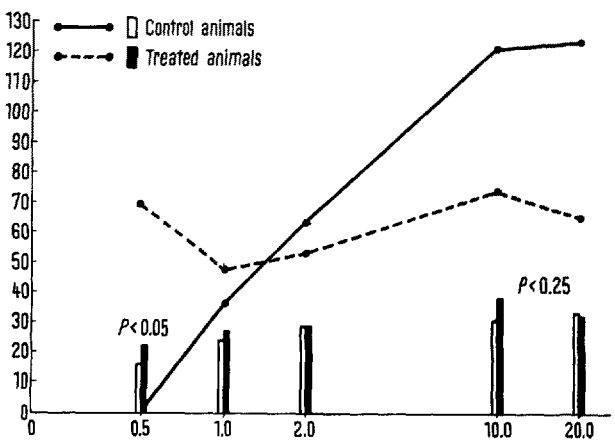
effect of 2.0 μg/kg i.v. is equal to that of the preceding dose, and that of 20.0 μg/kg i.v. is even lower than that of 10.0 μg/kg i.v.

On uterine contractility, it can be seen that in control animals there is a good dose-effect relationship by increasing the doses of angiotensin. In these animals the smallest active dose was 2.0 μg/kg i.v., the dose of 1.0 μg/kg i.v. being active only in 2 of the 7 guinea-pigs examined.

In pretreated animals, even at the dose of 0.5 μg/kg i.v., angiotensin always provokes a clear tonic contraction, by eliciting an effect higher than that elicited by 2.0 μg/kg i.v. in control animals. The second dose of the set (1.0 μg/kg i.v.) is still more active in pretreated than in control animals, but tachyphylaxis seems to be arising because the higher doses employed do not elicit potentiated effects; on the contrary the responses obtained in treated animals are always lower than those in control animals.

Discussion. The results obtained show that aldosterone pretreatment promotes a potentiation of the pressor activity of 0.5, 1.0 and 10.0 μg/kg i.v. of angiotensin, while the doses of 2.0 and 20.0 μg/kg i.v. of the same peptide are not potentiated, since tachyphylaxis takes place. Such a suggestion has been strengthened by the results obtained on uterine contractility. In fact our results show that the first 2 doses of angiotensin employed are clearly potentiated by aldosterone pretreatment (mainly the first one) in eliciting uterine contractions. With successively higher doses, the responses obtained in treated animals were always lower than those obtained in control animals. The potentiation of the lower doses of angiotensin by aldosterone is a confirmation of the results of previous experimental works both in vitro[9-11] and in vivo[7,8] and is due, in our opinion, to an alterate Na^+ distribution in the smooth muscle ensuing to aldosterone Na^+ retentive action. We suggest therefore that aldosterone is able to potentiate angiotensin activity on vascular as on extravascular smooth muscles, and can also induce tachyphylaxis to angiotensin. It was pointed out that a prolonged aldosterone administration decreases renal content of renin and renin secretion[14], and it was postulated that aldosterone is able to regulate the renin-angiotensin system by controlling renin secretion[15], thus acting as a curb to spontaneous pathological hypertensions. In our opinion the tachyphylaxis towards angiotensin induced by aldosterone administration might be another mechanism by which aldosterone itself could play an important role in regulating these functions.



Semilogarithmic graph. On the abscissa the doses of angiotensin in μg/kg i.v. The curves represent the effects (in arbitrary numerical values) of the various doses on uterine contractility. The columns represent the pressor effects (in mm Hg) elicited by the different doses employed. Statistical significance $P < 0.05$ and $P < 0.25$.

Résumé. Les auteurs examinent l'augmentation de l'action de l'angiotensine sur la pression carotidienne et sur la contraction utérine chez des animaux traités avec de l'aldostérone. Ils pensent aussi que le traitement conditionne le développement du phénomène taquiphylactique de l'angiotensine.

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Antihypertensive Effect of Co-Factors of the Synthesis and Precursors of Nucleic Acids in Experimental Hypertension

The present study is based on 2 premises: (1) The evidence obtained on the incretory antihypertensive function of the kidney[1,2] and on the role of sodium in the pathogenesis of hypertension[3-5] suggests that the excessive use of sodium chloride produces in humans a prolonged hyperfunction of incretory antihypertensive structures of the kidneys. In consequence of a gradual wearing-out of these structures, the antihypertensive renal function is reduced and hypertension develops.

(2) A prolonged continuous hyperfunction of most differentiated cells is followed first by activation of nucleic acids and protein synthesis in these cells. Then occurs normalization of the synthesis and much later there develops an inhibition of the synthesis which becomes the basis of the wear of structures and of the functional disturbance in the cells and organs[6-9].

All these facts have suggested that the disturbance of nucleic acids and protein synthesis may be of great importance in the wearing-out of the antihypertensive incretory renal structures and in the development of hypertension produced by an excessive use of sodium chloride. On the basis of this suggestion, an attempt has been made in the present work to prevent the wear of the antihypertensive structures with the aid of co-factors of the synthesis and the precursors of the nucleic acids and thus to act on the development of the salty hypertension in animals.

Material and methods. To produce saline hypertension, male rats of the Wistar strain immediately after birth received a drinking solution of 1% NaCl. Control rats of the same sex and weight drank water. Measuring of pressure on the caudate artery in experimental and control rats was begun at the age of 2 months by the generally used bloodless method of A. GROLMANN. To study the action of the factors which concerned us, animals were taken for experiment at the age of 3.5 months and 240–255 g weight. 10 animals which were given salt and 10 controls were used. In control animals which did not receive any salt the systolic arterial pressure during the first 2 weeks of the experiment was 87 $\pm$ 1.4 and in experimental ones which received salt 108 $\pm$ 2.2 mm Hg, i.e. it was increased by 21%. This difference between the groups was maintained during the whole period of measurements; it was authentic ($p < 0.01$) and showed that, under the influence of the excessive uptake of salt, the animal organism developed a moderate saline hypertension.

On the background of this hypertension, the first fortnightly course of treatment with co-factors of synthesis and the precursors of nucleic acids was carried out. It consisted of the animal receiving daily 24 mg of orotic, 2.5 mg folic acid per os and 3 μg of vitamin B_{12}/kg i.m. together with 1% of NaCl solution as drinking fluid.

These substances have been chosen in view of their previously established favourable influence on the intense hyperfunction in a number of organs and systems[10–12]. Along with that in the given dosage they have not exerted any marked influence on the level of the arterial pressure in intact animals. The above mentioned substances were simultaneously administered to hypertensive and control rats.

Results. Administration of co-factors of the synthesis and precursors of nucleic acids did not exert any marked influence on the level of the arterial pressure in control animals, whereas it acted on the level of the arterial pressure in hypertensive rats (Figure).

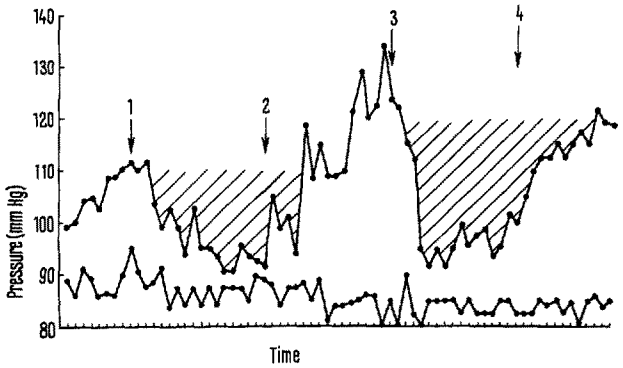
3 days after the beginning of treatment the pressure in these animals had definitely decreased, and during the last 10 days of the course, the mean pressure for the group fell to 91 $\pm$ 1.9 mm Hg; in other words the level of the pressure decreased by 15% as compared to the initial values and did not differ from the level in control animals which were not given salt. After cessation of the course the pressure increased again to 120 $\pm$ 3.2 mm Hg, i.e. there was a restoration of the authentic saline hypertension ($p < 0.01$).

2 weeks after the first course, on the background of the restored hypertension, a second course was carried out. It consisted in administration of co-factors of synthesis and precursors of nucleic acids in the same doses and duration of administration as used in the first course. As a result of the repeated course, the pressure fell to 95 $\pm$ 2 mm Hg, i.e. it was decreased by 21% and did not differ from the pressure in control animals which were not given salt. In the days following cessation of the second course, the pressure increased again to the previous hypertensive level.

The graph in the Figure represents the dynamics of systolic arterial pressure for experimental and control animals; each point on the curves represents the mean pressure of the whole animal group on the given day.

In summary these experiments suggest that a relatively brief, fortnightly administration of factors able to activate the nucleic acids synthesis produces a regular fall of the increased arterial pressure in animal saline hypertension.

This fact is not a proof of a radical effect of the combination used of co-factors of the synthesis and precursors of the nucleic acids in saline hypertension of animals and still more in human hypertension. At the same time the authentic effect obtained apparently agrees with the assumption that the perfect functioning of the mechanisms of regulation of the vascular tone depends on the process of nucleic acids and protein synthesis, and, respectively, the disturbance of the adaptive ensuring of function of the antihypertensive mechanism may indeed play a role in the development of the hypertensive process.



Dynamics of systolic pressure in intact animals (lower curve) and in animals with experimental saline hypertension (upper curve). Shaded zone represents the antihypertensive effect of co-factors of the synthesis and precursors of nucleic acids and proteins. Pressure in mm Hg; time from the beginning of the experiment in days. The first and the third arrows show the beginning of treatment, the second and the fourth arrows cessation of treatment.

Выводы. Введение крысам с умеренной солевой гипертонией комбинации, состоявшей из фолиевой и оротовой кислот и витамина B_{12}, приводило к снижению артериального давления до нормального уровня и в то же время не влияло на артериальное давление у контрольных животных.

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