REACTIVE GLIOSIS IN THE INJURED BRAIN:
The effect of cell communication and Nrf2-mediated cellular defence

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ABSTRACT

Stroke and other brain injuries trigger an extensive glial cell response referred to as reactive gliosis. Reactive gliosis is characterized by hypertrophic and proliferating astrocytes, proliferating microglia and NG2-positive cells, which eventually form a bordering glial scar around the damaged area. Although reactive gliosis may protect the injured brain initially, the resulting glial scar inhibits neuronal regeneration. This thesis focuses on the role of intercellular communication and endogenous oxidative defence systems on reactive gliosis after injury.

Neural cells frequently utilize gap junction channels to transport molecules between cells. We hypothesised that blocking gap junction communication would limit reactive gliosis. Two different gap junction channel blockers, octanol and carbenoxolone, were given to rats 30 min before a minor traumatic brain injury. Two days after injury, octanol decreased the extent of reactive astrocytes and NG2-positive cells, and reduced the number of reactive microglia around the wound. Carbonoxolone did not affect reactive astrocytes, but both octanol and carbenoxolone significantly decreased cell proliferation. Thus, blocking gap junction communication may attenuate the progression of reactive gliosis.

Astrocytes play an essential role in antioxidant defence, much of which is regulated by the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Nrf2 is activated by xenobiotics like sulforaphane which provides long-term protection against radical damage, even though sulforaphane is cleared from the body within a few hours. We hypothesized that this brief sulforaphane stimulation would be sufficient to induce prolonged Nrf2-induced gene expression. In primary rat astrocyte cultures, brief exposure to sulforaphane increased Nrf2-dependent gene expression; mRNA and protein levels were elevated for up to 24 h and 48 h respectively. Moreover Nrf2-dependent mRNA and proteins accumulated after repeated exposure and sulforaphane-stimulated astrocytes were more resistant to oxidative damage. Thus, stimulation of the Nrf2 pathway with sulforaphane results in prolonged elevation of endogenous antioxidants.

We further hypothesised that sulforaphane-induced Nrf2 stimulation would modify stroke outcome when given after permanent focal ischaemia. Sulforaphane (a single dose or repeated dose starting 15 min after injury) did not significantly affect motor-function, infarct volume, proliferation, or glial cell activation 1 and 3 days after photothrombosis in mice. Thus, sulforaphane does not provide neuroprotection in the photothrombotic stroke model in mice when given 15 min after stroke onset.

In summary, this thesis describes the kinetics of Nrf2-mediated gene expression in cultured astrocytes, and the role of intercellular communication and Nrf2 activation on aspects of reactive gliosis after brain injury.

Keywords: astrocyte, gap junction, Hmox1, microglia, Nrf2, Nqo1, oxidative stress, reactive gliosis
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I. Trauma-induced reactive gliosis is reduced after treatment with octanol and carbenoxolone
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II. Repeated transient sulforaphane stimulation in astrocytes leads to prolonged Nrf2-mediated gene expression and protection from superoxide-induced damage.
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III. The effect of sulforaphane on infarct size, glial activation, cell proliferation and functional outcome following photothrombotic stroke in mice.
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