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Identification of the novel $P2Y_{14}$ receptor in porcine isolated pancreatic arteries

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$P2Y_{14}$ is the newest member of the P2Y family of receptors for adenine and uridine nucleotides and nucleotide sugars. $P2Y_{14}$ is activated by UDP, UDP-glucose and its analogues, besides the synthetic analogue MRS 2690 (diphosphoric acid 1- alpha-d-glucopyranosyl ester 2-[(4'-methylthio) uridin-5''-yl], which has been shown to be more potent than UDP-glucose. The aim of this study was to characterise the effect of $P2Y_{14}$ receptor agonists in porcine isolated pancreatic arteries. Segments of porcine pancreatic arteries were prepared for isometric tension recording in oxygenated Kreb's solution warmed to 37^{o}C. UDP-glucose (1μM - 1mM), UDP (1μM - 1mM) and MRS 2690 (10nM - 100μM) were added cumulatively after preconstriction with U46619, a thromboxane A_2-mimetic. Agonists were investigated in the absence and presence of P2 receptor antagonists. Pancreatic arteries were stained for $P2Y_{14}$ receptor using standard indirect immunofluorescence techniques. UDP, UDP-glucose and MRS 2690 induced concentration-dependent contraction in pancreatic arteries, with a rank order of potency of MRS 2690 (10-fold) > UDP-glucose ≥ UDP (n=5-12). Both suramin (100μM) and PPADS (pyridoxal-phosphate-6-azophenyl-2', 4'-disulphonic acid) (10μM), P2 receptor non-selective antagonists, significantly augmented the response to UDP and UDP-glucose ($P < 0.01$) (n=6-12), but not that to MRS 2690 (n=4-5). The ectonucleotidase inhibitor ARL 67156 (100μM) had no significant effect on responses to UDP-glucose, UDP and MRS 2690 (n=4-6). $P2Y_{14}$ immunoreactivity was found in the endothelium and vascular smooth muscle cells. The relative potencies of UDP, UDP-glucose and MRS 2690 in eliciting vasoconstriction in porcine pancreatic arteries, together with immunostaining for $P2Y_{14}$, are consistent with an involvement of the $P2Y_{14}$ receptor. Augmentation of the response to these agonists by P2Y receptor antagonists may be due to the inhibition of ectonucleotidase activity. ARL 67156 failed to enhance the response to UDP and UDP-glucose, but it is unclear whether it can inhibit ectonucleoside triphosphate diphosphohydrolase isoform 5, which is responsible for breaking down UDP and UDP-glucose (Murphy-Piedmonte et al., 2004). The lack of effect of suramin and PPADS on the response to MRS 2690 may suggest that MRS 2690 is more stable than UDP and UDP-glucose, which may account for its greater potency.

Murphy-Piedmonte, D. M., Patrick A. Crawford, P. A. & Kirley, T. L. (2004). BBA-Proteins and Proteomics. **1747**, 251-259.