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Participation of Histamine in the Cardiovascular Reactions in Response to ACTH

Udział histaminy w reakcjach układu krążenia po podaniu ACTH

Участие гистамина в реакциях системы кровообращения под влиянием АКТГ

ACTH is a hormone which exerts various effects in men and animals, among others through its actions on the cardiovascular system. It is generally assumed that the effect of ACTH on the cardiovascular system is mainly dependent on corticosteroids release, raising the blood pressure. Recently it has been demonstrated that, besides this indirect mechanism, ACTH acts on the cardiovascular system in extra-adrenal manner (10, 14, 19). These extra-adrenal effects of ACTH have not yet been elucidated. In our previous work (20) it was demonstrated that the ACTH- induced decrease of the blood pressure was associated with a rise of histamine level in blood. This has been in agreement with the recent report of Rüegg (18), who showed that ACTH and its derivatives are strong histamine-releasing agents. On the other hand histamine produced a release of ACTH in the pituitary gland (2, 17). Clinical observations of Kaiser (6) have shown that in some allergic skin diseases and in bronchial asthma i.e. in conditions characterized by increased histamine release, a greater therapeutic effect was obtained after ACTH than after corticosteroids treatment.

These findings made us suppose the possibility of interactions between ACTH and histamine. The question which we have studied here is whether histamine is involved in the effect of ACTH on the cardiovascular system.

MATERIAL AND METHODS

The experiments were carried out on 30 rabbits weighing 3–4 kg under general anaestesia with urethane 1 g/kg. The arterial blood pressure was recorded with Ludwig mercurial manometer in the common carotid artery. The venous pressure was determined with an aqueous manometer in the jugular vein. The heart rate was recorded with a one-channel electrocardiograph in bipolar leads using needle electrodes placed subcutaneously on the extremities.

The investigations were performed in two groups: in the first, these parameters were determined after intravenous injection of ACTH POLFA in a dose of 14 mg/kg, in the second one the ACTH effect was determined 10 minutes after the blockade of H_1 or H_2 histamine receptors.

H_1 receptors were blocked with Mepyramine Malate (May and Baker), 2,5 mg/kg, i.v. H_2 receptors were blocked i.v. with cimetidine (Lek Ljubliana Yugoslavia) in a dose of 50 mg/kg. The blocking effect of antagonist was tested with histamine (Histaminum dihydrochloricum POLFA) in a dose of 40 μg/kg.

The observations were conduced during one hour after ACTH injection. The results obtained were subjected to statistical analysis using *t* test of Student.

RESULTS AND DISCUSSION

The effects of ACTH on the arterial blood pressure before and after previous blockade of H_1 and H_2 receptors are shown in Fig. 1A. It is evident that blocking agents alone caused no significant changes in the arterial blood pressure. Treatment with histamine H_1 antagonist (Fig. 1B) following ACTH injections caused the fall of the arterial pressure to 68.3 ±4.4 mm Hg in the 10th minute after ACTH injection, similarly as in the group of rabbits receiving no blocking agents. However, this initial decrease was followed by a gradual rise of the pressure to 80.0 ±3.9 mm Hg and 88.2 ±4.6 mm Hg respectively in the 30th and 60th minute of the experiment. The pressure rise in the 30th and 60th minute was statistically significant ($p < 0.05$) in relation to the initial decrease. The arterial blood pressure reached 90% of the initial value in the 60th minute after ACTH administration and it was not significantly different from the initial value.

The arterial blood pressure response to ACTH after H_2 receptors blockade (Fig. 1C) was similar to the reaction observed after H_1 receptors blockade but a fall of the arterial blood pressure lasted a short time and was statistically significant in the first minute after ACTH administration only. In this time the arterial blood pressure decreased from 91.3 ±6.1 mm Hg to 80.3 ±6.0 mm Hg

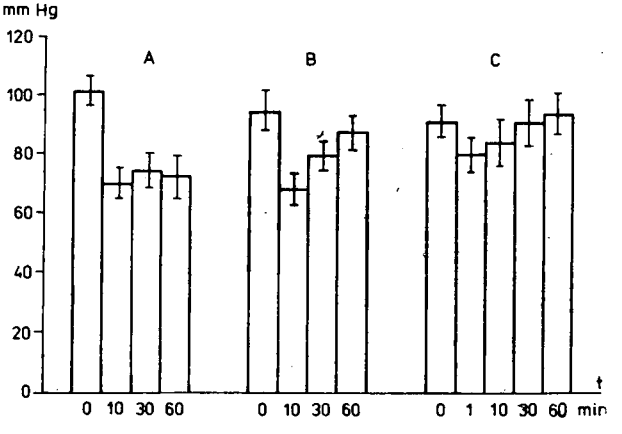

Fig. 1. A – the effect of ACTH (14 mg/kg) on the arterial blood pressure ($n = 14$), B – the same effect after H_1 receptors blockade ($n = 12$), C – the same effect after H_2 receptors blockade ($n = 10$)

($p = 0.05$). In the 10th minute after ACTH there was a rise of the blood pressure to 84.6 ±7.9 mm Hg and then to 91.6 ±7.8 mm Hg and 94.3 ±7.1 mm Hg, respectively, in the 30th and 60th minute.

The present study failed to confirm the great rise in the heart rate after ACTH administration described previously (20), when the heart rate had been calculated from the kymographic record. In the present experiment, more accurate calculations based on the elecrocardiographic records (Fig. 2) showed that ACTH produced only a slight rise in the heart rate in the first minutes, and a slight decrease from the 10th minute on. Similar changes were observed when histamine H_1 receptors blockade was followed by ACTH administration. In the first minute of hormone action the heart rate increased only from 275 ±4 to 278 ±5/min., and then it decreased to 249 ±6/min. The heart rate decrease at the end of the experiment was at the border of statistical significance of the

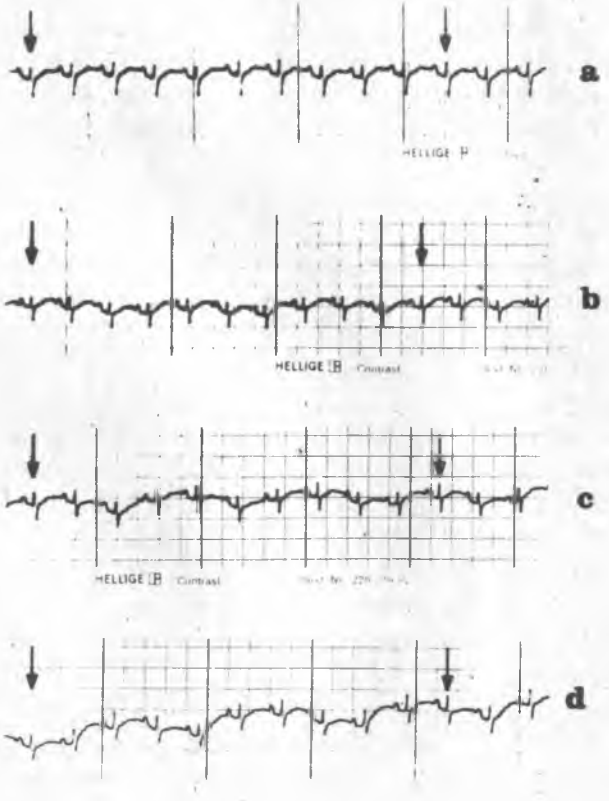

Fig. 2. Fragment of an electrocardiogram demonstrating the effect of ACTH administration (14 mg/kg) on the heart rate: a – before ACTH administration, b – 1 min after ACTH, c – 30 min after ACTH, d – 60 min after ACTH. Arrows show the distances between 10 cardiac cycles; paper speed 50 mm/s

differences ($p = 0.05$). The blockade of histamine H_2 receptors did not affect the heart rate response to ACTH in a statistical manner. A little decrease of the heart rate was observed only at the end of the experiments, similarly as in the previous groups.

The venous pressure showed no statistically significant changes either after ACTH administration only or after pretreatment with histamine antagonist following ACTH administration. It oscillated between 7.9 and 10.9 mm of water during the experiment. The present study has shown that the ACTH-induced fall in arterial blood pressure is modified by histamine antagonists pretreatment. It could be evidence to indicate the possibility of histamine being involved in ACTH action.

Cardiovascular response to histamine depends upon the kind of receptors and animals used in experments (1, 5, 16). In rabbit vascular response to histamine, just as in other animals, both H_1 and H_2 receptors are stimulated. However, in the rabbit unlike in other species, where histamine elicits the fall of arterial pressure due to vasodilatation, injections of histamine can cause biphasic changes in blood pressure: an initial pressor response followed by a depressor phase. The pressor response is due to vasoconstriction via H_1-receptor mechanism and the depressor response is due to vasodilatation via H_2-receptor mechanism (16).

Analogically, if histamine were involved in the ACTH – induced fall of arterial pressure, one could expect extension of the arterial blood pressure decrease after H_1-receptors blockade and its reduction after H_2-receptors blockade. In both situations, the reduction of arterial pressure decrease was found in our experiments. But it should be pointed out that the reduction after H_2-receptor antagonists pretreatment was more pronounced.

It is interesting that so significant ACTH – induced fall in arterial pressure is not associated with a change of the heart rate. If histamine were involved in the ACTH actions, heart rate increase should be found because both histamine receptors were thought to be involved in the positive chronotropic response to histamine (13). It was worth noting that the effect of histamine antagonists appeared with some delay in relation to the effect of ACTH and all antagonists failed to prevent pressure fall just after ACTH administration. It is possible that the action of ACTH is not homogeneous and in the first rapid phase, histamine does not participate in it.

The rapid pressure fall after ACTH administration suggests the participation of the nervous system. It is possible that ACTH, similarly as many peptide substances, may have an effect on the release of neurotransmitters from nerve endings. The connection of ACTH with activities of various nervous structures is confirmed by its presence not only in hypophysis but also in certain parts of the limbic system, thalamus and hypothalamus (7, 9). Olpe (15) demonstrated its excitatory effects on noradrenergic neurons of the *locus coeruleus*. However,

in the supposed action of ACTH via the nervous system the participation of histamine could not be excluded because histamine is one of neurotransmitters or neuromodulators in the central nervous system (4, 8, 11, 12). Further investigations may establish other mechanisms involved in cardiovascular response to ACTH.

Conclusions

1. Blockade of both H_1 and H_2 histamine receptors changed the effect of ACTH on the arterial blood pressure: it caused the ACTH-induced fall in the arterial blood pressure followed by its gradual return to the initial level.

2. Endogenous histamine may be involved in the cardiovascular response to ACTH.

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STRESZCZENIE

W ostrych doświadczeniach na królikach wykazano zmianę działania ACTH na ciśnienie tętnicze po zablokowaniu receptorów histaminowych. Zarówno substancje blokujące receptory H_1, jak i H_2 nie zapobiegają spadkowi ciśnienia w trwającej kilka minut pierwszej fazie działania ACTH. Powodują natomiast jego stopniowy wzrost i powrót do wartości początkowej w 60 minucie doświadczenia. Wydaje się prawdopodobne, że histamina jest aminą pośredniczącą w reakcji spadku ciśnienia tętniczego po podaniu ACTH.

РЕЗЮМЕ

В острых опытах на кроликах, при блокаде гистаминовых рецепторов, доказали изменения в действии АКТГ на артериальное давление крови. Как вещества блокирующие рецепторы H_1 так и H_2 не предупреждают снижения давления крови в первой стадии действия АКТГ, продолжающейся несколько минут. Вместо того вызывают его постепенный рост и возврат в 60 минуте опыта к исходной величине. Кажется вероятным, что тистамин является амином-посредником в реакции падения артериального давления крови после подачи АКТГ.