N-acetyl cysteine enhances motor neuron survival in a rat model of neonatal nerve injury

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1 Introduction

In obstetrical brachial plexus injury (OBPI), the nerves of the brachial plexus are damaged during delivery. An overlooked component of disability following OBPI may be the retrograde death of motor and sensory neurons crucial for repair and regeneration. Animal studies have shown that up to 70% of neurons may die following neonatal proximal nerve injury. Rescuing motor and sensory neurons from retrograde neuronal death with neuroprotective pharmaceuticals may improve the regenerative capacity of the peripheral nervous system and improve axon regrowth following surgical reconstruction.

N-acetyl cysteine (NAC) and acetyl-L-carnitine (ALC) have demonstrated neuroprotective properties in rat models of adult peripheral nerve injury, preventing retrograde motor and sensory neuron death. Both drugs are approved for clinical use with a long history of safety. NAC is currently used in pediatric patients to treat acetaminophen toxicity and respiratory distress following premature birth. NAC and ALC may also prevent retrograde neuronal death following neonatal peripheral nerve injury.

2 Objectives

1. Examine the extent of motor and sensory neuron death in a rat model of neonatal crush and transection injury.
2. Investigate whether treatment with NAC or ALC following neonatal nerve injury reduces retrograde motor or sensory neuron death.

3 Methods

1. Surgeries and time points
Neonatal Lewis rats were used and a blinded observer completed all analyses. Animals were injured 3 days after birth with either a crush or transection injury of the sciatic nerve. Regeneration was prevented following transection injury by ligation and resection of the distal nerve stump. Spinal cords were harvested for neuronal counts.

Treatment protocol
Following crush or transection injury, animals were treated with intraperitoneal injections twice daily for four weeks with NAC (750mg/kg) or ALC (300mg/kg).

4 Results

- Neuron survival and regeneration

Figure 1. Four weeks after injury, fluorogold dye was applied to the sciatic nerve 5mm proximal to the site of injury to backlabel surviving neurons. A nerve sample 5mm distal was harvested to assess axon regeneration with histomorphometry.

Figure 2. Both crush and transection injury result in significant motor and sensory neuron death. Following a neonatal sciatic nerve injury at post-natal day 3 (P3), both crush and transection injury result in significant neuronal death. Transection injury prevents neuronal regrowth, and results in significantly more motor and sensory neuron death (p < 0.01).

- Sensory neuron survival

NAC and ALC treatment did not significantly improve sensory neuron survival following neonatal sciatic crush or transection injury.

5 Conclusions

- NAC significantly improved motoneuron survival following crush injury and is promising as a treatment to improve motoneuron survival following OBPI.
- Transection injury results in greater motor and sensory neuron death than crush injury, and while there was a trend towards greater neuron survival in animals treated with NAC this difference was not statistically significant.
- Neither NAC or ALC improved sensory neuron survival following neonatal nerve injury.

References

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