Adipokines as inflammatory mediators

K Vuolteenaho[1], A Koskinen[1], T Moilanen[0,2], E Moilanen[1]. *[1]The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland, [2]Coxa Hospital for Joint Replacement, Tampere, Finland*

Adipose tissue, especially visceral adipose tissue, is an active endocrine organ that has multiple effects in the whole organ system. Adipocytes, the cells in the adipose tissue, secrete adipokines in addition to classical mediators of inflammation such as tumour necrosis factor (TNF)-α and interleukin (IL)-6. Adipokines (e.g. adiponectin and leptin) were first discovered to be produced by adipose tissue and to regulate energy metabolism and appetite. According to recent findings, leptin and other adipokines are produced by many tissues and cells in addition to adipocytes (also including joint tissues), and they are involved in the regulation of inflammation and arthritis. We have investigated the associations and effects of adiponectin and leptin on inflammation and cartilage destruction in osteoarthritic (OA) patients.

In arthritis, degradation of cartilage is mediated by matrix metalloproteinases (MMPs) and interleukin-6 (IL-6) contributes to joint inflammation. We have shown, that both leptin and adiponectin enhance production of MMPs and IL-6 in OA cartilage. Leptin-induced MMP-1, MMP-3 and IL-6 production was dependent on activation of JNK pathway. In addition, p38 was involved in the leptin-induced MMP-1 synthesis. The effect of adiponectin on IL-6 production was mediated through MAP kinases Erk1/2, p38 and JNK, while p38 pathway was involved in the adiponectin-induced effect on MMP-1 and MMP-3 production.

These *in vitro* results were also supported by our *in vivo* findings. In the synovial fluid from OA patients, leptin correlated positively with MMP-1 ($r=0.41$, $p<0.001$) and MMP-3 ($r=0.51$, $p<0.001$) as well as with IL-6 ($r=0.33$, $p=0.002$). There was also an association between adiponectin and IL-6 ($r=0.39$, $p<0.001$), MMP-1 ($r=0.31$, $p=0.004$) and MMP-3 ($r=0.27$, $p=0.011$). Furthermore, we have shown that increased plasma adiponectin levels are associated with the radiographic severity of OA, and that the adiponectin concentration correlates positively with the levels of the widely used biomarkers of OA, i.e. COMP and MMP-3.

In OA patients, leptin levels have been reported to be higher in synovial fluid than in serum, and we have showed that synovial fluid leptin concentrations correlate with BMI. In obesity, leptin resistance in the hypothalamus prevents the expected responses to adequately high leptin produced by adipose tissue, i.e. increased energy expenditure, and reduced food intake and body weight due to increased expression of suppressor of cytokine signaling – 3 (SOCS-3). We have shown involvement of SOCS-3 in leptin signalling in chondrocytes by siRNA experiments. More interestingly, we have shown lower SOCS-3 expression in cartilage from obese patients. These results suggest that leptin is a possible factor linking obesity and OA.

In conclusion, these findings support the idea of leptin and adiponectin as catabolic and proinflammatory factors in the pathogenesis of OA, and may serve as targets for disease-modifying drug development.