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TADEUSZ GARBULIŃSKI, ***O chemizmie działania azotynów w organizmie [Sur le chimisme de l'action des nitrites dans l'organisme]***, une partie du travail *Farmakodynamika azotynów i azotanów w narządzie krążenia w nowym oświetleniu*, Zeszyty Naukowe Wyższej Szkoły Rolniczej we Wrocławiu, Weterynaria VII, nr 26, p. 3 - 41 (en polonais).

SUMMARY

In experiments *in vivo* on cats, rabbits and frogs it was found that the nitrites have properties of oxidizing epinephrine, choline and cysteine. Moreover, the experimental results of KOSZTOJANC *et aliis* on the relation between the influence of acetylcholine on the heart and the presence of the SH-group, and also the present author's own results, go to show that the nitrites and nitroglycerine lower the tension both of the parasympathetic system by inhibition of the acetylcholine production in consequence of the oxidation of choline and cysteine, and of the sympathetic system by the oxidation of epinephrine. Hence there arise the well-known changes in the circulatory system. Oxygen, as the final electron acceptor, cannot be reduced in the absence of the electron transporter, which in the organism is the cytochrome system together with oxidase. The nitrites, in their rôle of donors of the oxygen atom, imitate the action of cytochrome oxi-

dase. HEUROWITZ, KEILIN and PAULING discovered the linkage of nitrogen oxide (NO) with ferricytochrome c, catalase and hemoglobin, and SZCZEPKOWSKI found *inter alia* that identical absorption bands (5630 Å and 530 Å) are given by nitrogen oxide and ferricytochrome c, also under the influence of the nitrite ion. Between Fe, $NaNO_2$ and O_2 there exists a physical affinity as regards their common paramagnetic properties.

These data and personal research have finally led to the conclusion that a nitrite together with ferricytochrome c is able to produce a repeating cycle of catalysis of molecular oxygen activation:

$$\text{Ferricytochrome c} + NO_2 \rightarrow \text{Cytochrome c} + NO + O,$$
$$\text{Cytochrome c} + NO + O_2 \rightarrow \text{Ferricytochrome c} + NO_2 + O.$$

The active oxigen, just as in action of the oxidases, may be used in the organism for the oxidation of many substrates.

Experiment I. Cat. 0,1 ml of a 1:1000 dilution of epinephrine was introduced into the femoral vein. The arterial blood pressure rose from 90 to 140 mm Hg. The same amount of epinephrine administered together with a tablet of nitroglycerine (0,6 mg) did not cause a rise in the arterial blood pressure, but a fall of 30 mm Hg. The post-epinephrine elimination of the rise in the arterial blood pressure by the nitrites and nitroglycerine depends on the excitability of the organism, on the doses of epinephrine and these of nitrites. Nitrites have a favourable influence on respiration and protect the organism from the apnoea often appearing after the introduction of epinephrine.

Experiment II. Frog. A vascular preparation was made by the Trendelenburg method. In the course of 3 minutes after the introduction of 0.2 ml of epinephrine in a dilution of 1:100000, 19 drops of Ringer's fluid flowed out of the severed abdominal vein. The same dose of epinephrine together with 0.15 mg of nitroglycerine caused a flow of 29 drops in 3 minutes.

Experiment III. Rabbit. A segment of intestine in Ringer's fluid. The introduction of 0.2 ml of a choline solution into the vicinity of the intestine caused a contraction along the long axis and an intensification of the peristaltic movements. The same quantity of choline given together with a tablet o nitroglycerine (0.6 mg) caused a contrary effect: the intestine became relaxed and peristaltic movements were retarded. This effect cannot be obtained in any degree by the introduction of nitroglycerine, even with a small dose of acetylcholine. 0.2 ml of a 0.02 per cent of acetylcholine solution introduced into the vicinity of the intestine together with 0.6 mg of nitroglycerine causes a violent contraction of the intestine and an intesification of the peristaltic movements, because the chemical structure of acetylcholine renders its oxidation by the nitrites impossible.

Experiment IV. Frog. 0.2 ml of a 1 per cent solution of cysteine arrests the action of the isolated heart of the frog. 0.2 ml of a 2 per cent solution of sodium nitrite together with a similar quantity of cysteine suppresses the inhibitory action of the latter on the heart. A heart loaded with an excess of cysteine, beating slowly (every 8 seconds), improved its action to the initial state after the introduction of 0.2 ml of a 2 per cent solution of $NaNO_2$. A similar control dose of $NaNO_2$ weakened the force of the cardiac contraction for 10 sec., but sometimes had no effect on it at all.

As is known from investigations on the action of nitrites on the circulatory system, the arterial blood pressure may show a transient fall after nitrites, sometimes for several minutes or longer, but always as a result of the decrease in the amplitude of the cardiac contraction, of which the electrocardiographic data give evidence. The research of KLISIECKI and HOŁOBUT has shown that a change even involving half the cross-section of the vascular net does not alone alter the pressure, if the heart is intact and sound. A sound heart by an increase in the energy of contraction can easily deal with an increased blood-flow, and without accelerating the pulse manages to pump 10 times as much blood into the aorta in the same time. Weak hearts, however, react to the reflex from the sinus caroticus in connection with the decreasing blood pressure after nitrites by accelerating the pulse. Much of the blood can flow into the right heart through the dilated coronary vessels, and be retained in the pulmonary circulation (KLISIECKI); this is confirmed by the rise in the blood pressure in the pulmonary artery after nitrites, accompanying a fall in the arterial blood pressure, as observed by BRADFORD, DEAN and WOOD. The present writer's own observations agree with these data. A fall in the blood pressure after nitrites is also found after severing the vagus nerves, atropinization and ergotaminization.

The decrease in the amplitude of the myocardium contractions is probably due to the action of the nitrites on the tissue respiratory metabolism of the myocardium and the lessening of tension in both collateral nervous systems. The acceleration of the heart action after the administration of nitrites is a reflex, and is caused by a fall in the arterial blood pressure. The denervation of the heart annuls this reflex.

The catalytic reaction of the activation of molecular oxygen by the nitrites together with ferricytochrome c, specified in the introduction, has been confirmed in the course of further research by still other data, e.g. by the influence of the nitrites on the poisoned cytochrome system, the condensation of the reagent „Nadi", etc.

ODBITKA

POSIEDZENIE Z DNIA 28 KWIETNIA

TADEUSZ GARBULIŃSKI

O chemizmie działania azotynów w organizmie

Komunikat

Stwierdzono *in vivo* własności utleniające azotynów w stosunku do adrenaliny, choliny i cysteiny oraz ich nieskuteczność wobec ciał nie podlegających oksydoredukcji, jak acetylocholina. W związku z tym powstają w narządzie krążenia i innych narządach znane zmiany. Są one fizjologicznym następstwem obniżenia napięcia całego systemu wegetatywnego. Azotyny w swej roli dawców tlenu atomowego imitują działanie oksydazy cytochromowej i przypuszczalnie wraz z cytochromem c są zdolne wytworzyć powtarzający się cykl katalizy aktywowania tlenu drobinowego:

$$\text{Cytochrom c} + HNO_2 + H^+ + e^- = \text{cytochrom c NO} + H_2O,$$

$$2(\text{cytochrom c NO}) + O_2 + H_2O = 2(\text{cytochrom c}) + 2HNO_2 + O.$$

Doświadczenie dowodowe jest w opracowaniu.