

P034 Inhibitory function of PPAR β in the sensing of the TLR4 ligands *E. coli* and LPS by macrophages

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Peroxisome proliferators-activated receptors (PPARs) are a group of cytosolic receptors which are activated by fatty acids and eicosanoids. PPARs are members of the larger family of nuclear receptors which regulate gene transcription. PPARs may also have effects independent of gene transcription. Drugs which activate PPARs have been shown to have anti-inflammatory properties in some systems by inhibiting the expression of pro-inflammatory genes. In the current study we have investigated the effects of PPAR β agonists on the induction of NOSII activity by whole heat-killed Gram-negative *E. coli* or by LPS in murine macrophages (J774). Induction of NOSII in these cells by *E. coli* or LPS is mediated by TLR4. LPS (1 μ g/ml) or *E. coli* (3x10⁷ CFU/ml) stimulated macrophages to release increased levels of NO (measured by the Griess reaction) as a direct result of induction of NOSII protein after 24 hours of stimulation. Three PPAR β agonists, GW0742, GW501516 and L165041, had no direct effect on NO release by unstimulated macrophages. However, pre-treatment of cells for four hours with GW0742, GW501516 or L165041 caused concentration dependent inhibition of NO release induced by LPS or *E. coli*. PPAR β agonists are currently in phase II clinical trials for the treatment of dyslipidaemia. These data demonstrate an inhibitory effect of PPAR β agonists on TLR4 ligand-induced responses and illustrate a potential immunosuppressive effect of drugs designed to activate PPAR β .