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SUMMARY. — *The pharmacokinetics of fructose-1, 6-diphosphate administered to the rat by intravenous injection was studied. Labelled fructose-1, 6-diphosphate was measured in blood, where it reaches the highest amount 10 min after administration, and in different organs. Residual radioactivity was measured in organs 20 min after administration, the highest values being found in the kidney and the lowest in the brain. The hydrolytic activity of the various organs toward fructose-1, 6-diphosphate was measured in organ extracts and was found to be maximal in the kidney and minimal in the brain.*

RIASSUNTO. — *È stata studiata la farmacocinetica del fruttosio-1, 6-difosfato iniettato al ratto per via intravenosa. Il fruttosio-1, 6-difosfato marcato è stato determinato nel sangue, dove raggiunge la massima concentrazione 10 min dopo la somministrazione, e in diversi organi. La radioattività residua degli organi è stata misurata 20 min dopo la somministrazione ed è risultata massima nel rene e minima nel cervello. L'attività idrolitica dei vari organi nei confronti del fruttosio-1, 6-difosfato è stata misurata in estratti degli organi stessi ed è risultata massima per l'estratto di rene e minima per quello di cervello.*

Introduction

The use of physiological metabolites in parenteral nutrition is a current clinical practice (1) (2) and that of fructose-1, 6-diphosphate (FDP) has been advocated in recent years (3).

FDP in effect seems endowed not only with characteristics of an energy providing metabolite, but also with some specific pharmacological effects, mostly in the treatment of the adynamic ileus (4) and of acute myocardial ischaemia (5).

The pharmacological effects of FDP seem related with its hydrolysis and power of stimulating an uptake of potassium ions (6), but no study on the pharmacokinetics of such compound has been hitherto published.

The present communication deals with the distribution of radioactive FDP in rat tissues after intravenous administration, its rate of disappearance from the blood and the different ability of various rat tissues in hydrolyzing FDP *in vitro*.

Material and methods

23 Wistar male rats (230 to 250 g of body weight), after a standard fasting period of 18 h, were injected with uniformly labelled ^{14}C-FDP (The Radiochemical Centre, Amersham, U.K.) through the caudal vein. Radioactivity measurements were carried out with a Packard Scintillation Spectrometer using Instagel as a scintillation liquid.

The hydrolysis of FDP by the extracts of different organs was followed by detecting the release of inorganic phosphate according to Martin and Doty (7).

400 mg of cold FDP (Biomedica Foscama, Roma) together with an amount of U-^{14}C-FDP corresponding to 2,500,000 dpm were injected in a total volume of 0.5 ml of aqueous solution. The rats were killed by decapitation at different intervals (0, 5, 10, 15 and 30 min) after the injection and the organs were immediately removed and homogenized in cold 0.5 M NaCl/20 mM *tris*-HCl pH 7.5 (8 ml/g of fresh tissue). For the measurement of pharmacokinetic and tissue distribution, after 5 min homogenization 0.8 ml of 30% perchloric acid were added to 10 ml homogenate and the mixture was centrifuged in a Sorvall type ultracentrifuge at 500 x h for 3 min. The supernatant was then neutralized with 2 N KOH and the suspension centrifuged at 500 x g for 10 min, 1 ml of the clear final supernatant being added to 9 ml of Instagel for counting.

For the pharmacokinetic measurements in blood 1 ml of heparinized blood was collected and treated as described above for the organs.

The ability to hydrolyze FDP was studied by incubating at 37° for 15 min 0.45 M FDP in 1 ml of 0.5 M *tris*-HCl pH 7.5 with 5 mM $MgSO_4$ and 1 mg of protein of the extracted homogenates. The latter were prepared with 1 g of tissue and 8 ml of 0.5 M NaCl/20 mM *tris*-HCl pH 7.5: after 20 min of homogenization at 25° they were centrifuged in a Sorvall at 2,000 x g for 10 min and the supernatants were used for incubation with FDP. The protein content of the supernatants was measured by the biuret method (8).

Results and discussion

Fig. 1 illustrates the amounts of radioactivity found in blood at different times after the intravenous administration of U-^{14}C-FDP. The highest amount was found in blood after 10 min, while in the organs the residual radioactivity increased with time, the comparative measurements of radioactivity in tissues being carried out after 20 min from administration. The organ where the highest amount of residual radioactivity was found at 10 min was the intestine.

Table I summarizes the amount of radioactivity in different organs of rats injected with U-^{14}C-FDP and Table II summarizes the specific FDP-hydrolyzing activity of the same organs.

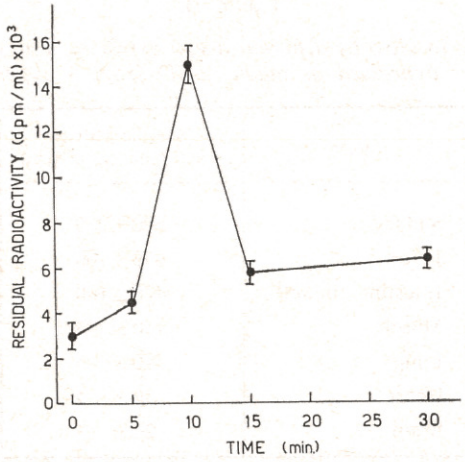

Fig. 1

Residual radioactivity in blood expressed as dpm/ml. Each value is an average of three experiments.

TABLE I

Distribution of residual radioactivity among rat organs measured 20 min after intravenous administration of U-^{14}C-FDP (2.5 x 10^6 dpm). The values are mean ± SD from 4 experiments.

Organ	Radioactivity (dpm)
Kidney	10,654±3,128
Liver	5,860±1,867
Intestine (ileum)	4,852±1,786
Muscle	3,864±1,200
Lung	3,737±2,263
Heart	2,950±1,086
Brain	2,541± 327

The pharmacokinetics of FDP is characterized by a different distribution in the organs measurable after the end of the blood peak. The kidney seems the organ where FDP is taken up in the highest amounts followed by the liver, intestine, muscle, lungs, heart and brain. A correction for the blood present in the different organs was always applied.

TABLE II

Hydrolysis of FDP in vitro *by different organ extracts. The values are specific activities expressed as mean ± SD from* 4 *experiments.*

Organ	Specific activity (ng P_i/min/mg protein)
Kidney	690±280
Liver	630±160
Intestine (ileum)	420±100
Muscle	110± 23
Lung	40± 5
Heart	30± 4
Brain	24± 3

The measurement of the hydrolytic power of the different organs toward FDP shows that the highest activity is associated with the kidney followed by the intestine, liver, heart, muscle, lungs and brain. The hydrolytic activity of the whole blood was negligible and this accounts for the slightly different order of hydrolytic power of the organs compared to that of the residual radioactivity. In any case the kidney shows the highest value of both residual radioactivity and hydrolytic power and the brain shows the lowest value of the two parameters. This gives some support to the idea that a possible pharmacological receptor for FDP on cell surface may be identified with a membrane bound phosphatase (9).

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