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Selectivity of action of some C15-modified prostaglandins D

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Prostaglandin D_2 (PGD_2) raises the blood pressure of the anaesthetized sheep by direct vasoconstriction and is some 70 times more active than $PGF_{2\alpha}$ (Horton & Jones, 1974; Jones, 1975). From preliminary studies on prostaglandins of the F series, it appeared that certain C15-modified analogues of PGD_2 might exhibit a greater selectivity of action than PGD_2. The 15-methyl ether, 15(R), 15-oxo and 13,14-dihydro-15-oxo analogues of PGD_2 have therefore been prepared. Equipotent molar ratios (PGD_2 = 1.0) for these four compounds and the corresponding $PGF_{2\alpha}$ analogues as pressor agents in the sheep are shown in Table 1. It can be seen that the modified prostaglandins D exhibit high pressor activity whereas the corresponding PGE_2 analogues are much less active than PGE_2 as depressor agents.

In the rabbit PGD_2 and PGE_2 are potent pressor and depressor agents respectively and similar equipotent molar ratios for many of the compounds in Table 1 have been found. In the rat PGE_2 (100 ng/kg intra-aortically) lowers the blood pressure. PGD_2 elicits a small pressor response at doses 50 times greater (on a body weight basis) than those effective in the sheep. At higher doses (5 μg/kg), PGD_2 gives a biphasic response. However, PGD_2 15-methyl ether, 13,14-dihydro-15-oxo PGD_2 and 15-oxo $PGF_{2\alpha}$ produce only pressor responses. It is suggested that these C15-modified prostaglandins are devoid of the significant PGE-like depressor activity shown by PGD_2.

On the rabbit oviduct *in vivo*, $PGF_{2\alpha}$ raises the intra-luminal pressure (Horton & Main 1965); PGD_2 15-methyl ether was found to be 140 times

Table 1 Comparison of C15-modified prostaglandins on the sheep blood pressure (intra-aortic injection)

	Equipotent molar ratios		
	Pressor response		*Depressor response*
ω-side chain characteristics	*PGD_2 analogues*	*$PGF_{2\alpha}$ analogues*	*PGE_2 analogue*
15(S)-hydroxyl	1.0	69	1.0
15(S)-methyl ether	5.6	107	> 100
15(R)-hydroxyl	1.9*	59*	550
15-oxo	8.4†	13	> 300
13,14-dihydro-15-oxo	5.7	550	> 300

Each ratio is the mean of at least three determinations.
* Racemic mixture
† Major component is the 12,13-ene isomer.

less active than $PGF_{2\alpha}$. (±)15(R) PGD_2 and 13,14-dihydro-15-oxo PGD_2 produced no effect at doses 100 and 330 times respectively, the threshold dose of $PGF_{2\alpha}$. Finally on the isolated rabbit jejunum, where PGD_2 is about 5 times less active than $PGF_{2\alpha}$, PGD_2 15-methyl ether and (±)15(R) PGD_2 are at least 100 times and the two 15-oxo PGD analogues at least 500 times less active than $PGF_{2\alpha}$.

Thus it would appear that simple chemical changes can be made at C15 which result in retention of PGD-like activity but loss of PGE- and PGF_α-like activities.

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Prostaglandins and changes in the gastric mucosal barrier and blood flow during indomethacin- and bile salt-induced mucosal damage

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The formation of gastric mucosal erosions by non-steroid anti-inflammatory drugs in the rat is greatly increased by the presence of bile acids in the gastric lumen (Semple & Russell, 1975), although this damage is prevented by prostaglandin methyl analogues (Whittle, 1975). Changes in gastric mucosal blood flow and in the resistance of the mucosa to acid back-diffusion (the mucosal 'barrier') have now been investigated as possible mechanisms underlying such erosion formation.

The gastric lumen of the urethane-anaesthetized rat was perfused with acidic saline (0.1-0.2 ml min^{-1}) and the loss of acid across the mucosa determined by titration. The potential difference (PD) across the mucosa, which is related to hydrogen- and sodium-ion flux and gives an indication of the integrity of the mucosal barrier (Chvasta & Cooke, 1972) was measured via calomel electrodes. Mucosal blood flow (MBF) was determined by [^{14}C]-aniline clearance (Main & Whittle, 1973).

During acid perfusion (100 mM HCl, pH 1), administration of sodium taurocholate (1 mg/ml, 2 mM) increased the acid-loss (from 0.48 ± 0.19 to 2.2 ± 0.3 μEq min^{-1} after 1 h; mean ± s.e. mean, $n = 4$), lowered PD (by −10.4 ± 1.5 mV, $n = 8$) and increased MBF (to 340 ± 15% of basal, $n = 4$). The rise in MBF appeared to correlate with acid back-diffusion and may represent a protective mechanism of the mucosa, since few erosions were seen after the 3 h perfusion. Indomethacin (20 mg/kg i.v.), injected during acid perfusion,