Regeneration and repair of the central nervous system

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217 Introduction to Human Neuroanatomy

The problem of CNS regeneration

• Spinal cord damage is a mortal condition (10-15 per million per year UK)
• Damage caused by stroke is permanent

Mortality associated with spinal injury has only recently fallen

• 2500 BC “an ailment not to be treated”
• WW1 only 10% survived a year- 1% more than 20 years
• 1960s 35% died
• 1983 7.87x normal mortality. 20 yr old can expect to live 30 years
What factors influence whether a cell regenerates?

- **External factors**
  - NGF, BDNF
- **Substrate factors**
  - laminin, In-1
- **Internal messengers**
  - kinases, proteases
- **Internal genetic state**
- **Environmental factors**
  - macrophages, hydrogels, glia
  - receptors

How can we tackle this problem?

- **Change the environment**
  - peripheral nerve graft
  - ensheathing glia
  - hydrogels
  - fetal tissue
  - proteases
  - blood substitutes
- **BUT only a few fibres regenerate**

- **Provide Growth Factors?**
  - NGF only works on peripheral nerves
  - BDNF?
  - Genetically engineered cells?

- **Improve the substrate?**
  - laminin
  - osmotic pumps
  - artificial substrates
Change the cell?

- Engineer more receptors
- Up-regulate internal messengers

- use different cells?
  - Fetal cells
  - Stem cells

Will mammalian spinal cords make the right connections even if we do get regeneration?

- No retinotopy in lizard regeneration?
- No retinotopy in regeneration along sciatic nerve?
- Retinal transplants do not form a retinotopic projection?

What can and can’t regenerate?

- Adult fish can regenerate everything!
- Larval amphibia too, adults slowly?
- Reptiles slowly and without specificity
- Mammalian PNS
- Mammalian olfactory tract
- Mammalian nerves can only sprout abortively
Are fish different?
• Why study preamniotes?
• Can differences give clues?
• Can we do novel experiments?
• How do their spinal cords regenerate?

Why study “Lower Vertebrates”?
• They regenerate quickly and are simple to maintain.
• Embryos are readily available
• They have many tracts in common with mammals
• They show many of the growth factors, ECM components and even “collapsins” found in mammals

Two approaches have been used
• 1. Assuming similar processes act in all species use them as a model system for testing the ability of fibres to regenerate under experimental conditions
• 2. To deliberately look for clues in the differences between the regenerating and non-regenerating species
How different are they?

- They grow throughout life
- Level of myelin inhibitory factor low in adult animals? (or localised?)
- Glial response to injury different?
- Extracellular environment more conducive to regeneration?

Are their neurons different?

- Added throughout life
- Less need for growth factors?
- Less cell death after axotomy
- Do NOT all regenerate

Inhibiting factors ARE present in fish CNS?

Regenerating fibres prefer the PNS?
(Bentley and Zottoli 1993)
Fish optic nerve not permissive for adult nerves (Sivron et al 1994)
What does a regenerated spinal cord look like?

- Which fibres regenerate?
- Do they grow back to their normal tracts?
- Do they find the correct targets?
- Is this process an extension of growth?
The problem of order

Spinal cord in culture

[Images of spinal cord in culture]
Direct cell heaters

- Work well in closed systems
- Ideal for imaging
  - as they allow DIC and Fluorescence concurrently
  - Small amounts of media
  - Allow long term culture

Only heat cells

Closed stage system