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Fructose-1, 6-diphosphate Dependence on the Toxicity and Uptake of Potassium Ions

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The toxicological effect of KCl in mice is counteracted by previous administration of fructose-1, 6-diphosphate sodium salt (FDP). The kinetic of this protection was evaluated in comparison with that of equimolar amount of fructose plus sodium phosphate. The protection should be related to a decrease of the plasma K+ excess, since FDP increases the K+ uptake in isolated rat erythrocytes.

A high plasma level of potassium is lethal to mice. For this reason potassium-induced mortality can be used to measure the efficacy of drugs in enhancing or decreasing the tissue uptake of K^+ (*Laborit,* 1958 ; *Lockwood* and *Lum*, 1974). Besides beta-stimulating adrenergic drugs are able to decrease the toxicity of KCL i.v. in experimental animals (*Lockwood* and *Lum*, 1974, 1977). Thus fructose-1, 6-diphosphate sodium salt (FDP), which increases the lipolytic action of norepinephrin in rat adipose tissue (*Prosdocimi, Caparrotta et al,* 1979), was tested in this case for its ability to influence K^+ uptake in rat erythrocytes and the preliminary results are compared with those obtained by toxicity measurements in mice.

Materials and methods

100 male and 100 female Swiss mice (23 ± 1 g body weight), fed with standard laboratory diet (Mignini, Perugia) were injected intravenously (i.v.) through the caudal vein with a standard volume of 10 ml/kg infused in 8 sec. The protective effect of FDP and that of sodium phosphate plus fructose (F + P) were evaluated by injecting them together with the lowest lethal dose KCl which in a previous paper was estimated to be 120 mg/kg (*Cattani, Costrini et al,* 1978). The two treatments, FDP and F + P, were also carried out at different time intervals before the KCl administration in order to evaluate their effect kinetically.

The direct effect of FDP on K^+ uptake was measured *in vitro* by incubating rat erythrocytes suspended in saline with FDP and KCl at 38° C. After centrifugation to deposit the erythrocytes (0° and 1,000 x g) FDP hydrolysis was estimated from the inorganic phosphate (P) liberation in the supernatant according to *Martin* and *Doty* (1949) and K^+ uptake from the residual amount of K^+ measured by atomic absorption (Perkin-Elmer Atomic absorption spectrophotometer 305 B).

The results are referred to the amount of hemoglobin (Hb) evaluated according to *Beutler* (1971).

TABLE I

Percent survival of mice pre-treated with fructose-1,6 - diphosphate sodium salt (FDP) or equimolar amount of fructose (F) plus sodium phosphate (P) or Saline and injected with 120 mg/Kg of KCl at different times after pre-treatments. The KCl administration and the pre-treatments are of 10 ml/Kg volume and are i.v. injected in 8 sec.
Number of animal within brackets. The protective effect of FDP was compared with that of F + P by χ^2 test.

Pre-treatments	Time (min) of injection of KCl after pre-treatments							
	0	20	60	90	120	180	240	300
Saline	0	0 %	0 %	0 %	0 %	0 %	0 %	0 %
(10 ml/Kg)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
FDP	40 %	40 %	40 %	40 %	50 %	30 %	30 %	20 %
(0.4 m mol/Kg)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
F + P	20 %	20 %	20 %	20 %	30 %	10 %	10 %	10 %
(0.4 + 0.8 m mol/Kg)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)

FDP versus F+P (all times) $\chi^2 = 7.16$ $p < 0.01$

Results

Table I summarizes, at different times after administration, the FDP and F + P protective effects. They are reported as percentages of mice survival after KCl lethal dose.

Results show that FDP protection on KCl i.v. toxicity in mice is significantly bigger than that one of F + P. This time-depending effect is maximum 120 minutes after the FDP administration.

Table II summarize the results of FDP hydrolysis and K^+ permeability in isolated rat erythrocytes. An hydrolysis of FDP [redacted] takes place after the interaction of FDP with the erythrocytic membrane. Such a hydrolysis is stimulated when K^+ is present in the incubation medium. Neither hydrolysis nor effects of K^+ are observed if fructose-1-phosphate or fructose-6-phosphate are used.

TABLE II

FDP-stimulated K^+ uptake by rat erythrocytes and parallel K^+-stimulated FDP hydrolysis measured as phosphate release. Final concentration of K^+ was 25 m mol/l. Mean values of ten experiments.

Treatments	K^+ uptake (nmol/min/mg Hb)	P release (nmol/min/mg Hb)
Control	0	0
+ FDP (10 m mol/l)	0,3	0,024
+ F + P (10 + 20 m mol/l)	0	—

The presence of FDP in the incubation medium induces a significant increase of the K^+ uptake in red cells while F + P does not induce it.

Discussion

The FDP protective action on the KCl i.v. toxicity in mice is in accordance with the previous findings showing that it activates the lipolysis in rat adipocytes increasing the ATP levels and the cyclic AMP synthesis *(Prosdocimi, Caparrotta et al,* 1979).

In fact beta-adrenergic stimulators, which are able to decrease the KCl i.v. toxicity in experimental animals (*Lockwood* and *Lum,* 1974, 1977), increase the cyclic AMP synthesis.

This activity is also in agreement with the FDP-induced increase of the K^+ uptake in isolated red cells. For this reason it is possible to suppose an FDP-induced decrease of the plasma K^+ excess.

There is an apparent disagreement between the toxicological and biochemical experiments regarding the effect of the control treatment with F + P. Further experiments will elucidate this point.

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