**Protection in IRAP deficient mice differs between photothrombotic and MCAO induced stroke.**

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**Introduction.** Ischemic strokeis a major cause ofdeath and disability. The only pharmacological treatment is the clot buster, recombinant tissue plasminogen activator, which <10% of Australian patients are eligible to receive1. Insulin-regulated aminopeptidase (IRAP) is a potential target for treatment, with IRAP deletion and IRAP inhibition protecting against damage induced by middle cerebral artery occlusion (MCAo) in mice2 and spontaneously hypertensive rats3 respectively. These benefits are yet to be tested in females or in models of cerebral microvascular occlusion.

**Aims**. To investigate the effect of IRAP gene deletion on photothrombotic stroke outcomes in male and female mice.

**Methods**. Photothrombotic stroke was induced in IRAP wild type (WT) and knock out (KO) male and female mice (n= 10/group, aged 6-8 months). Motor and sensory function were assessed at baseline and days 1 and 3 following surgery using the hanging wire and adhesive removal tests. At 3 days post-surgery, mice were culled, and brains were taken for analysis of infarct volume and expression of IRAP, activated astrocytes, and apoptosis.

**Results.** Photothrombotic stroke induced significant infarct in the cortex, impaired function, and increased levels of neuroinflammation and apoptosis. Male mice had significantly larger infarcts (WT:22.90 ±2.19 mm3, KO: 23.97 ± 2.90 mm3) than female mice (WT: 16.7 ±1.82 mm3, KO: 18.53 ± 2.48 mm3). IRAP deletion protected against weight loss in male mice; however, for all other outcomes, there was no genotype. Interestingly in the peri-infarct region of WT female mice had higher IRAP expression than male mice (9.11±1.07% vs 4.28 ± 0.58%)

**Discussion.** IRAP gene deletion did not protect against photothrombotic stroke. This contrasts with previous protection against MCAO-induced ischemic damage with IRAP gene deletion and IRAP inhibition, potentially due to lack a lack of penumbral region and contralateral blood flow in photothrombotic stroke. This suggests that part of the protection of IRAP gene deletion/inhibition may result from partial restoration of cerebral blood supply to the ischemic region.

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