Nerve growth, injury and repair: taking experimental strategies to the clinic

Will it ever function normally again?

1984
Chain-saw injury
Arm replantation failed; arm amputated in 1989
1998
Underwent arm transplantation

PNI – nerve will regenerate

May get neuropathic pain

Sensory Root injury – nerve does not regenerate

Spontaneous or central pain

The problems

- Regeneration over long distances
- Rapid cortical plasticity
- Target organ atrophy, degeneration
- Regeneration errors
Nerve regeneration

A. Distal to injury myelin & axon degenerate (Wallerian Degeneration)
B. Monocytes invade injury site & become macrophages that eat epilsoids
C. Distal Schwann cells remain & become active to stimulate regeneration via macrophages
D. Proximal nerve sprout (SPR) & growth cones (GC) migrate to Schwann cells (SCHW) formed Bands of Bungur.
E. SCHW cells & mast cells (MC) produce & secrete NTFs to attract sprout which grows along them (+ CAMs e.g. NCAM, Laminin, L1)
F. SCHW cells re-myelinate axon

Surgical nerve repair strategies

Nerve anastomosis: Used when inter-lesion distance is short.
- Advantage: uses only damaged nerve.
- Disadvantage: often get peripheral regeneration errors
- Must use non irrtivative sutures & no tension on nerve at suture line

Autologous Nerve graft: Gold standard
1. Used when inter-lesion distance is large (5-10mm).
2. Size is important – thickness related to neurovascularisation
3. Allergists require immuno-suppression (FK506 – tacrolimus)
- Advantage:
  1. can bridge quite large gaps.
  2. Fresh supply of SCHW cells
  3. Can use pre-degenerated grafts to improve axon outgrowth
- Disadvantages:
  1. damages intact part of PNS
  2. Causes CNS changes - neuropathic pain?
  3. Nerve may not regenerate fully

Artificial grafts e.g. Collagen or silicon tubes/ fibronectin mats. For shot gaps <5mm
- Advantages:
  1. doesn't use nervous tissue
  2. can induce growth promoting substances
  3. Allows NTFs & fibrin clots to accumulate in tube
  4. Biodegradable
  5. Simple & minimal trauma to nerve
- Disadvantages:
  1. graft doesn't take
  2. adverse immune response
  3. rigid - doesn't allow nerve to grow - may strangle it!

Surgical nerve repair strategies

PNI

- We know a lot about the molecular & cellular basis of peripheral regeneration but little of it has been translated into the clinic
- NTFs – problems with route of administration, dose, side effects
  - Immuno-supression
  - Magnetic stimulation
  - Hyperbaric oxygen

Longer term problems or delayed repair problems

A. Poor functional recovery after peripheral nerve injury is due to:
  1. Progressive loss of the skills of maintenance in mature axons growth
  2. Chronically devascularized Schwann cells fail to produce a suitable growth environment
  3. Nerve regeneration of damaged nerves

B. Strategies to improve functional/recovery after peripherial nerve injury include:
  1. Protocols to maximise use of autogenous nerve such as delayed nerve free grafting
  2. Use TGF b nerve growth promoting stimuli of autologous denervated nerve autografts
  3. Use electrical stimulation to increase the rate of regeneration across the graft gap
Sensory Recovery

Tinel's sign:
- Wrist by 100dpo (200mm)
- Fingertips by 1yr (360mm)
2 yrs - discriminate pain, hot/cold, sharp blunt in hand & fingers.

Reversal of phantom limb sensation

Motor recovery
- Grip and pinch movement - 3 months
- Intrinsic hand muscles - 12 months
- 1st interosseus muscle - 16 months

Why don’t sensory neurons regenerate into the CNS?

Is it because they can’t or won’t cross the dorsal root entry zone?

Repair strategies for spinal root injury

Surgical
- Nerve transfer
- Nerve graft
- Root reimplantation

Experimental
- Neurotrophic factors
- OECs
- Irradiation
- Antibody treatment
  - Anti-Nogo
  - Anti-TGFβ
- Chondroitinase

Spinal root injury

Excruciating pain - immediate in onset
- Constant pain “crushing”, “burning”, “electric shock-like pains” (up to 40/hr)
- Pain α & roots damaged

Root reimplantation (CNS to PNS growth)
Clinical outcome: the first patient

- C6-T1 total avulsion
- Implant C6, graft to C7 1 month later
- EMG activity in biceps first seen at 9 months
- Functional movement seen at 15 months
- Some pain diminution with motor recovery
- Poor prognosis with delay of operation
- Non-selective innervation of muscles
- No innervation of hand muscles
- No sensory recovery seen

DREZ BORDER CONTROL

- Implant
- Vehicle
- Immediate
- Delay

Sensory regeneration: summary

- Dorsal roots fail to regenerate beyond DREZ after avulsion injury.
- Priming the avulsed nerve & bypassing the DREZ provides localised growth into spinal cord
- Neurotrophins enhance growth of regenerating dorsal root axons into CNS during a critical period of time
- DHNS will grow into the PNS via an implanted root that bypasses the DREZ.

2. Building bridges: OEC’s
OECs form a ladder-like bridge at the DREZ to allow axons to cross and re-enter the cord.

~10% of DRGs enter the DC 2w after rhizotomy.

(50% OEC 50% olfactory nerve fibroblasts)

Summary

- Dorsal roots fail to regenerate beyond DREZ after avulsion injury.
- Priming the avulsed nerve & bypassing the DREZ provides localised growth into spinal cord.
- Neurotrophins enhance growth of regenerating dorsal root axons into CNS only during a critical period of time.
- DHNS will grow into the PNS via an implanted root that bypasses the DREZ.
- Combinations are the way to go.