ROLE OF BIOENERGETIC CHANGES IN THE MECHANISM OF ACTION OF NONSTEROID ANTI-INFLAMMATORY DRUGS

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The anti-inflammatory action of sodium mefenamate and salicylate is manifested to a greater degree in rats with inflammation due to ovalbumin than to dextran. In ovalbumin inflammation, sodium salicylate has a stronger action than mefenamate, and this correlates with the greater decrease in the blood concentrations of ATP, NAD, NADH, and lactic acid and the more complete abolition of the uncoupling of oxidative phosphorylation in the liver mitochondria than after injection of mefenamate. It is postulated that the fall in the level of high-energy compounds by the feedback principle leads to intensification of phosphorylation, with the consequent abolition of the inflammatory disturbances. This may account for the anti-inflammatory action of the preparations.

KEY WORDS: inflammation; anti-inflammatory agents; oxidative phosphorylation; energy metabolism.

One of the mechanisms of action of anti-inflammatory preparations is considered [2, 4] to be the uncoupling of oxidative phosphorylation, with a consequent reduction in the energy supply for the inflammatory process. However, sodium salicylate or phenylbutazone did not prevent a marked increase in the ATP concentration in an inflammatory focus, and the two drugs differed in their effect on different models of inflammation [3].

It was therefore decided to compare the effects of several anti-inflammatory agents in models of inflammation characterized by different changes in energy metabolism [1].

EXPERIMENTAL METHOD

Inflammation was produced in rats by injecting 0.1 ml 6% dextran or 1.5% ovalbumin beneath the plantar aponeurosis of the hind limb. The development of inflammation was recorded oncometrically for 3 h. Sodium mefenamate was injected intraperitoneally in a dose of 3 mg/100 g body weight 30 min before and 30 min after injection of the inflammatory agents, and sodium salicylate in a dose of 40 mg/100 g body weight was injected 1 h before inflammation was produced. Respiration and phosphorylation in the liver mitochondria (on succinate), their ATPase activity, and the content of NAD and NADH in liver homogenates were investigated in the experimental animals. The blood levels of ATP, ADP, inorganic phosphorus (P_i) and lactate were determined. The methods used were described earlier [1].

EXPERIMENTAL RESULTS AND DISCUSSION

Anaerobic glycolysis was increased equally (a sharp rise in the lactic acid level) in ovalbumin and dextran forms of inflammation (Fig. 1), whereas the content of NAD and, in particular, of NADH in the liver and also of high-energy compounds in the blood rose more in dextran inflammation. In ovalbumin inflammation the breakdown of high-energy compounds is evidently inhibited, as is shown in particular by the de-

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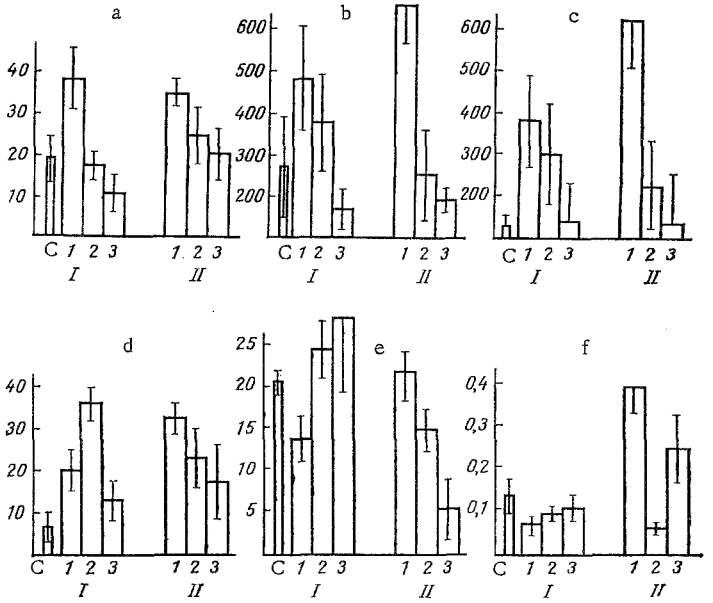

Fig. 1. Effect of sodium mefenamate and salicylate on energy metabolism indices during inflammation caused by ovalbumin (I) and dextran (II): a) lactic acid (in mg %); b) NAD (in μg/g tissue); c) NAD · H_2 (in μg/g tissue); d) ATP + ADP (in μg/ml); e) P_i (in μg/ml); f) ATPase (in mg P/g tissue). 1) Inflammation (without drugs); 2) administration of sodium mefenamate during inflammation; 3) administration of sodium salicylate during inflammation. C) corresponding indices in control animals. Mean values with confidence limits shown.

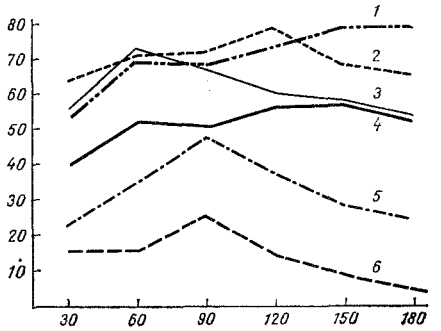

Fig. 2. Effect of sodium mefenamate and salicylate on increase in limb volume during ovalbumin and dextran inflammation. Abscissa, time after injection of inflammatory agent (in min; ordinate, increase in limb volume (in %): 1) dextran inflammation; 2) the same, administration of sodium salicylate; 3) the same, administration of sodium mefenamate; 4) ovalbumin inflammation; 5) the same, administration of sodium mefenamate; 6) the same, administration of sodium salicylate.

crease in ATPase activity of the liver mitochondria and in the P_i concentration in the blood; in dextran inflammation, on the other hand, synthesis of high-energy compounds evidently predominates, for P_i is not reduced and ATPase activity may actually increase. Differences in the state of energy metabolism are reflected in the degree of inflammation (Fig. 2), the intensity of which was lower after injection of ovalbumin than after injection of dextran.

TABLE 1. Comparative Effect of Sodium Mefenamate and Salicylate on Oxidative Phosphorylation in Ovalbumin Inflammation

Experimental conditions	Oxygen consumption, μ atoms O_2/g tissue			Phosphorylation, μ atoms P/g tissue			P/O		
	$M \pm m$	P	P'	$M \pm m$	P	P'	$M \pm m$	P	P'
Control	5,3±0,5	—	—	8,4±1,2	—	—	1,5±0,1	—	—
Inflammation: without preparations	7,05±0,5	<0,05	—	6,1±0,8	>0,05	—	0,86±0,08	<0,001	—
sodium mefanamate	10,3±0,42	<0,001	<0,001	10,9±0,61	>0,05	<0,001	1,1±0,08	<0,01	>0,05
sodium salicylate	8,8±0,9	<0,01	>0,05	14,2±1,77	<0,02	<0,002	1,6±0,1	>0,25	<0,01

Legend. P) Significance of differences between control and experiment; P') the same, between experiments using drug and without it.

The anti-inflammatory activity of sodium mefenamate and salicylate was in general more marked in ovalbumin than in dextran edema. These preparations also differed in their effects on the indices of energy metabolism in ovalbumin and dextran inflammation (Fig. 1). In ovalbumin inflammation salicylate had a well-marked anti-inflammatory action and considerably reduced the accumulation of lactic acid and the total blood level of ATP and ADP. The sharp rise in the blood P_i level and the increase in ATPase activity of the liver mitochondria under these circumstances could indicate predominance of hydrolysis of high-energy compounds. During dextran edema, on the other hand, when salicylate had a much weaker anti-inflammatory action, the level of high-energy compounds also remained higher; despite the increased ATPase activity the P_i concentration fell sharply, possible evidence of predominance of ATP synthesis over its hydrolysis. The accumulation of lactic acid was reduced by a lesser degree.

Mefenamate in ovalbumin inflammation increased the total ATP and ADP concentration. During dextran edema, however, although the ATP and ADP level fell following administration of mefenamate, it remained much higher than in the intact animals. The sharply reduced ATPase activity of the liver and the lowered blood P_i level observed under these conditions could indicate limitation of ATP breakdown.

Ovalbumin inflammation (Table 1) was accompanied by an increase in the oxygen consumption of the liver mitochondria, accompanied by a small decrease in phosphorylation, resulting in a decrease in the P/O ratio (uncoupling of oxidation and phosphorylation). Sodium salicylate activated phosphorylation sharply but caused little change in the rate of oxidation, so that the P/O ratio was restored almost to normal. Sodium mefenamate, with a weaker anti-inflammatory action, stimulated both the oxygen consumption of the mitochondria and also (to a lesser degree) phosphorylation; although the P/O ratio rose a little, it did not reach the normal level.

These results show that during inflammation oxidative phosphorylation is uncoupled and ATP synthesis is largely maintained by a sharp rise in the rate of anaerobic glycolysis, a less productive process in this respect. Anti-inflammatory preparations, by inhibiting glycolysis and restoring the coupling of oxidative phosphorylation, increase the energy supply for correction of the disturbances arising during inflammation.

LITERATURE CITED

1. A. F. Leshchinskii, Z. I. Zuza, and T. S. Barkagan, Byull. Éksp. Biol. Med., No. 4, 27 (1972).
2. S. S. Adams and R. Cobb, Nature, 181, 773 (1958).
3. R. Domenjoz, in: Rheumatoid Arthritis, London (1971), pp. 513-550.
4. M. W. Whitehouse and J. M. Haslam, Nature, 196, 1323 (1962).