

POLYUNSATURATED FATTY ACIDS ARE PHARMACOACTIVE WHEN GIVEN
TRANSDERMALLY : ANTI-INFLAMMATORY ACTIVITY IN POLYARTHRITIC RATS

M. WHITEHOUSE, C. HANN, G.FORD*, and B. VERNON-ROBERTS

Omega-3 polyunsaturated fatty acids (PUFA) may regulate inflammation by at least 3 mechanisms involving eicosanoids, namely: (i) providing alternative substrates for the enzyme cyclooxygenase which transforms arachidonate (20:4n6) to prostaglandin (PG)-E₂, with DGLA (20:3n6) and EPA (20:5n3) yielding the less pro-inflammatory PGE₁ and PGE₃ respectively; (ii) inhibiting cyclooxygenase e.g. DHA (22:6n3), or (iii) forming 13- or 15-lipoxygenase products that inhibit 5-lipoxygenase and hence leukotriene formation. PGE₁ and PGE₃ can mimic PGE₂ as natural feedback regulators of inflammatory cytokines e.g. IL-1.

A problem with supplying PUFA's as dietary triglycerides is their incorporation into chylomicra lipoproteins, requiring lipoprotein lipase (LPL) to liberate the PUFA's. LPL is inhibited by tumour necrosis factor-alpha produced by activated mononuclear phagocytes so that PUFA availability from dietary lipids may be compromised by inflammatory disease. To circumvent this problem we have investigated the effect of supplying PUFA's transdermally (i.e. bypassing the intestine) to inflamed rats as triglyceride, methyl ester or zinc salts. These require the action of a lipase, esterase or no enzyme respectively to make available free PUFA in vivo.

Experimental: Zinc salts and methyl esters (purity >95%) of C₁₈-C₂₂ PUFA's were applied as solutions/dispersions in DMSO-glycerol (4:1,v/v), 2.5ml/kg to shaved dorsal skin of PVG rats for 4 days beginning on Day 12 after inoculating an arthritogenic Freund's adjuvant in their tailbase. Triglycerides were mixed with 0.25 vol of a 'thinner' (cineole, 2-propanol, methyl salicylate) for dorsal application, 2ml/kg.

Results: Methyl esters were rather irritant to the skin. Zinc salts were well tolerated. Triglycerides required a thinner to be rapidly rubbed into the skin. Based on PUFA content, zinc salts were more potent than the esters. Thus the ED₅₀'s to reduce rearpaw swelling (day 16) for alpha-linolenate (18:3n3) were approx. 100, 250 and >600 μmol/kg presented as Zn salt, methyl ester and canola (10% 18.3) or linseed oils (42% 18.3) respectively.

I = inhibition of rear paw swelling by Zn(PUFA)₂ applied dermally in DMSO-glycerol

100μmoles/kg Zn	%I	50μmoles/kg Zn	%I
Linoleate	<10	Arachidonate	66
gamma-linolenate	62	DGLA	89
alpha-linolenate	>90	EPA	70
Crepenynate	76	DHA	84

Institute of Medical and Veterinary Science, Adelaide, South Australia 5001 and
*CSIRO:Food Research, North Ryde, New South Wales 2113