SUBSTRATE STIMULATION OF RENAL TUBULAR SECRETION OF PENICILLIN AND DIODONE IN DOGS

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Chronic experiments on dogs showed that repeated (three times a day for 3 days) intramuscular injection of 40 mg/kg penicillin or 100 mg/kg diodone leads to an increase in the maximal rate of secretion of these substances in the kidneys. The results are regarded as direct proof of the existence of substrate stimulation of tubular secretion of organic substances.

KEY WORDS: renal function; tubular secretion; penicillin; diodone.

Substrate stimulation of tubular secretion in the kidneys was discovered initially in young rats but not in old animals [6]. However, the writers have shown that penicillin or diodone, if injected repeatedly into rats, causes significant acceleration of the excretion of these substances by the kidneys [1, 2]. Similar data have meanwhile been published by other investigators for p-aminohippurate [3, 4].

This paper describes direct evidence of the presence of substrate stimulation of secretory transport of diodone and penicillin in dogs.

EXPERIMENTAL METHOD

The maximal rate of tubular secretion of diodone and penicillin was determined in dogs with the ureters exteriorized by the Pavlov–Tsitovich method [7]. For this purpose, a solution containing 0.8% sodium chloride, 0.01% potassium chloride, 2% inulin, and 4% diodone (or 2.25% penicillin) was infused at the rate of 2-5 ml/min through a subcutaneous vein of the hind limb. The collection of 10-min samples of urine (two to three clearance periods) began after 1 h. In the middle of each period blood was taken from a vein of the opposite limb. The concentration of inulin (by the resorcin method) and diodone (iodometrically) or penicillin (by a microbiological method using Staphylococcus 209P as the test organism) was determined in the blood and urine. When the penicillin concentration in the plasma was determined, its binding with proteins was conventionally taken to be 50% [5, 8].

EXPERIMENTAL RESULTS

As a first step the maximal rate of renal tubular secretion of diodone was determined in four dogs. The animals were then given diodone by intramuscular injection in a dose of 100 mg/kg three times a day for 3 days. The maximal rate of secretion of diodone was then again determined after 10 injections (on the fourth day of observation). Under these circumstances an increase in the parameter studied was observed in all the animals; in three dogs it was very considerable, and on average it was 44% higher than the initial level (Fig. 1A). It is worth noting that the rate of glomerular filtration was not increased in these experiments. This is evidence in support of the specificity of the action of diodone on the secretory-transport systems in the renal tubules.

The possibility of injections of penicillin having some effect on the maximal rate of its secretion by the renal tubules was investigated in experiments on four other dogs. Penicillin was injected into the animals intramuscularly in a dose of 40 mg/kg three times a day for 3 days. In all the animals the maximal rate of

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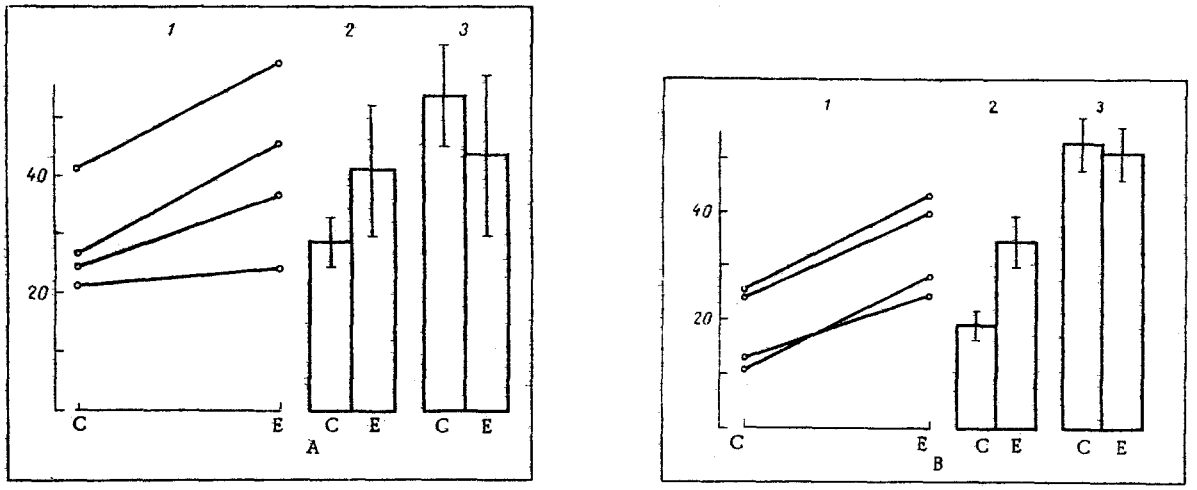

Fig. 1. Effect of injection of diodone (A) and penicillin (B) for 3 days on rate of their maximal secretion in dogs. Ordinate, maximal secretion (in mg/min) and filtration (in ml/min): 1) changes in secretion in individual dogs; 2) mean indices of secretion; 3) mean indices of filtration. C) Control (initial values); E) experiment.

tubular secretion of penicillin on the fourth day of observation was significantly higher than the corresponding values in the initial period and on average the test index was 81% higher (Fig. 1B). Penicillin, incidentally, caused no appreciable change in the rate of glomerular filtration. Consequently, in this case also, the selective action of repeated injections of the preparation on the secretory-transport systems in the renal tubules could be postulated.

In an additional series of experiments on four dogs an attempt was made to discover the phenomenon of substrate stimulation of the secretory process by injecting diodone or penicillin with longer time intervals between injections, namely once a day for 10 days. Although the total number of injections in this case was not reduced, no increase took place in the maximal rate of secretion of the substances injected into the dogs in these experiments. This is in agreement with results obtained earlier on rats injected with diodone at daily intervals [1].

Since in the present experiments there was an increase in the maximal ability of the tubular cells to transport the secreted substances, it must be assumed that the phenomenon of substrate stimulation of secretion is due either to an increase in the number of carriers in the secreting cells or to an increase in the affinity of existing carriers for substrates. Earlier results showing that inhibitors of protein synthesis prevent substrate stimulation of secretion [1] support the first point of view. The basis of this phenomenon is thus evidently substrate induction of the synthesis of carrier proteins.

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