096P ROSIGLITAZONE-INDUCED VASORELAXATION IN THE RAT AORTA

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Thiazolidinediones are a group of peroxisome proliferator-activated receptor gamma (PPAR-γ,) agonists which were the first class of insulin sensitizers to be introduced for the management of type II diabetes mellitus. In addition to their beneficial effects on glucose control, Nolan *et al.* (1994) reported that treatment of type II diabetic patients with troglitazone resulted in a decrease in blood pressure. It has been proposed that troglitazone and rosiglitazone exert direct vascular effects, via inhibition calcium channels (Song *et al*., 1997). In the present study, we have investigated the involvement of nitric oxide (NO), and Ca^{2+} channels in vasorelaxation to rosiglitazone in rat isolated thoracic aorta.

Male Wistar rats (225–250g) were stunned by a blow to the back of the head, and then killed by exsanguination. Thoracic aortae were removed and placed in organ baths containing oxygenated Krebs-Henseleit solution, and were mounted as 2-3mm rings for isometric recording (Tep-areenan *et al.,* 2003). The rings were then set to a resting tension of 10mN and allowed to equilibrate for 1h. Following equilibration, the rings were contracted with methoxamine (100μM). The role of NO was investigated by carrying out some experiments in the presence of 300μM N^G-nitro-L-arginine methyl ester (L-NAME). In some cases the role of the endothelium was investigated by rubbing the inner surface with a wooden stick to remove the endothelium. In some preparations, the effects of rosiglitazone were investigated against calcium influx; briefly aortae were bathed in calcium-free buffer and then contractile responses to $CaCl_2$ were determined in the presence of 100mM KCl (Tep-areenan *et al.,* 2003).

The acute presence of rosiglitazone (100nM-30μM) did not induce significant relaxation in the rat aorta (n=6). However, prolonged exposure to rosiglitazone (30μM) elicited significant vasorelaxation (20.6±6.2%, mean±s.e.mean) 50 minutes after being added and then caused time-dependent relaxations of methoxamine-induced tone (n=11) such that after 120 minutes, the relaxation to rosiglitazone was 36.8±8.0%. Removal of the endothelium abolished vasorelaxation to rosiglitazone (30μM, n=5). Rosiglitazone (30μM)-induced vasorelaxations in rat aorta were reduced significantly ($P<0.05$, Student's t-test) in the presence 300μM L-NAME (Control: 26.0±7.2 %, n=6; L-NAME: 4.4±2.7 %, n=5). In Ca^{2+}-free buffer the addition of $CaCl_2$ (10μM–30mM) caused concentration-dependent contractions in the rat aorta depolarised by 100mM KCl. Pre-treatment with 30μM rosiglitazone did not affect maximal contractions induced by $CaCl_2$ (Vehicle: 5.49±0.50mN; rosiglitazone: 4.80±0.40mN; n= 4).

In conclusion, the present findings demonstrate that rosiglitazone causes vasorelaxation on prolonged exposure, and this is largely mediated via endothelium-derived NO.

Nolan *et al.* (1994). *New Engl. J. Med.,* **331**, 1188-1193.
Song *et al*. (1997). *Diabetes,* **46**, 659-664.
Tep-areenan *et al.* (2003). *Eur. J. Pharmacol.* **465**, 125-132.