Final Report

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Title of Project: **PP2A and tau – novel treatment targets in ischemic stroke**

Summary:
Research
Stroke is a leading cause of death and disability worldwide. Ischemic stroke accounts for more than 85% of the stroke cases in people >50 years old. Stroke is characterised as a focal neurological deficit that results from a disruption of blood flow and subsequent neuronal death in that area of the brain. Current acute stroke treatment is focused on interventions to prevent mortality, minimise acute brain damage and /or resultant neurological disability.

Ischemic stroke also triggers secondary neurodegenerative injury pathways in the brain resulting in debilitating comorbidities including chronic fatigue, spasticity, mood disturbances, cognitive decline and post-stroke-epilepsy. Unfortunately, current treatments are not able to prevent these debilitating comorbidities. To date, the pathophysiological mechanisms that underlie these long-term neurodegenerative consequences remain unknown, however they hold promise as potential targets for therapeutic intervention to improve the long-term health outcomes for individuals following stroke.

Considering that the prevalence and enormous socioeconomic burden of these chronic consequences is huge, it is imperative that experimental research studies are performed as the first step to identify the underlying mechanisms, as well as develop targeted therapeutic interventions, followed by proof of concept and translational studies.

The microtubule associated protein tau is key to microtubule stability and axonal transport within neuronal cells. Hyperphosphorylation of tau (h-tau) causes this protein to dissociate from microtubules creating aggregates of protein, reducing neuronal stability and promoting neurodegeneration. H-tau is observed across a wide range of neurodegenerative diseases including traumatic brain injury, epilepsy, Alzheimer's Disease and other dementias.

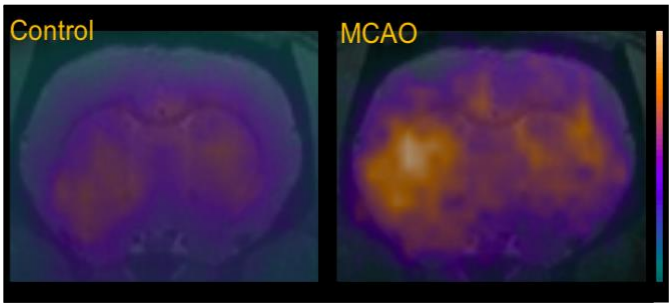
Previous work from our group have shown that sodium selenate is novel and unique form of selenium that activates PP2A/PR55 phosphatase (the main tau phosphatase) decreases h-tau and improves outcomes of traumatic brain injury, dementia and epilepsy.

Given the pathophysiological overlap between these brain conditions and ischemic stroke, we wondered whether tau may also be a central mediator of the long-term neurodegenerative consequences of ischemic stroke.

Outcome

The Brain Foundation research gift have allowed us to investigate tau as potential biomarker and treatment target to improve outcomes after ischemic stroke.

We conducted positron emission tomography (PET) imaging using a world-first, novel Tau tracer to examine the expression of the Tau protein in a rat model of stroke. We found that tau is increased in brain areas known as the striatum and adjacent cortical regions, as early as 1 day after ischemic stroke. This work provides important proof of concept for the utility of this tracer to study the role of Tau in stroke. Similarly, we showed that tau and h-tau protein expression is increased, PP2A expression is decreased in the same brain regions and in peripheral blood. Moreover, tau-PET and tau protein changes correlate with motor problems that present after ischemic stroke.



Tau-PET shows enhanced tau tracer uptake. Tau-PET coronal images of the rat brains. Rat with ischemic stroke (i.e. MCAO) shows showing increased binding (reflecting an increase in tau) in the striatum and cortex 24 hours following stroke in contrast to control rats. Orange indicates areas of increased binding

Our findings show that tau protein and brain imaging biomarkers may be means to identify pathological changes after stroke and to guide patient-specific interventions. Furthermore, our findings highlight tau as a potential treatment target to prevent motor problems that occur after stroke. We will next test the effects of the anti-tau drug, sodium selenate, to investigate if by pharmacologically targeting tau we can prevent stroke-related deficits and improve outcomes after ischemic stroke.

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