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Investigating the functional expression of the novel $P2Y_{14}$ receptor in porcine isolated pancreatic arteries

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The $P2Y_{14}$ receptor is the most recent member of the P2Y of receptors for adenine and uridine nucleotides and nucleotide sugars. It is activated by UDP, UDP-glucose and its analogues, besides the synthetic analogue MRS 2690 (diphosphoric acid 1-α-D-glucopyranosyl ester 2-[(4'-methylthio)uridin-5"-yl] ester), which has been shown to be 7-10 fold more potent than UDP-glucose. The aim of this study was to investigate the functional expression of the $P2Y_{14}$ receptor in porcine isolated pancreatic arteries. Segments of pancreatic arteries were prepared for isometric tension recording in oxygenated Krebs-Henseleit buffer warmed to 37^{o}C. UDP-glucose (1 µM – 1 mM), UDP (1 µM – 1 mM) and MRS 2690 (1 µM – 30 µM) were applied cumulatively after preconstriction with U46619 (10 - 100 nM), a thromboxane A_2-mimetic. Agonists were investigated in the absence and presence of compound-2, a $P2Y_{14}$ receptor selective antagonist (Guay *et al.*, 2011) (kindly donated by Merck Sharp & Dohme). UDP-glucose, UDP and MRS 2690 induced concentration-dependent contraction with a rank order of potency of MRS 2690 (10-fold) > UDP-glucose ≥ UDP. Contraction was significantly reduced in the presence of Compound-2; the contraction to 100 µM UDP-glucose and to 10 µM MRS 2690 was reduced by 55 ± 10% ($P < 0.05$, n=7) and by 46 ± 9% ($P < 0.01$, n=9) respectively in the presence of the antagonist. In separate experiments, an enhanced UDP-glucose response, by 930 ± 108% ($P < 0.001$, n=11), was uncovered if the tissue was precontracted with U46619, and relaxed back to baseline with 1 µM forskolin before the addition of UDP-glucose. The relative potencies of UDP, UDP-glucose and MRS 2690 in eliciting vasoconstriction in pancreatic arteries, together with the inhibition that occurs in the presence of a $P2Y_{14}$ receptor selective antagonist are consistent with an involvement of $P2Y_{14}$ receptors in porcine isolated pancreatic arteries. Augmentation of the contractile response to UDP-glucose after contraction with U46619 and relaxation with forskolin suggests that cyclic AMP-dependent mechanisms are involved in the response to UDP-glucose which shows $P2Y_{14}$ is involved in heterotrimeric Gi-protein-mediated signalling.

Guay D, Beaulieu C, Belley M, Crane SN, DeLuca J, Gareau Y, *et al.* (2011). *Bioorganic & Medicinal Chemistry Letters*21(10)**:** 2832-2835.

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