Activation of PPARβ/δ prevents the high glucose-induced impairment of cAMP-mediated relaxation in rat coronary arteries

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Activation of peroxisome proliferator-activated receptor β/δ (PPARβ/δ) causes protective effects on obesity, insulin sensitivity and metabolic syndrome. Very recently, the PPARβ/δ agonist GW0742 has been shown to reduce endothelial dysfunction in spontaneously hypertensive rats (Zarzuelo *et al.,* 2011). Besides endothelial dysfunction, coronary arteries show a reduced cAMP-mediated dilation in experimental models of diabetes. We hypothesized that activation of PPARβ/δ may exert protective effects in the diabetic vascular dysfunction. Thus, the aim of the present study was to analyze the effects of PPARβ/δ activation on the altered relaxation to cAMP in coronary arteries following short term exposure to high glucose.

Male Wistar rats (250-280g) were killed by cervical dislocation. Coronary and pulmonary arteries (250-400 μm internal diameter) were incubated for 20 hours in medium containing normal ($5x10^{-3}$ M) or high ($30x10^{-3}$ M) glucose in the absence (DMSO, final concentration 0.1-0.2%) or the presence of the PPARβ/δ agonist GW0742 (10^{-6} M or 10^{-5} M) or GW0742 (10^{-5} M) plus the PPARβ/δ antagonist GSK0660 (10^{-6} M). Vascular reactivity was assessed using isometric wire myographs and potassium currents were recorded with the patch clamp technique. Statistical analysis for multiple comparisons was carried out by two-way ANOVA followed by Bonferroni post hoc test.

The relaxant response induced by the adenylate cyclase activator forskolin ($3x10^{-9}$ - $3x10^{-7}$ M) in arteries pretreated with serotonin (10^{-6} M) was reduced in high glucose-incubated vs low glucose-incubated coronary arteries (60.5 ± 7.6% vs 94.6 ± 3.7% relaxation at $3x10^{-7}$ M $p<0.01$). Treatment with GW0742 (10^{-5} M) improved the relaxation to forskolin in high glucose-incubated coronary arteries (93.9 ± 8.5% relaxation at $3x10^{-6}$ M $p>0.05$ vs low glucose). This effect was prevented in arteries co-incubated with GSK0660 (57.9 ± 7.2% relaxation at $3x10^{-6}$ M $p<0.01$ vs low glucose). The Kv1 channel blocker DPO-1 (10^{-6} M) inhibited the relaxation induced by forskolin in coronary arteries incubated with low glucose or with high glucose + GW0742. However, this drug did not affect the relaxation induced by forskolin in coronary arteries incubated with high glucose (45.1 ± 6.6%). Accordingly, DPO inhibited Kv currents in coronary arteries incubated with low glucose but not in those incubated with high glucose (41 ± 9% and 1.4 ± 11% inhibition at +40mV, respectively). In pulmonary arteries. The relaxation induced by forskolin was similar after incubation with low glucose, high glucose or high glucose + GW0742 (82.5 ± 5%, 93 ± 12% and 80± 6% relaxation at $3x10^{-7}$ M, respectively). Moreover, DPO-1 did not affect the relaxant response induced by forskolin in these arteries.

In conclusion, activation of PPARβ/δ prevents high glucose-induced alteration of cAMP relaxation in coronary arteries. This improvement appears to be partly due to the ability of the PPARβ/δ agonist to restore a relaxant component which depends on Kv1 channel function.

Zarzuelo MJ *et al.,* (2011). *Hypertension* **58**:733-43.
Supported by SAF2010-22066.