The NMDA receptor glycine site mediates xenon neuroprotection against traumatic brain injury in vitro

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Introduction

Traumatic brain injury (TBI) is the most common cause of death and disability in people under 45 in developed countries. TBI consists of two distinct injury components, primary injury that occurs at the time of impact (and is irreversible) and secondary injury that develops in the hours and days after impact, which is potentially preventable.

Xenon has been shown to be neuroprotective against ischemic injury. This effect is mediated by competitive inhibition at the glycine binding site of NMDA receptors. The current study used an in vitro model of TBI to investigate the mechanism of xenon neuroprotection following traumatic injury. In addition, the relative neuronal injury effects of the other noble gases; argon, neon, and krypton were investigated in this model.

Methods

Modelling traumatic brain injury in vitro using a custom built weight drop device

Organotypic hippocampal slice cultures

TBI impact device

Noble gas Application

Results; xenon and argon provide neuroprotection after TBI

A) Helium has no effect on traumatic injury

B) Effect of noble gases on traumatic injury

C) Xenon prevents development of secondary injury

D) Argon attenuates development of secondary injury

Development of the in vitro TBI

Conclusions

- Investigations into the neuroprotective properties of the noble gases helium, neon, argon, krypton and xenon found that xenon and argon both provided potent neuroprotection to following TBI whereas helium, neon and krypton were devoid of biologic effects.

- It was found that exposure to 50% xenon prevents the development of secondary injury in the slices following traumatic injury for 48 hours, after this point it is strongly attenuated. Argon attenuates the development of secondary injury but to not the same extent as xenon.

- Investigation into the mechanism of this neuroprotection by xenon identified competitive inhibition at the glycine binding site of NMDA receptors as a key mechanism. The same was not true for argon, which appears to provide neuroprotection by a mechanism distinct to the NMDA-receptor glycine site.

- Further work will involve elucidating the mechanism by which argon provides neuroprotection in this model, and also testing the neuroprotective properties of xenon and argon in vivo models of traumatic brain injury.