

Effects of rosiglitazone and sumatriptan on human isolated small and large coronary arteries

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Introduction

- Species differences in receptor type, expression level or coupling can lead to marked differences in responses between laboratory animals and humans, so there is a need for testing compounds on relevant human tissues where available.
- Recently, the FDA expressed concerns over a potential increased risk for heart attacks in relation to rosiglitazone¹ (PPAR γ agonist used in diabetes management). Coronary vasoconstriction a known side effect of some drugs such as triptans² (which can increase the risk of a heart attack), has been demonstrated in human isolated tissues.
- In the current study, the coronary constrictor potential of rosiglitazone was compared to sumatriptan and 5-HT in human isolated small and large coronary arteries (HCA) from non-diseased hearts.

Methods

Hearts from 5 donors (3 male and 2 female, age range 20-65 years) who died of non-cardiac disorders were obtained from ethically approved organ procurement organisations. From these, left anterior descending or right coronary artery, with no visible atherosclerosis, were dissected and cut into either small (sHCA, 0.3-0.5mm internal diameter (i.d.)) or large (lHCA, 1-2mm i.d.) vessel rings. Vessels rings were suspended in organ baths containing Krebs' physiological salt solution, gassed with 95% O₂ / 5% CO₂ and maintained at 37°C, and were either normalised to 13kPa (sHCA) or stretched to a passive tension of 15mN (1.5g). After initial viability assessments with KCl (30-100mM), compounds were assessed under either endothelin (ET-1) or U-46619 pre-contraction (pre-contracted to ~20-35% of the KCl response, lHCA only) or basal conditions. Subsequently, function of the endothelium was assessed pharmacologically (see Figure 1).

Results

In vessel rings from all five donors, KCl (30-100mM), PGF_{2 α} (1 μ M), ET-1 (0.1-10nM) and U-46619 (0.1-3nM) caused contraction, whereas sodium nitroprusside (100 μ M) caused relaxation. Substance P (1-10nM) caused relaxation in the majority of rings tested, demonstrating a functional endothelium.

Sumatriptan and 5-HT but not rosiglitazone (1nM-10 μ M) caused concentration-dependent contractions that were similar in both sHCA and lHCA. Pre-contracting the vessels with either ET-1 or U-46619 had no effect on the magnitude of effect or potency of the three test compounds. Compared to sumatriptan, 5-HT was ~3-10-fold more potent and caused approximately double the contraction magnitude. Vehicle (DMSO, up to final concentration 1%) caused small but variable relaxation. See Figures 2, 3 and Table 1.

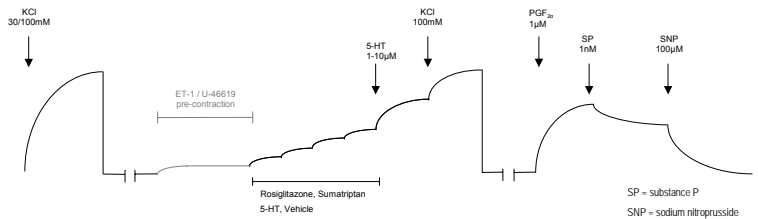


Figure 1. Schematic of experimental protocol

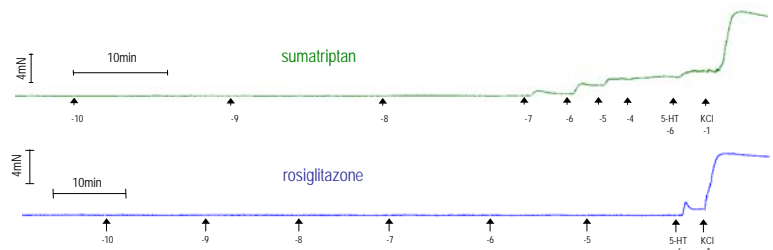


Figure 2. Original traces (above) of the effects of sumatriptan (green) and rosiglitazone (blue) in sHCA. 5-HT (1 μ M) and KCl (100mM) showed clear contractions at the end of the treatment concentration-effect curves. Concentrations are log M.

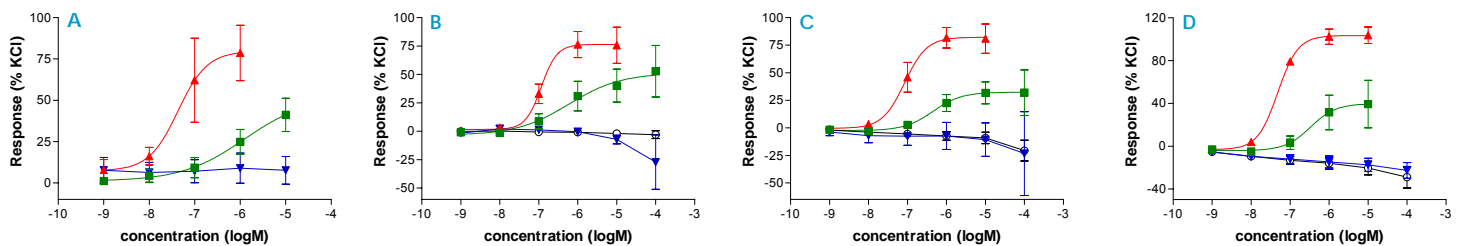


Figure 3. Graphical representation (above) of concentration-effect curves to rosiglitazone (\blacktriangledown), sumatriptan (\blacksquare), 5-HT (\blacktriangle) and vehicle (\circ) in sHCA-basal tone (A), lHCA-basal tone (B), lHCA – ET-1 pre-contraction (C) and lHCA – U-46619 pre-contraction (D). Data expressed as a % of the final challenge to KCl (100mM).

Table 1. Summary table of results. Data are mean \pm s.e.mean (n = 3-7 rings, 5 donors), or #range (n = 2 rings, 2 donors). E_{max} = % KCl 100mM.

Treatment CEC	sHCA			Basal tone			lHCA			U-46619 elevated tone		
	pEC ₅₀	E _{max}	(n)	pEC ₅₀	E _{max}	(n)	pEC ₅₀	E _{max}	(n)	pEC ₅₀	E _{max}	(n)
Rosiglitazone	-	6.3 \pm 8.5	4	-	-18.5 \pm 12.7	7	-	-9.8 \pm 3.8	6	-	-22.7 \pm 8.9	3
Sumatriptan	6.4 \pm 0.3	37.3 \pm 11.1	4	6.5 \pm 0.1	40.4 \pm 15.7	7	6.3 \pm 0.1	31.7 \pm 10.7	7	6.5 \pm 0.1	41.0 \pm 27.8	3
5-HT	7.2 \pm 0.3	84.1 \pm 18.4	3	6.8 \pm 0.1	80.4 \pm 13.9	4	7.0 \pm 0.2	83.0 \pm 13.7	5	7.4 (7.3-7.4) [#]	103.7 (96-111.4) [#]	2
Vehicle	not-tested			-	-1.9 \pm 1.6	3	-	-12.2 \pm 8.3	5	-	-29 (-18.9- -39.1) [#]	2

Discussion

- Rosiglitazone did not contract HCA.
- The magnitude of effect and potency of both sumatriptan and 5-HT were independent of the size of the HCA (<0.5mm vs. 1-2mm i.d.) or tonal level used.
- Further studies are ongoing to understand the significance of these findings in relation to the reported clinical side effects of rosiglitazone.

References

- ¹ www.fda.gov/bbs/topics/NEWS/2007/NEW01636.htm. ² MAASSENVANDENBRINK, A *et al* (1998). Coronary side-effect profiling of current and prospective antimigraine drugs. *Circulation*, 98, 25-30