Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol13Issue3abst251P.pdf

Angiotensin 2 Type 1 Receptor Blockade Partly Restores Vascular Dysfunction in a Murine Model of Rheumatoid Arthritis

Vascular dysfunction is a recognised feature in rheumatoid arthritis (RA), leading to increased cardiovascular morbidity. Blockade of Angiotensin 2 (AT) type 1 receptor (AT1R) with losartan (Los) has been demonstrated to reduce swelling of the knee joint diameter (KJD) found in the Freund's complete adjuvant (FCA) rat model of chronic monoarthritis (1) suggesting that the AT1R pathway is integral to the development of the disease. Since AT is well known as a modulator of vascular function, the aim of the study was to determine if blood vessel reactivity of the femoral artery (FA) is altered in the FCA murine model of monoarthritis via an AT1R-dependent pathway.

C57B16J adult male mice were assigned randomly to three groups; non-inflamed controls, FCA + vehicle and FCA + Los (the latter group received a prophylactic dose of 15mg.kg $^{-1}$ Los 1h before induction with FCA and every 48h thereafter). Both FCA-induced groups were sacrificed after 28 days, and the ipsilateral FAs were harvested and mounted in a wire myograph for tension recording. The endothelium-dependent and –independent vasorelaxation of FAs were assessed by use of ACh (1nM-10μM) and SNP (1nM-10μM), respectively. Data are expressed as mean$\pm$s.e.m ($n \geq 3$) and analysed using ANOVA.

At day 28, KJD had increased by 81.1$\pm$9.2% in the FCA + vehicle group. KJD in the FCA + Los group was also elevated (31.2%$\pm$6.6%) but by a considerably smaller extent ($p<0.0001$) when compared to that of the non-inflamed control. In FAs from this group the endothelium-dependent relaxation found in response to the maximum concentration of ACh was 87.6$\pm$5.7%, however, in the FCA + vehicle group the response to ACh was abolished (0.5$\pm$0.4%, $p<0.0001$ with respect to control). In those mice treated with Los, the relaxation to ACh was 19.2$\pm$6.3%, which was partly restored ($P<0.0001$) towards normal levels. Endothelium-independent relaxation as determined by SNP was significantly reduced ($p<0.0001$) in the FCA + vehicle group compared to controls (5.0 $\pm$ 4.3% vs 77.4 $\pm$7.8%, respectively). In the FCA + Los group, however, maximal SNP produced a relaxation (74.5 $\pm$ 14.3%) that was found to be no different ($p>0.05$) to that generated from the non-inflamed controls.

This is the first study in mice to report that prophylactic treatment with Los decreases swelling of the KJD following treatment with FCA and confirms that the AT1R pathway plays a key role this model of monoarthritis. This corroborates earlier studies in the rat, and extends these by demonstrating endothelium-dependent and –independent vasorelaxation of the FA is effectively abolished in the FCA model, but restored (only in part for endothelium-independent vasorelaxation) by Los treatment. This could have important therapeutic implications in the treatment of vascular dysfunction in RA.

(1) Price,A.,Lockhart,J. C., Ferrell, W.R., Gesell, W., McLean, S., and Sturrock, R.D. (2007). Angiotensin II Type 1 Receptor as a Novel Therapeutic Target in Rheumatoid Arthritis. *Arthritis Rheum.* Vol. 56 (2), pp. 441-7