Lowering of Blood Ketone Bodies Induced by Drugs Preventing Free Fatty Acid Mobilization[1]

The formation of ketone bodies such as acetoacetic acid, β-hydroxybutyric acid and acetone, occurs mostly in the liver whenever the availability of acetyl-CoA exceeds its utilization via other metabolic pathways like direct oxidation through the Krebs cycle or synthesis of fatty acids or cholesterol[2]. The ketone bodies are oxidized by extrahepatic tissues; but when the rate of their synthesis overcomes the rate of utilization, they are accumulated in the blood, producing ketosis.

Since acetyl-CoA is the end product of the fatty acid oxidation and the uptake of fatty acids by the liver depends upon the concentration of free fatty acids (FFA) in the blood[3], it follows that certain types of ketosis may be the consequence of an increased FFA mobilization. Therefore drugs preventing the mobilization of FFA may be able also to decrease the rate at which ketone bodies are formed. This paper intends to present experimental evidence in favour of this concept.

Male Sprague-Dawley rats, of an average weight of 180 ± 15 g, were fasted for 18 h before the experiments. Plasma ketone bodies were determined according to WERK[4], and plasma FFA according to DOLE[5] with minor modifications. Washing with 0.05% H_2SO_4 according to TROUT[6] was adopted in order to avoid an interference of the drugs in the titration.

3,5-Dimethylpyrazole (3,5-DMP)[7], nicotinic acid[8] and salicylic acid[9], known to be powerful inhibitors of FFA mobilization, were challenged for their effect on the level of blood ketone bodies.

Fasted animals show a two-fold increase of plasma ketone bodies in respect to fed animals.

In Table I is reported the effect of 3,5-DMP given by oral route on plasma FFA and ketone bodies. The lowest dose able to decrease the concentration of ketone bodies was 1.5 mg/kg. Increasing this dose did not cause a linear enhancement of the effect.

Results in Table II also concern the effect of the oral administration of 3,5-DMP (7.5 mg/kg). Its activity in relation with the time is the same both on plasma FFA and ketone bodies.

The effect of nicotinic acid and salicylic acid are also reported in Table II. It is interesting to note that nicotinic acid shares with 3,5-DMP the same activity in lowering plasma FFA and ketone bodies, while salicylic acid, which is poorly active on FFA mobilization induced by fasting[10], fails also to counteract the accumulation of ketone bodies.

These results support the hypothesis that the increase of ketone bodies in the blood during fasting is a metabolic consequence of an increase of plasma FFA, because this ketosis can be prevented by inhibiting with suitable drugs the mobilization of FFA from adipose tissue. Furthermore 3,5-DMP and nicotinic acid may have a new possible therapeutic activity in the treatment of ketosis.

Table I. Effect of different doses of 3,5-DMP on plasma FFA and ketone bodies

Treatment mg/kg (oral route)[a]	FFA[b]	% values of plasma ketone bodies (as acetone) ± S.E.
Saline	100	100 ± 7
3,5-DMP 0.75	29	97 ± 4
3,5-DMP 1.5	29	57 ± 4[c]
3,5-DMP 3.7	31	62 ± 4[c]
3,5-DMP 7.5	18	40 ± 6[c]
3,5-DMP 15	30	50 ± 2[c]

[a] Time between treatment and determination was 60 min; absolute values for fasted rats were for plasma FFA 940 ± 20 μEq/l and for ketone bodies in the plasma 14.2 ± 1.1 mg/100 ml. The value of ketone bodies for fed rats was 4.0 ± 0.3 mg/100 ml. Each figure represents the mean of at least 5 determinations. [b] The determination of plasma FFA was performed on pooled plasma. [c] $p < 0.01$ in respect to animal treated with saline.

Table II. Effect of 3,5-DMP, nicotinic acid and salicylic acid given by oral route on plasma FFA and ketone bodies

Drug mg/kg oral	Time between treatment and sacrifice (min)	FFA[a]	% values of plasma ketone (acetone) ± S.E.
3,5-DMP 7.5	0	100	100 ± 9
3,5-DMP 7.5	30	30[b]	45 ± 1[b]
3,5-DMP 7.5	60	18[b]	40 ± 5[b]
3,5-DMP 7.5	120	33[b]	65 ± 11[b]
Nicotinic acid 50	60	21[b]	30 ± 10[b]
Salicylic acid 100	60	83	90 ± 1

[a] FFA determination was performed on pooled plasma. Each figure represents the mean of at least 5 determinations. [b] $p < 0.01$ in respect to controls.

Riassunto. Vengono presentati alcuni dati che dimostrano come sostanze che abbassino il livello degli FFA plasmatici nei ratti diminuiscano anche il livello dei corpi chetonici. Viene discussa la possibilità che la formazione dei corpi chetonici possa dipendere dal controllo della liberazione degli FFA nel tessuto adiposo.

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