Control of an injured spinal cord: Perspectives after regeneration

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Overview

Neuromorphic Engineering

Lamprey experiments

Development

CPG chip and human spinal cord prosthetic devices
Lamprey: Model for Spinal Cord Injury

Functional regeneration: Restoration of normal behavior

After injury

Whole animal swimming

Fictive swimming - “swimming” by isolated spinal cord
Whole animal swimming: Functional and Dysfunctional

(a) functional  (b, c, d) dysfunctional
Functional versus Dysfunctional Regeneration

• Functional regeneration is most common in animals recovered at room temperature.

• Dysfunctional regeneration is most common in animals recovered at the normal cold room temperature.

(reason for this difference is unknown.)
What’s required for locomotion?

Spinal cord functions

• Functional Central Pattern Generator (CPG) for locomotion
• Proper coordination across the lesion site
• Proper sensorimotor integration with mechanics of the body

Brain functions

• Effective initiation of locomotion
• Appropriate control of swim speed and force
What’s required for locomotion after spinal cord injury?

- **Initiation and control**
  - *Across lesion*

- **Coordination of segments**
  - *Limbs, trunk and breathing*

From Kandel, Schwartz & Jessel
What’s required for locomotion?

CPG Functions

• Rhythmicity - segments must all burst regularly

• Intersegmental coupling - must maintain all the segments at a common frequency
Segmental bursting frequencies are intrinsically different

Fictive swimming - normal unlesioned spinal cords

Full coupling > one frequency

Weak coupling > two frequencies
What is known about CPG?

Theory: If frequency difference is too great, then there must be strong coupling to hold the segments together.

Therefore:

If the frequency differences of the segments are too great

or

If the coupling is too weak then the segments will burst at different frequencies.
Control of segmental frequency

• Neuromodulators can and do alter the frequencies of segmental oscillators.

• Notable is serotonin. Serotonin in lamprey is both intrinsic to the spinal cord and descends from the brainstem.
Seroitonin Immunoreactivity: Normal distribution

Broadly distributed serotonin immunoreactivity along the length of the spinal cord
Serotonin immunoreactivity after injury

Segment immediately below lesion site: some restoration after 6 months
Serootonin immunoreactivity after injury

Distal to lesion site - no recovery even after 1 year
Serotonin after injury

- Rostral segments: serotonin distribution is normal
- Caudal segments: serotonin distribution is abnormal
  - Descending fibers are gone
  - Local fibers are preserved
Distribution of modulator after spinal injury

• THEREFORE: neuromodulatory transmitter is maldistributed after spinal injury.

• THEREFORE: control of segmental frequencies will be disturbed after spinal injury.
Intersegmental coordination

*Remember: If the frequency differences are too great,
*then the coupling must be strong to maintain proper coordination.

• What is known about normal system?

• What is known about regenerated system?
Normal intersegmental Coupling: Distributed and Strong
Coordinating system in spinal injured animals

• Animals vary considerably in their regeneration

• In regenerated spinal cords
  - Functional animals have stronger coupling
  - Dysfunctional animals have weak coupling
Intersegmental coordination and functional status

- Cross correlation of bursting in isolated spinal cord
- NRCCH: normalized cross correlation - max = 1.0
Origin of dysfunctional behavior

• Improper serotonin regeneration
  >> improper frequency regulation in caudal versus rostral segments
  >> exaggerated frequency differences across lesion site

• Weakened intersegmental coordinating system is insufficient to maintain proper segmental relationships with the extreme frequency differences

• This could account for some of the problems of the dysfunctional animals
Spinal cord regeneration in mammalian species

- Short distance regeneration now known for some fibers descending from the brain
- Long distance regeneration now known for serotonergic and dopaminergic neurons
- Nothing is known about the regeneration of propriospinal neurons - the intersegmental coordinating neurons.
Need another solution!

• Even the primitive relatively simple lamprey that regenerates spontaneously has problems.

• What can we expect in the more complex less robust spinal cords of humans?

• Full behavioral recovery in humans is VERY far away.
Neuroprosthetic device?

• Why do we need one?
  - *Because regeneration while coming is not coming rapidly.*
  - *Many young men want to walk – NOW*

• Lamprey experiments suggest significant problems may arise with regeneration.
  - *Therefore, regeneration may be difficult to make adaptive in the near future.*