EFFECT OF REGIONAL HYPOXEMIA ON THE BLOOD SUGAR IN THE SYSTEMIC CIRCULATION

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In experiments on the humorally isolated hind limb of a dog, retaining its nervous connections with the rest of the body, it was shown that the change to hypoxemic conditions of perfusion induces reflex secretion of considerable quantities of glucose from the liver into the systemic circulation. The primary cause of this reflex is evidently deprivation of the muscle tissue of energy-providing materials.

Investigations by other workers [1-6, 9, 10] and previous experiments of the present writers [7, 8] suggest that interoceptive metabolic reflexes lie at the basis of the mechanisms controlling the chemical composition of the internal milieu of the organism.

These previous experiments [7, 8] showed that regional hypoglycemia in the humorally isolated hind limb leads to a hyperglycemic response in the systemic circulation. However, they did not explain whether this reaction is strictly specific, i.e., whether a hyperglycemic reflex arises in response to a reduction in the glucose level in blood supplying the muscle tissue or whether it is induced by secondary biochemical changes in the tissues resulting from energy deprivation due to glucose deficiency. Probably these reflexes may also be observed when there is oxygen deficiency in the blood.

The object of the present investigation was to study the role of regional hypoxemia in the production of a metabolic interoceptive reflex.

EXPERIMENTAL METHOD

Acute experiments were performed on male dogs weighing 20-25 g under barbiturate anesthesia (thiopental, hexobarbital), which does not induce a hyperglycemic response. From 30 to 40 min after the onset of deep anesthesia the main vessels of the limb were isolated and ligated while the main nerve trunks were taken on ligatures. A tourniquet was applied to the soft tissues, avoiding the nerve trunks. The medullary canal of the femur was opened with a dental drill in its middle part and plugged. The peripheral ends of the femoral artery and vein were connected to an artificial circulation apparatus (an experimental model with foam-disk oxygenator and roller pump with an output of 50 to 100 ml perfusion fluid per minute). To obtain earlier and clearer information of the role of the liver in the reflex hyperglycemic response in the systemic circulation, in most experiments the hepatic vein (in some cases the portal vein also) was cannulated.

Regional perfusion continued for 3-3.5 h. The perfusion was divided into 3 periods depending on the conditions: in the first hour – "background" perfusion with normally oxygenated blood, in the second hour – hypoxemic perfusion, produced by replacing donors' blood with plasma, in the third hour – resumption of perfusion with normally oxygenated donors' blood.

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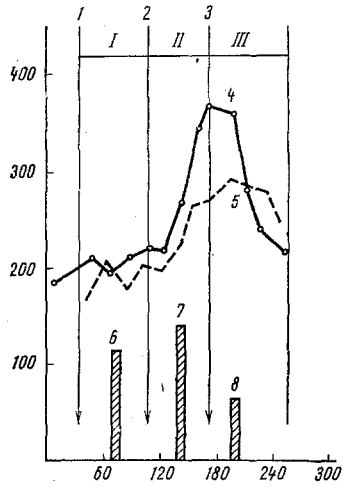

Fig. 1

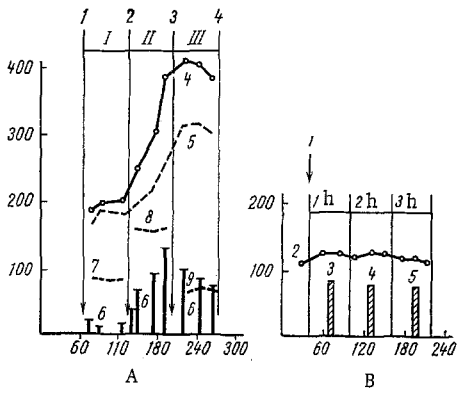

Fig. 2

Fig. 1. Effect of regional hypoxemia of the dog's hind limb on blood glucose concentration in hepatic vein and femoral artery of the unperfused limb: 1) beginning of "background" regional perfusion of hind limb with normally oxygenated blood, I) period of "background" perfusion; 2) change to perfusion with plasma, II) period of hypoxemic perfusion with plasma; 3) resumption of perfusion with normally oxygenated blood, III) period of perfusion with normally oxygenated blood; 4) blood glucose concentration in hepatic vein; 5) blood glucose in femoral artery of unperfused limb; 6, 7, 8) glucose concentration in perfusion fluid during stages I, II, and III of perfusion, respectively. Abscissa, time (in min); ordinate, glucose concentration (in mg%).

Fig. 2. Effect of regional hypoxemia of the humorally isolated hind limb of a dog on reflex "discharge" of glucose by the liver into the systemic circulation (A) and of prolonged perfusion of the limb with normally oxygenated blood on the glucose concentration in blood flowing from the liver (B). A: 1) Beginning of regional perfusion of hind limb with normally oxygenated blood, I) period of "background" perfusion with normally oxygenated blood; 2) replacement by perfusion with plasma, II) period of hypoxemic perfusion with plasma; 3) restoration of perfusion with normally oxygenated blood, III) period of perfusion with normally oxygenated blood; 4) glucose concentration in blood from hepatic vein; 5) glucose concentration in blood from portal vein; 6) quantity of glucose discharged from the liver (in mg for every 100 ml blood flowing through the liver); 7, 8, 9) glucose concentration in regional perfusion fluid. B: 1) Beginning of perfusion; 2) glucose concentration in blood from hepatic vein; 3, 4, 5) glucose concentration in regional perfusion fluid. Abscissa, time (in min); ordinate, quantity of glucose (in mg%).

The glucose concentration was determined every 15-20 min in blood of the systemic circulation. In some experiments this was blood taken from the femoral artery of the unperfused limb, but in most experiments it was blood flowing through the hepatic vein from the liver. In some cases the glucose concentration was investigated simultaneously in blood from the portal vein. Finally, the glucose concentration in the perfusion fluid was monitored periodically. Glucose was estimated by the glucose oxidase enzymic method [11].

EXPERIMENTAL RESULTS

Altogether 10 experiments were carried out and they gave consistent results. After the change to hypoxemic conditions of regional perfusion of the humorally isolated hind limb, a clear reflex hyperglycemic effect was observed in the systemic circulation (Fig. 1). This effect took place despite a sufficiently high level of glucose in the regional perfusion fluid.

In one experiment (Fig. 2), in order to detect reflex hyperglycemia the blood glucose concentration was determined simultaneously in blood from the portal and hepatic veins. By comparing these values it was possible to determine the increase in the absolute quantity of glucose discharged by the liver into the blood stream in response to hypoxemia of the humorally isolated limb. Whereas before regional hypoxemia the liver secreted 20-25 mg glucose into every 100 ml of blood, 15 min after the beginning of hypoxemia it secreted 3 times as much glucose, and by the end of the hypoxemic phase of regional perfusion the original output of glucose was exceeded by 120 mg, i.e., by approximately 7 times. These effects were absent during control perfusion for 3 h with normally oxygenated blood (Fig. 2B).

The results of these experiments thus suggest that the cause of the reflex hyperglycemia in the systemic circulation consists of certain chemical changes in the tissue cells connected with their energy deprivation. These changes undoubtedly arise not only in response to deficiency of glucose, but also to deficiency of oxygen, and they lead to the appearance of general adaptive metabolic reflexes. On the feedback principle they trigger various mechanisms aimed at restoring normal tissue energy metabolism (in particular, increasing the output of glucose from the liver, quickening respiration, reducing the pressure in the vessels of the perfused limb, and so on).

One example of a manifestation of this adaptive reflex in pathology, in the writers' opinion, is the hyperglycemia of diabetes. It can be regarded as the result of an interoceptive metabolic reflex arising as the result of energy deprivation of the cells, principally of the muscle tissue, produced by a deficiency in the amount of glucose reaching the muscle fibers through insulin deficiency [4].

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