Cyclic AMP and Cyclic GMP in Rats Paw Edema by Prostaglandins

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Summary. Experimental results indicate that rat's paw oedema development by PGs is inhibited by 3'5'AMP and increased by 3'5'GMP. This research confirms the opposite effect to that of cyclic nucleotides. The respective behaviour of 3'5'AMP and 3'5'GMP in their primary oedema-induced activity is discussed.

Several sets of experimental data indicate that 3'5'AMP may play a direct role in release and formation of chemical phlogistic mediators[2]. The inhibitory effect of 3'5'AMP on histamine release from sensitized pulmonary and heart tissue[3], as well as from sensitized human leucocytes[4], has been pointed out. The reduced death incidence and kinins release in sensitized guinea-pig subjected to anaphylactic shock was previously demonstrated by us following 3'5'AMP pretreatment[5].

On the other hand, 3'5'AMP is effective in regressing formation or release of phlogistic mediators (such histamine and kinins) as well as in reducing their effect markedly. The inhibiting effect on capillary permeability in guinea-pig after histamine, serotonin and bradykinin i.d. injection of 3'5'AMP was previously pointed out by us[6]. Further data have since demonstrated that rats paw edema from carragenin can be inhibited by 3'5'AMP[7].

Prostaglandins too are involved in the pathogenesis of phlogistic processes; their presence have been pointed out, for example, in inflammatory exudates, in scalded tissue, and in eczematous skin[8]. They are also able to determine an increase in capillary permeability in rat, guinea-pigs, man[9] and induce rat's paw edema, like that due to other inflammatory mediators such as histamine, serotonin and bradykinin. The present study investigates the possible inhibiting effect of cAMP on PG as well. Cyclic GMP, as well as 3'5'AMP, was also tested, several

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Table I. Increase of rat's paw volume induced by different prostaglandins (PGE_2; $PGF_2\alpha$), 3'5'AMP and 3'5'GMP

Subplantar injected substances	No. experiments	Paw volume % increase at different time		
		30 min	60 min	120 min
PGE_2 (100 µg/paw)	14	+ 31.92 ± 1.59	+ 28.42 ± 1.91	+ 18.45 ± 1.27
$PGF_2\alpha$ (100 µg/paw)	14	+ 18.71 ± 1.20	+ 32.38 ± 0.98	+ 33.71 ± 1.27
3'5'GMP (1 mg/paw)	10	+ 6.33 ± 1.20[a]	+ 4.10 ± 2.81[a]	+ 19.77 ± 1.66
3'5'AMP (1mg/paw)	10	+ 6.11 ± 1.48[a]	+ 4.02 ± 1.56[a]	+ 4.26 ± 1.19[a]
Physiological solution (0.1 ml)	8	+ 6.12 ± 1.56	+ 3.91 ± 1.70	+ 4.27 ± 2.13

[a] These values are not significantly different from controls (edema caused by physiological solution).

Table II. Effect of 3'5'AMP and 3'5'GMP (10 mg/kg i.p.) on rat's paw edema caused by local injection of PGs (100 ng)

Treatment	Percent change of PGE_2 edema after				
	30 min	60 min	120 min	Edema (%)	No. experiments
3'5'AMP	61.8 ± 1.69	53.7 ± 2.01	64.5 ± 1.47	− 40.0	10
3'5'GMP	85.4 ± 1.62	134.6 ± 1.77	186.3 ± 1.91	+ 30.5	10
	Percent change of PGF_2 edema after				
	30 min	60 min	120 min	Edema (%)	No. experiments
3'5'AMP	85.6 ± 1.46	26.4 ± 1.73	32.9 ± 2.13	− 56.0	10
3'5'GMP	76.7 ± 1.90	88.2 ± 2.20	98.9 ± 1.56	− 10.7	14

The values are given as percent with respect to the average edema of untreated animals.

recent data indicating a role of this substance in regulating cellular functions, often opposing 3′5′AMP[10].

Methods and results. Wistar male rats, fasted for 12 h, of the approximated weight of 200 g were used.

Edema was produced in the left prosterior paw, following Winter method, by a subplantar injection of 100 ng/rat of PGE_2 and $PGF_2\alpha$ dissolved in 0.1 ml of physiological solution. Fluid paw volume was measured with a pletismograph before the injection and 30, 60 and 120 min after.

The paw's volume increase after subplantar injection of 0.1 ml physiological solution was assumed as a control value. 10 mg/kg total weight of 3′5′AMP and 3′5′GMP was injected i.p. 15 min before subplantar injection of PG. The dose was chosen for its scarse or no effects on cardiovascular function, which had been confirmed beforehand. The production of edema in rats paw, following a 3′5′AMP or 3′5′GMP injection alone, was also controlled at the dose of 1 mg in 0.1 cm^3 by subplantar injection.

Prostaglandins were kindly supplied by Dr. PIKE (Upjohn Kalamzoo, USA) and 3′5′AMP and 3′5′GMP by Dr. TOFANETTI (Boehringer, Mannheim, BRD). Results are listed in Tables I and II.

Discussion. Inhibition of histamine release and enzymatic lysosomal extrusion[11], as well as macrophagic migration, and leucocyte chemiotactic reaction is known to be determined by an increase of intracellular 3′5′AMP concentration, following a stimulation of adenylcyclase or an inhibition of phosphodiesterases[4,12]. On the contrary, an increase of intracellular 3′5′GMP concentration results in opposite effects[10].

The present observations on rat's paw edema from PG confirm the opposite effect of these cyclic nucleotides. In effect prostaglandins edema development is inhibited by 3′5′AMP, whereas 3′5′GMP does not interfere with, or increase, the edema responsiveness to PG administration. The inhibiting effect of 3′5′AMP is more evident in PGF induced edema, the time course of which was not modified by 3′5′GMP. Also PGE-induced edema is inhibited by 3′5′AMP, whereas it is slightly increased by 3′5′GMP pretreatment.

The respective behaviour of the cyclic nucleotides also shows some differences in their primary edema-induced activity, since 3′5′AMP shows no effect with regard to this (and behaving thus as a physiological solution), whereas a late, weak edema is induced by 3′5′GMP administration. The fact that a different behaviour is shown by cyclic nucleotides by themselves, or when tested on a PGE or PGF induced edema, suggests that a different mechanism of action underlies this difference.

This is the case of rat liver: the release of enzymes from lysosomes fraction is inhibited by β-stimulating drugs or 3′5′AMP administration and stimulated by 3′5′GMP[13], and the behaviour of protease release by human leukocytes[14] and of smooth muscle[15] contraction mechanisms is similar.

Other experiments have also shown that 3′5′AMP pretreatment, or β_2-stimulating drugs administration (which are well known stimulators of adenylate cyclase activity) have an inhibiting effect on $PGF_2\alpha$-induced bronchospasm. 3′5′GMP pretreatment does not modify the $PGF_2\alpha$-induced bronchospasm and counteracts the manifestation of the bronchodilator effect due to PGE_2[16].

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Diphasic Action of the Aliphatic Amide, HOE 17879, on Hepatic Microsomal Drug Metabolizing Enzymes in the Mouse

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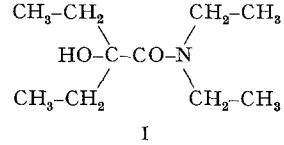
Summary. α-Hydroxy-α-ethylbutyryl-diethylamide (HOE 17879) influences the hepatic microsomal drug hydroxylating enzyme system of mice in a two-phasic way: First it reduces the overall reaction of drug hydroxylation but not the single enzymes whilst in the second period it increases enzyme activities.

A great number of substances exert a diphasic action upon the hepatic microsomal drug-hydroxylating enzyme systems by inhibiting them in the first period of action, and increasing their activities in the second period of action due to induction of their biosynthesis (see [2–9], for instance). This paper describes the diphasic action on liver microsomal drug-metabolizing enzymes of the aliphatic amide, HOE 17879 (α-hydroxy-α-ethylbutyryl diethylamide, I), a substance which possesses little pharmacological activity by itself[10] but influences, in a diphasic manner, the narcosis times of a series of narcotics capable of being metabolized in the liver[11]. Because of its relatively simple structure, this substance might well be a tool for studying these enzyme inhibition effects which lead afterwards to enzyme biosynthesis induction. By the authors cited above, only the overall reaction of drug hydroxylation has been studied. For us, it seemed to be interesting to investigate the behaviour of the single components of the microsomal respiratory chain,



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too, e.g. of NADPH dehydrogenase, NADPH: cytochrome c oxidoreductase ('cytochrome c reductase'), NADPH: neotetrazolium chloride oxidoreductase ('neotetrazolium reductase'), and cytochrome P-450, in order