Effects of P2Y14 Receptor Agonists, UDP-glucose and MRS2690, on Porcine Coronary Artery Contractility

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P2Y receptors are G protein-coupled receptors that are activated by adenine and uridine nucleotides and nucleotide sugars (Abbracchio et al., 2006). There are eight P2Y receptors (P2Y1,2,4,6,11,12,13,14); P2Y14 is the most recently discovered, and is activated by UDP-glucose and UDP, but not by ATP, ADP or UTP (Chambers et al., 2000; Abbracchio et al., 2003). MRS2690 is a selective P2Y14 receptor agonist with greater potency than UDP-glucose (Ko et al., 2007). The focus of attention with regard to the P2Y14 receptor has been its role in allergic responses and immunity. Recent evidence indicates that the P2Y14 receptor may mediate contraction of porcine pancreatic arteries (Alsaqati et al., 2011). The present study sought to investigate whether the P2Y14 receptor has a role in regulation of porcine coronary artery contractility.

Pig hearts were obtained from breeds of the modern hybrid pig, of either sex (exact weight unknown) and were transported on ice from a local abattoir. Segments of coronary arteries were mounted for isometric tension recording in warmed oxygenated Krebs-Henseleit buffer (Rayment et al., 2007). Tissue viability was assessed by eliciting contractions with 60 mM KCl. Arteries were preconstricted with U46619, a thromboxane A2 mimetic, to 55-85% of the KCl contraction. Cumulative concentration response curves to UDP-glucose and MRS2690 were constructed. In separate experiments suramin (100 µM) and PPADS (10 µM), non-selective P2 receptor antagonists, and MRS2578 (10 µM), a P2Y6 receptor antagonist, were added 10 min before U46619 addition. U46619 was prepared as a stock solution of 10^{-2} M in ethanol. Data were compared for statistical analysis by two-way ANOVA with Bonferroni post test. P<0.05 was taken as significant. Immunohistochemical staining for P2Y14-like protein was carried out on cross-sections of coronary arteries using a C-terminally directed P2Y14 receptor antibody.

UDP-glucose (0.1-1000 µM) elicited concentration dependent contraction of the coronary arteries (n=11). The selective P2Y14 receptor agonist MRS2690 (0.001-10 µM) also elicited concentration-dependent contraction and was more potent than UDP-glucose (n=6). Contractile responses to MRS2690 were unaffected by suramin, PPADS and the P2Y6 antagonist MRS2578 (n=6-12). Contractile responses to UDP-glucose were unaffected by PPADS, attenuated by MRS2578 (P<0.5) and augmented by suramin (P<0.001) (n=7-16) (eg. at 100 µM UDP-glucose responses were: control, 0.83 ± 0.15 g (n=16), PPADS, 0.88 ± 0.16 g (n=7), suramin, 1.45 ± 0.17 g (P<0.001, n=9), MRS2578 0.33 ± 0.07 (P<0.05, n=7)). Immunohistochemical staining showed expression of P2Y14-like protein on the smooth muscle and endothelium of the coronary arteries, which was not present when primary antibody had been omitted.

The relative potencies of MRS2690 and UDP-glucose in mediating contraction of porcine coronary arteries is consistent with an involvement of P2Y14 receptors. Contractile responses to UDP-glucose were mediated partly via P2Y6 receptors.