Anti-inflammatory activity of esters of phenylglycine

Phenylglycine n-heptyl ester has been shown in both *in vitro* and *in vivo* tests to be a potent inhibitor of bradykinin, 5-hydroxytryptamine (5-HT), histamine and dextran in rats and of acetylcholine, histamine, 5-HT and anaphylaxis in guinea-pigs (Gecse, Zsilinszky & others, 1971). More recently, this compound and the corresponding ester of phenylalanine were found to inhibit carrageenan and dextran responses in rat paws as well as arthritis induced by Freund's adjuvant in rats (Thomas & West, 1973).

We have now tested a series of straight-chain esters of phenylglycine for their anti-inflammatory effects. Inflammation was induced by subcutaneous injections of dextran or carrageenan (1 mg in 0·1 ml normal saline) into the right hind-paws of groups of 6 Wistar rats obtained from the ASH colony. The increase in paw volume was recorded every hour for 6 h on a volume differential meter. Esters were administered i.p. 20 min before the inflammatory stimulus. The percentage inhibition of inflammation was calculated by comparing the mean percentage increase in the paw volume of the control group (Vc) with the mean percentage increase in the paw volume of the treated group (Vt) at the same time interval, using the equation:

$$\% \text{ inhibition} = \frac{Vc - Vt}{Vc} \times 100$$

Table 1 shows the results for the heptyl ester, the ID50 values calculated graphically being 34·2 mg kg^{-1} against dextran and 61·5 mg kg^{-1} against carrageenan. For comparison purposes, the other esters were therefore first tested at dose levels of 50 mg kg^{-1} against dextran and of 100 mg kg^{-1} against carrageenan. Typical results are

Table 1. *Inhibition by phenylglycine heptyl ester of the dextran response in rat paws at 1 h and of the carrageenan response at 5 h.*

Phenylglycine heptyl ester (mg kg^{-1})	Inhibition (%)	
	Dextran	Carrageenan
25	45·6	20·8
50	56·0	38·2
100	86·8	70·0

Table 2. *Inhibition by esters of phenylglycine of the dextran response in rat paws at 1 h and of the carrageenan response at 5 h.* The ester doses were 50 mg kg^{-1} against dextran and 100 mg kg^{-1} against carrageenan.

Ester of phenylglycine	Inhibition (%)	
	Dextran	Carrageenan
Methyl	20	0
Ethyl	26	0
Propyl	6	0
Butyl	0	0
Pentyl	18	30*
Hexyl	43*	78*
Heptyl	56*	87*
Octyl	54*	79*
Nonyl	51*	74*
Decyl	57*	84*

* Significant at $P<0·05$ level.

recorded in Table 2 where the inhibitions are shown at 1 h after dextran and at 5 h after carrageenan.

Statistically significant inhibitions were obtained only with esters of phenylglycine with high molecular weight alcohols, the threshold being hexyl for dextran oedema and pentyl for carrageenan inflammation. Some of the esters of the low molecular weight alcohols were also tested at doses up to 300 mg kg^{-1} against carrageenan and were inactive as inhibitors. When Wistar rats from the NELP colony (resistant to dextran—Harris & West, 1963) were tested using carrageenan as the inflammatory agent, esters of the high molecular weight alcohols were active while those of the low molecular weight alcohols were not. All the esters when given orally failed to inhibit the dextran and carrageenan responses, and phenylglycine and the corresponding alcohols were also inactive orally as well as by the intraperitoneal route. The active esters had LD50 values of about 300 mg kg^{-1}.

Dextran oedema is mediated mainly by the release of 5-HT and histamine (Parratt & West, 1957), whereas the later phases of carrageenan inflammation involve kinins and prostaglandins (Di Rosa & Willoughby, 1971). The anti-inflammatory activity of the esters may therefore be due, at least in part, to their antagonism of the actions of these endogenous mediators.

The effect of the active esters on the complement system is now being tested. The results of preliminary tests suggest that they do not inhibit complement activity *in vitro*, but they may deplete the complement levels *in vivo*.

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