perfused lung (Thomas et al 1981). If the cell is not capable of metabolizing AA then the free fatty acid will be released and any AA-dependent process will be impaired. This suggestion could account for the inhibition of platelet aggregation reported by Hwang (1981). The net result of imbiding alcohol in vivo will depend on the relative importance of AA-dependent processes in the tissue concerned and the effect of any of its metabolites produced.

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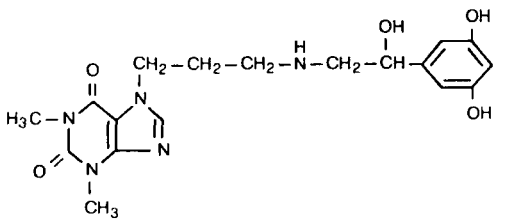
In vitro effect of reproterol upon pulmonary, cardiac, vascular and intestinal 3′,5′-monophosphate phosphodiesterase nucleoside

E. Marmo*, F. Di Mezza, L. Giordano, M. G. Matera, R. De Carlo, E. Ruggiero, *Department of Pharmacology and Toxicology, I Faculty of Medicine and Surgery, University of Naples, Italy*

Reproterol [7-(3(β,3,5-trihydroxyphenethyl)amino-1-)-propyl]-theophylline hydrochloride], (I), is a water-soluble theophylline phenethylamine derivative with a catecholamine component linked to dimethyl-xanthine through a propyl group (Habersang et al 1977a; Klingler 1977); it has a potent bronchospasmolytic action which has been demonstrated experimentally (Habersang et al 1977b) and clinically (Diewitz 1977; Konietzko 1977; Mándi et al 1977a,b; Nolte et al 1977; Tabori et al 1977; Zečević et al 1977).



Reproterol activates the tracheo-bronchial adenylcyclase (β_2-adrenergic effect) to a greater extent than the cardiac and hypothalamic enzyme (Marmo et al 1981).

The methylated xanthines, such as theophylline, also have a tracheobronchodilator effect by blocking the phosphodiesterases, which are enzymes responsible for the degradation of cyclic 3′5′-(c)AMP. As a result, there is an increase in cAMP and relaxation of the smooth muscle in the trachea and bronchi (Robinson et al 1968). In view of the presence of a methylxanthine in reproterol, it was decided with this study to assess the possible inhibitory effect of reproterol upon pulmonary, cardiac, vascular (abdominal aorta) and intestinal (duodenum) phosphodiesterase (PDE) in the guinea-pig. The drug was compared with theophylline.

Phosphodiesterase activity was measured in lung, heart, abdominal aorta and duodenum of male guinea-pigs, 400–500 g, as described by Brooker et al (1968), Lippmann (1974), Somerville et al (1970), Tateson & Trist (1976) and by Weinryb et al (1973). The IC50 was determined (inhibitory concentration 50, probit method of Finney 1952). The drugs used were reproterol hydrochloride (Farmades SpA Rome) and theophylline monoethanolamine. All doses are stated as theophylline base.

In vitro, reproterol had a dose-dependent inhibitory effect upon pulmonary, cardiac, vascular and intestinal phosphodiesterase (Tables 1, 2). This effect corresponds with that of its theophylline content (Tables 1, 2) which

Table 1. Effects upon cAMP phosphodiesterase (PED) activity. Each value is the mean ± s.e.m. of 5 preparations. Reproterol concentrations indicated as theophylline base.

Drug μM	Inhibition % ± s.e. of PDE in Lung	Heart	Aorta	Intestine
Reproterol				
200	12 ± 2	27 ± 3	10 ± 1	4 ± 1
500	36 ± 4	48 ± 5	22 ± 3	16 ± 2
1000	60 ± 7	90 ± 9	38 ± 4	27 ± 4
2000	97 ± 8		86 ± 7	75 ± 8
Theophylline				
250	11 ± 2	26 ± 5	8 ± 1	3 ± 1
500	30 ± 4	49 ± 6	21 ± 7	14 ± 3
1000	58 ± 6	86 ± 9	35 ± 8	22 ± 4
2000	91 ± 9		90 ± 9	80 ± 9

* Correspondence.

Table 2. Effects upon cAMP phosphodiesterase (PDE) activity.

Drug	Organ	IC50 (with confidence limits) μM (as theophylline)
Reproterol	Lung	705 (413–1190)
	Heart	444 (261–756)
	Aorta	1000 (534–1890)
	Intestine	1310 (693–2510)
Theophylline	Lung	779 (459–1310)
	Heart	469 (261–833)
	Aorta	1030 (582–1800)
	Intestine	1319 (731–2400)

provides evidence that, for reproterol, the inhibition of 3'5'-monophosphate phosphodiesterase nucleoside (PDE), which hydrolyses cAMP to AMP and which controls the intracellular concentration of cAMP (Robinson et al 1974), is one of the molecular mechanisms underlying its anti-asthma effects. This effect can be attributed to the presence of theophylline in the reproterol molecule and is additional to its ability to activate the β-adrenoceptors directly. The release of inflammatory mediators (histamine, SRS-A, etc) is inhibited by the intracellular rise in cAMP (Bourne et al 1974) through a mechanism which is not known but which involves the reduction of the permeability of mast cells to calcium (Foreman et al 1975).

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Stabilization of a sustained release-type injection vehicle for a synthetic corticotrophin analogue

SINYA FUTAGUCHI, KUNISHIRO ODAGUCHI, AKIRA TANAKA, MASAHARU HIRATA*, *Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan*

Adrenocorticotrophin (ACTH) is a pituitary peptide hormone which stimulates the adrenal cortex to secrete corticosteroids. Preparations of ACTH and its synthetic analogues are currently used to test adrenal functions or to clinically treat rheumatoid arthritis and asthma (Haynes & Murad 1980). Since the biological half-life of ACTH is short, various depot-type injections have been devised for therapeutic treatment using gelatin, zinc hydroxide or carboxymethyl cellulose (British Pharmacopoeia 1980; Hedner 1963). Adsorption of the peptide onto the zinc hydroxide (or zinc phosphate) dispersion in the vehicle results in marked prolongation of corticotrophic activity of ACTH upon intramuscular injection, which could be due to either delayed absorption into circulating blood or protection of the peptide from enzymic inactivation at the extravascular injection site. The formulation can be applied to synthetic short-chain ACTH analogues such as [Gly^1]-ACTH-(1-18)-NH_2 (Otsuka & Inouye 1975; Tanaka 1971). Although freshly prepared zinc-[Gly^1]-ACTH-(1-18)-NH_2 dispersion showed a pronounced depot effect when injected into rat thigh muscle, the dispersion became aggregated within 24 h when stored at 25 °C and the depot effect was lost. However, the dispersion could be stabilized by including histidylhistidine (Hirata et al 1974) making possible a long-lasting corticotrophic activity.

The zinc-[Gly^1]-ACTH-(1-18)-NH_2 dispersion was prepared by first mixing 10 mg [Gly^1]-ACTH-(1-18)-NH_2, 5 mg L-histidyl-L-histidine, 90 mg NaCl, 100 mg benzyl

* Correspondence.