Prostaglandins D and F with highly selective agonist actions

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Prostaglandins (PGs) E_2, D_2 and $F_{2\alpha}$, although highly potent agonists in many biological systems, exhibit a low selectivity of action. For example, it can be demonstrated that PGD_2 has considerable PGE-like activity, causing relaxation of circular smooth muscle in the cardiovascular, respiratory and reproductive systems. Our recent studies have been concerned with detecting prostaglandin analogues which show a higher selectivity than the naturally occurring compounds.

The typical actions of $PGF_{2\alpha}$, including induction of luteolysis, are mimicked by a number of prostaglandins having an aryloxy substituent in the ω-chain (Dukes, Russell & Walpole, 1974; Binder, Bowler, Brown, Crossley, Hutton, Senior, Slater, Wilkinson & Wright, 1974). Of particular interest is ICI 81008 (17,18,19,20-tetranor-16-*m*-trifluoromethylphenoxy $PGF_{2\alpha}$) which we have shown to be of the same order of potency as $PGF_{2\alpha}$ in stimulating both the rabbit oviduct *in vivo* and the rabbit jejunum *in vitro*, and in producing a delayed, bretylium-sensitive, pressor effect in the sheep. However, in the sheep and rabbit ICI 81008 is at least 2000 times less active than PGD_2 and at least 30 times less active than $PGF_{2\alpha}$ in producing an immediate, bretylium-insensitive, pressor effect. In contrast, the 13,14-dihydro-15-oxo analogue of PGD_2 has one-fifth of the immediate pressor activity of PGD_2 in the sheep and rabbit, but is devoid of activity on the previously mentioned PGF-sensitive systems.

By comparing activities on rabbit and sheep blood pressures with those obtained on rabbit oviduct and rabbit jejunum it has been possible to place a number of compounds in order of selectivity as follows: 13,14-dihydro-15-oxo PGD_2; PGD_2 15-methyl ether and 15-oxo $PGF_{2\alpha}$; PGD_2; $PGF_{2\alpha}$; 13,14-didehydro $PGF_{2\alpha}$; ICI 81008.

It should be noted that 13,14-dihydro-15-oxo PGD_2, PGD_2 15-methyl ether and ICI 81008 show very low activity on PGE-sensitive systems such as the guinea-pig ileum *in vitro*. Recently prostacyclin (PGX) has been shown to be an extremely potent inhibitor of human platelet aggregation *in vitro* and to be some 10 times more active than either PGD_2 or PGE_1 (Bunting, Gryglewski, Moncada & Vane, 1976; Johnson, Morton, Kinner, Gorman, McGuire, Sun, Whittaker, Bunting, Salmon, Moncada & Vane, 1976). In our studies PGD_2 15-methyl ether and 13,14-dihydro-15-oxo PGD_2 had very low platelet inhibitory activity being 3000 times and more than 5000 times less active than PGD_2 respectively.

These observations will be discussed in relation to the existence of separate prostaglandin receptors.

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