Investigating the Counter Regulatory Renin Angiotensin System Axis in the Stroke Prone Spontaneously Hypertensive Rat in Ischaemic Stroke

Several studies have assessed the potential of targeting the renin angiotensin system (RAS) with therapeutics for ischemic stroke. The counter regulatory RAS peptide, angiotensin-(1–9) has been shown to act via the angiotensin II type 2 receptor (AT2R) to oppose detrimental effects of RAS dysregulation. We hypothesise that Ang-(1–9) may have a beneficial effect on stroke outcome in the spontaneously hypertensive stroke prone rat (SHRSP). Initial qPCR experiments have assessed temporal changes in RAS gene expression (angiotensin converting enzyme 2; ACE2, AT2R; AGTR2, Mas receptor; Mas) following 35 min transient middle cerebral artery occlusion (tMCAO) followed by varying reperfusion times: no reperfusion 35 min, 2 hour (n=4) and 24 hour (n=4), compared to sham surgery (n=7).

In infarcted tissue, there was a significant 10- and 11-fold reduction in ACE2 and Mas expression respectively, 24 hour post tMCAO vs sham (RQ+RQmax: ACE2: sham 1.0±0.2; 24 hour post tMCAO 0.1±0.01, p<0.01, Mas: sham 1.0±0.2; 24 hour post tMCAO 0.09±0.03 p<0.01). However, in the same tissue, AGTR2 showed a 4-fold increase in expression after 35 min occlusion vs sham (RQ+RQmax: sham 1.0±0.3; 35 min MCAO 4.2±0.2, p<0.05). Additionally, in the subcortical remainder tissue, ACE2 and AGTR2 expression decreased by 2.5- and 5-fold respectively 24 hour post tMCAO (RQ+RQmax: ACE2: sham 1.0±0.1; 24 hour post tMCAO 0.4±0.1, p<0.05, AGTR2: sham 1.0±0.4; 24 hour post tMCAO 0.2±0.1 p<0.05).

These results demonstrate altered counter regulatory RAS gene expression in the ipsilateral hemisphere in the 24 hours following tMCAO in SHRSP. Additional experiments have demonstrated successful transduction of a control reporter gene-expressing, adeno-associated virus serotype 9 (AAV9) expressing enhanced green fluorescent protein (eGFP) (AAV9-eGFP) in the SHRSP brain via stereotactic delivery after both 4 and 7 days. Future studies will assess the therapeutic potential of Ang-(1–9) in tMCAO induced experimental stroke in SHRSP by delivering Ang-(1–9) via stereotactic delivery of an AAV9 vector.