

Control of neuroprotection through NMDA receptor-dependent regulation of antioxidant status

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Title of project or programme

Control of neuroprotection through NMDA receptor-dependent regulation of antioxidant status

Principal Investigators of project/programme grant

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- United Kingdom

Source of funding information

Medical Research Council

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2211558.60

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Total duration of award in months

60

The project/programme is most relevant to

- Neurodegenerative disease in general

Keywords

Research abstract in English

Neuronal death is implicit in all neurodegenerative conditions. Activation of the NMDA subtype of glutamate receptor (NMDAR) regulates calcium-dependent survival and death pathways through a 'bell-shaped' dose-response curve: modest activity is neuroprotective, but too much and too little NMDAR activity is harmful. Published and preliminary work show that oxidative stress contributes to neuronal death induced by both NMDAR hyper- and hypo-activity and that conversely, modest synaptic NMDAR activity boosts antioxidant defenses.

We will investigate the regulation of intrinsic neuronal antioxidant defenses by protective NMDAR signaling and determine how boosting defenses can prevent death due to NMDAR hypo- and hyper-activity. Studies will involve mechanistic investigation using primary neurons, and testing hypotheses in mouse models of NMDAR hypo- and hyperactivity-induced damage. To translate our neuroprotection studies into human neurons we will exploit recent advances to study neurons derived from human embryonic stem cells. Aims:

1. Determine novel activity-dependent mechanisms that boost intrinsic antioxidant defenses in neurons. We will investigate events that trigger enhancement of the glutathione antioxidant system, and also disinhibition of Nrf2, a transcription factor which induces antioxidant genes. Characterisation of endogenous pathways that control antioxidant defenses may help understand neurological disorders associated with oxidative damage, and reveal new therapeutic targets. Further, by elucidating the antioxidant effects of synaptic NMDAR activity we can predict the potentially harmful consequences of NMDAR blockade.

2. Define antioxidant strategies for protecting neurons from damage due to too much or too little NMDAR activity.

Using genetic approaches and recently-developed pharmacological activators of neuronal Nrf2, we will investigate how boosting antioxidant defenses reduces neurodegeneration due to NMDAR hypo- or hyper-activity. In treating disorders associated with excitotoxicity, this approach may be better-tolerated than NMDAR blockade, and be effective in injury models where NMDAR pro-death and pro-survival signals operate at different times post-trauma.

3. Determine the differences between activity-regulated genes in mouse vs. human neurons, and the extent to which antioxidant pathways can be manipulated to block excitotoxic/oxidative death.

Defining neuroprotective/destructive pathways in rodent systems will generate hypotheses applicable to human neurons. However, species-specific differences may exist and cloud their direct translation. We will define the similarities and interspecies differences in activity-regulated gene expression and neuroprotection between human and mouse neurons, providing a bridge for translating mouse results into man. We will also investigate the capacity for human neuronal antioxidant defenses to be manipulated, potentially assisting development of neuroprotective drugs, or neuroprotective strategies in future stem cell-based therapies.

Lay Summary