Actions of prostaglandins on the arterial system of the sheep: some structure-activity relationships

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Injection of prostaglandin D_2 (PGD_2) into the thoracic aorta of the sheep produces within a few seconds a short lasting rise in systemic arterial blood pressure; the isomeric PGE_2 elicits a fall in blood pressure by this route (Horton & Jones, 1974). A direct action on arterial resistance vessels is indicated for both effects. $PGF_{2\alpha}$ is about 60 times less active than PGD_2 as a pressor agent and $PGF_{2\beta}$ about 150 times less active than PGE_2 as a depressor agent.

Two further observations have been made.

(a) If a sheep is given an intravenous infusion of PGA_1 (0.6-5.0 mg kg^{-1} h^{-1}), a pronounced fall in blood pressure is produced from which there is partial recovery during the infusion. PGE_2 now fails to produce a depressor response whereas PGD_2 and $PGF_{2\alpha}$ are unaffected. Under these conditions $PGF_{2\beta}$ gives a pressor response.

(b) In the pregnant ewe, the depressor response to intra-aortic PGE_2 is attenuated (Horton & Maule Walker, 1974). The sensitivity to the pressor actions of PGD_2 and $PGF_{2\alpha}$ is maintained however. $PGF_{2\beta}$ produces a biphasic response, pressor to depressor, which can be mimicked by injecting an appropriate mixture of PGD_2 and PGE_2.

These results indicate that a particular prostaglandin can act on two systems in the peripheral vasculature to cause vasconstriction and vasodilatation, the resultant effect being dependent on its relative potencies on the two systems and the relative sensitivities of the systems.

A number of other prostaglandins have been investigated and two major structure-activity relationships have emerged.

(i) Oxidation of the 15(S)-hydroxyl to a ketone results in loss of depressor activity. Thus 15-oxo PGE_1 elicits no change in blood pressure at doses 100-300 times the dose of PGE_1 producing a fall of 10 mm Hg. In contrast, pressor activity is either unaffected or enhanced and 15-oxo $PGF_{2\alpha}$ is 5-10 times more active than $PGF_{2\alpha}$. 15-oxo $PGF_{2\beta}$ is a pressor agent of low potency.

(ii) Saturation of the 5,6-*cis* and 13,14-*trans* double bonds results in marked loss of pressor activity. Thus PGD_2 and 15-oxo $PGF_{2\alpha}$ are about 8 times more active than PGD_1 and 15-oxo $PGF_{1\alpha}$ respectively and about 100 times more active than 13,14-dihydro PGD_1 and 13,14-dihydro-15-oxo $PGF_{1\alpha}$ respectively. Depressor activity is little affected by these changes and the potencies of the 2-, 1-, and 13,14-dihydro-1-series analogues with either the E, 11-deoxy E, A or B ring structures differ by less than a factor of three.

Of the compounds tested it is suggested that 15-oxo $PGF_{2\alpha}$ shows the highest specificity for the pressor system, and 13,14-dihydro PGE_1 the highest specificity for the depressor system.

Further studies will be concerned with the identification of systems in other tissues showing similar agonist structure-activity relationships. In this connexion, the recent report by Dawson, Lewis, McMahon & Sweatman (1974) showing that $PGF_{2\alpha}$, 15-oxo $PGF_{2\alpha}$ and PGD_2 are of the same order of potency as bronchoconstrictor agents is of great interest.

References

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