PPARalpha agonist fenofibrate and PPARgamma agonist GW1929 differently regulate classical and alternative activation pathways in macrophages

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Objectives: Peroxisome proliferator activated receptor (PPAR) agonists, i.e. fibrates and thiazolidinediones, are commonly used drugs in the treatment of diabetes and dyslipidemia. Their targets, PPAR isoforms PPARalpha and PPARgamma have also been shown to have a role in the regulation of immune and inflammatory responses. In the present study, we investigated the effects of PPAR agonists on macrophage activation. In addition to the pro-inflammatory “classical” (M1) activation, we also focused on interleukin (IL) 4 and IL-13 induced “alternative” (M2) macrophage activation, which is an important activation stage in tissue repairing processes and in combating parasites.

Methods: J774 macrophages were cultured with PPAR agonists fenofibrate or GW1929 (100 µM), together with bacterial lipopolysaccharide (LPS, 10 ng/ml) or with a combination of IL-4 and IL-13 (10 ng/ml) to induce classical (M1) or alternative (M2) activation, respectively. Expression of inducible nitric oxide synthase (iNOS) and production of nitric oxide (NO) and IL-6 were measured as markers of classical activation, while arginase-1, Fizz1 and Ym-1 expression were investigated as markers of alternative macrophage activation.

Results: PPARalpha agonist fenofibrate and PPARgamma agonist GW1929 both inhibited LPS-induced production of the classic inflammatory mediator IL-6 by 64 % (p<0.01) and 73 % (p<0.01), respectively. Likewise, the production of another inflammatory mediator, nitric oxide (NO) was reduced by 49 % (fenofibrate) and 54 % (GW1929). Both fenofibrate and GW1929 also reduced the expression of iNOS protein by 91 % and 94 %, respectively. Interestingly, fenofibrate inhibited also IL-4 and IL-13-induced expression of alternative activation markers arginase-1 (by 88 %, p<0.01) and Fizz1 (by 100 %, p<0.01), while PPARgamma agonist GW1929 enhanced Ym-1 expression (by 198 %, p<0.01).

Conclusions: These results suggest that PPARalpha and PPARgamma agonists differently regulate classical and alternative types of macrophage activation. Both PPARalpha and PPARgamma activation down-regulated classical proinflammatory (M1) activation while only PPARalpha activation suppressed alternative (M2) activation. The results may have implications in the pharmacotherapy of inflammatory diseases especially in association with metabolic syndrome and obesity.