, oxytocic, and antidiuretic effects of arginine-vasopressin, which is somewhat weaker that the effect of the imported antagonist (compound II). However, the universal nature of the antagonistic action of compound I relative to the effects of arginine-vasopressin is such that it can be used as pharmacologic tool with which to study the mechanisms of hormone-receptor interaction.

LITERATURE CITED

1. W. A. Jeffers, M. M. Liverzey, and J. H. Austin, Proc. Soc. Exp. Biol. Med., **50**, 184 (1942).
2. H. O. Shild, Pharmacol. Rev., **9**, 242 (1957).
3. H. O. Shild, J. Physiol. (London), **101**, 115 (1942).
4. J. Skopkova, R. Hrbas, and T. Barth, Endocr. Exp., **15**, 129 (1981).