Lecture 31: Regeneration and repair

Learning objectives

- Define the types of regeneration - axonogenesis, neurogenesis and brain plasticity
- Differentiate between peripheral nerve regeneration and central nerve regeneration
- Understand the different routes to neural regeneration - dedifferentiation, transdifferentiation and reprogramming
- Define the types of neural stem cells - multipotent and pluripotent (different types)
- Understand transplantation therapies for Parkinson's disease

Regeneration

- Different organisms have different capacities to regenerate
- Lower the organism is in the evolutionary chain, the greater its capacity to regenerate - eg. worms can regenerate whole body
- Some species can regenerate limbs - eg. reptiles can regrow a structure/part of their body or an internal organ, like a tail or a portion of the liver
- Tissue can regenerate is many organisms - eg. humans can regenerate their skin
- Cells can regenerate in virtually all organisms

Nerve damage and regeneration

- Restoring function after nerve damage can occur by:

1. Axonogenesis (mainly for peripheral nerves)
    - Axon regrowth from pre-existing, injured neurons through the injury site to re-establish connections
2. Brain plasticity (rewiring)
    - New connections are formed to replace ones that are damaged to re-establish the function of the neural pathway
3. Neurogenesis
    - The production of new neuronal cells from precursor populations that subsequently produce neurites to make connections with host cells
    - Brain can, to an extent, generate new neurons within the hippocampus (vital in learning and memory)

- Regeneration of CNS require progenitor cells to migrate, re-establish cell contacts, self-renew and undergo specification and spatial patterning to form neurons and glia that will integrate into host tissue to replace the damaged structure
- To what extent will this be possible in mammalian brains?
    - Mammalian CNS axons tend to not reinnervate because of factors secreted by oligodendroglia cells that inhibit growth

Axonogenesis

- For example, axons that have been severed at the optic nerve
- RGCs would usually send light information down the optic nerve, cross over at the optic chiasm, and then synapse onto the LGN (lateral geniculate nucleus), superior colliculus and visual cortex
- But if the optic nerve is severed, the capacity to re-establish the axonal connection is very limited
- The RGC will die because they have no connection to the visual cortex and hence the axons fails to regenerate
- Scar tissue is also formed when the optic nerve is cut which creates a physical barrier and thereby prevents axonogenesis

- Even if the optic nerve does not induce the RGCs to die off, the axon still has limited capacity to re-establish contact with the distal end of the axon
- This is because it relies on the growth cones at the end of the axon:
    - As the axon migrates to its final destination (during development), there is a growth cone at the end of the axon
    - Growth cone - group of cells that respond to a chemical stimulus that's at the final destination - for axon guidance
    - So if the axon is severed, the growth cones may not be enough, they may be misrouted, or they may grow back to the opposite optic nerve
- Restoration of function is still limited even if axon synapsed with LGN :
    - May synapse on wrong target cell
    - May synapse in the wrong area or layer in the brain
    - May have the wrong synaptic strength
- Even if the axon makes it to the visual cortex
    - Regenerated connections are too few or too weak to drive a response
    - Plasticity is inadequate

Brain plasticity (rewiring)

- For example, the brain of a ferret
- Ferret brain is very immature at birth and is still establishing its neural connections
- The more immature the brain, the better capacity it has to establish connections
- Researchers looked at the visual and auditory pathways in the ferrets
- The rewiring took place on its own

Neurogenesis

- Was initially thought to occur only during embryonic stages
- In the 1990s, adult neurogenesis was clearly demonstrated in the SVZ and SGZ
- Stem cells called *neuroepithelial cells* are found within the brain at the ventricular zone (SVZ) in the fetal brain
- They undergo massive proliferation to become intermediate progenitor cells and then migrate (during development)

Adult neurogenesis

- Most active area of neurogenesis is the hippocampus
- Hippocampus - region deep within the brain involved in learning and memory
- Thousands of new cells are produced in the hippocampus everyday, although many die within weeks of their birth
- Some of these new neurons survive and integrate themselves into the working brain
- The more we learn, the more the new neurons survive in the hippocampus
- Cells that are born before a learning experience are more likely to survive to become neurons, but only if the person actually learns
- Extent and purpose of neurogenesis in adults is unclear
- Increased neurogenesis in hippocampus of adult mice in an enriched environment and following exercise

Classification of neural stem cells

- During embryonic brain development, the stem cells in the brain are the ones that originated from the neuroepithelial cells
- As brain development progresses, progenitor cells will originate (from radial glial cells)

- But in adult neurogenesis, B cells will give rise to neurons, oligodendrocytes and astrocytes (ie. B cells can act as stem cells)

Stem cell hierarchy

- **Totipotent** stem cells:
    - Cells able to give rise to all embryonic somatic cells and germ cells
    - They can build a whole animal
    - The zygote and a few early cells of the morula are totipotent
    - Not really used in stem cell therapy
- **Pluripotent** stem cells:
    - Originate from the blastocyst (after the fertilised egg has undergone cell division to a limited extent) and the blastocyst is a descendent of the zygote (ie. totipotent stem cells)
    - These cells are descendants of totipotent stem cells and can give rise to cells of the 3 germ layers (endoderm, mesoderm and ectoderm)
- **Multipotent** stem cells:
    - These produce cells of a particular lineage or closely related family
    - They are somewhat committed to their fate, as they have already been established as being either ectoderm, mesoderm or endoderm cells (therefore not very useful for stem cell therapy)
    - Ectoderm = the NS; skin
    - Mesoderm = musculoskeletal, vascular and lymphatic systems; kidney and gonads
    - Endoderm = gastrointestinal tract; glans; lungs; liver; pancreas

Three routes to regeneration

1. **Dedifferentiation**
    - When a cell is committed to its fate, it will not have the capacity to further proliferate/regenerate
    - But we can trigger dedifferentiation (ie reverse back to the precursor progenitor cell)
    - After reverting back to its origin, this immature origin cells will then have the capacity to proliferate so it can differentiate again and replace damaged cells

2. **Transdifferentiation**
    - Similar to dedifferentiation in that the cell is committed to its fate
    - But the cell can be encouraged to transdifferentiate to a close family member cell - will transdifferentiate to another type of committed cell provided that this cell's origin is the same as its own

3. **Reprogramming**
    - Can cause the cell to reprogram - cells committed to their fate can be reprogrammed to become embryonic stem cells by injecting transcriptional factors that can regulate the transcription of certain genes
    - The embryonic stem cell that it will become is the pluripotent stem cell

Sources of pluripotent stem cells

- Embryonic Stem (ES) cells from the inner cell mass of blastocyst
- Embryonic Germ (EG) cells from primordial germ cells
- Germ-line derived Pluripotent Stem (gPS) cell from spermatogonial stem cells of neonatal and adult testes

- Three major routes of somatic cell reprogramming to pluripotency:
    1. *Fusion of somatic cells and ES cells* - this generates a hybrid cell that has the capacity to become stem cells

2. *Nuclear transfer of ES cells* - transfer the nucleus from an embryonic cell to a recipient, adult cell
3. *Induced pluripotent stem cells* - any adult, somatic cell can be injected with transcriptional factors causing the cell to assume a pluripotent status

Parkinson's disease: Good candidate for stem cell therapy

- Neurodegenerative disease - late onset but progressive
- Debilitating disorder with motor disturbances including tremor, rigidity, bradykinesia and postural instability
- Degeneration of the nigrostriatal dopaminergic pathway
- No cure yet - treatment includes dopamine replacement therapy, L-DOPA, dopamine agonists, MAO-B inhibitors

Parkinson's is a good candidate for stem cell therapy because...

- Localised degeneration of a neural pathway
- Ability to generate/harvest large numbers of dopaminergic neurons for transplantation
- Readily detectable improvements in motor symptoms
- Demonstrated to work with transplantation of fetal mesencephalic or adrenal grafts with <u>partial and short-term</u> restoration of motor functions
- Sources of stem cells (for forming DA neurons):
    - *Human fetal neural stem cells* - isolated from ectoderm derived from germinal zone, multipotent but difficult to differentiate into dopaminergic (DA) neurons
    - *Human adult neural stem cells* - unlikely to obtain large numbers for transplantation
    - *Pluripotent embryonic stem cells or induced pluripotent stem cells* - this is the future of stem cell therapy because it can be grown for large scale production

<u>Lecture 32: Learning and memory</u>

Learning objectives

- Understand the definition of memory
- Learn the different stages of memory - acquisition, retention, consolidation and retrieval
- Distinguish between the different forms of memory - declarative vs procedural, and STM vs LTM vs working memory
- Learn the brain structures involved in different forms of memory processing
- Understand the concept of hebbian theory of synaptic plasticity
- Learn the processes involved in long term potentiation and its association with memory
- Understand the association between dendritic spine densities and memory

Learning, memory and intelligence

- Learning is the process by which we acquire knowledge about the world
- Memory is the process by which that knowledge of the world is encoded, stored, and later retrieved
- Intelligence is a very general mental capability that involves the ability to reason, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience
- Measures of human intelligence:
    - General intelligence (cognitive and mental ability) measured by IQ
    - Psychometric tests to measure intelligence cover reasoning, processing speed, executive function, memory and spatial ability
    - Cortical volume (ie. volume of cortex) has been positively correlated with intelligence (especially volume of prefrontal and temporal cortex)

Different types of memory

- Short-term memory (STM):
    - Memories that last for seconds to hours
    - Vulnerable to disruption and readily lost
- Long-term memory (LTM):
    - Converted from STM by consolidation
    - Lasts longer with re-consolidation
    - Can last for years
- Working memory:
    - Temporary form of information storage
    - Limited in capacity and requires rehearsal
    - Retention of a telephone number that has just been given to you by repetition
- Declarative (explicit) memory:
    1. Episodic - autobiographical information with temporal/spatial context
    2. Semantic - memory for facts and events with no associations
- Nondeclarative (implicit) memory:
    1. Procedural - memory for skills and habits (eg. riding a bike, you never forget it)
    2. Classical conditioning - emotional responses (eg. Pavlov's dog)
    3. Non-associative - habituation, sensitisation

The temporal lobe and declarative memory

- The temporal lobe structure include:
    - Hippocampus
    - Subiculum
    - Parahippocampus
    - Rhinal cortical areas
- These structures are responsible for processing declarative (episodic + semantic) memories
- Effects of Temporal Lobectomy study on epileptic subject:
    - Removal of temporal lobes had no effect on perception, intelligence, personality
    - Removal of temporal lobe stopped epileptic seizures
    - Anterograde amnesia (inability to form new memories) so profound that he could not perform basic human activities (and partial retrograde amnesia, memory loss for events before trauma)
    - Subject didn't recognise the scientist that had studied him for nearly 50 years
    - Impaired declarative memory, but spared procedural memory

Striatum and procedural memory

- Procedural memory:
    - Type of LTM of how to perform different actions and skills (eg. tying shoelaces)
    - Forms very early in life as you begin to learn how to walk, talk, eat and play, so ingrained that they are almost automatic
- Striatum is comprised of the caudate nucleus and putamen (part of the basal ganglia)
    - Patients with Parkinson's disease have impaired procedural memory because the striatum is damaged

Hippocampus and spatial memory

- Hippocampus:
    - There are *place cells* in the hippocampus - neurons that becomes active when we enter a particular place in our environment (are involved in long-term potentiation)
    - Ie. place cells that only fire when a person is at a particular location
    - There are also *grid cells* - a place-modulated neuron that form an essential part of the brain's coordinate system for metric navigation
- Spatial memory:
    - Responsible for recording information about one's environment and its spatial orientation
    - Spatial memory is required to navigate around a familiar city (functions like a GPS)

Prefrontal cortex and working memory

- Working memory:
    - Limited capacity system that allows one to temporarily store and process information
    - Temporary store enables one to complete or work on complex tasks while being able to keep information in mind
    - Eg. the ability to work on a complicated mathematical problem utilises ones working memory
- Prefrontal cortex:
    - Highly developed in humans - very large region of the brain in humans
    - Important in problem solving, complex planning and self-awareness
    - Interconnected with medial temporal lobe (which includes the hippocampus)

Different stages of memory formation

1. **Acquisition**
    - Sensory information is perceived and acquired
    - Influenced by attention, motivation, and ability to learn
2. **Retention/Encoding**
    - Crucial first step to creating a new memory
    - The perceived item of interest is converted into a construct that can be stored within the brain
    - Requires consolidation to commit to longer term memory
3. **Consolidation**
    - Stabilisation of memory trace after acquisition
    - Two specific process:
        1. Synaptic consolidation - occurs within the first few hours after learning or encoding
        2. System consolidation - where hippocampus-dependent memories become independent of the hippocampus over a period of weeks to years
    - Utilises a phenomenon called *long-term potentiation* (LTP) which allows a synapse to increase in strength
4. **Retrieval**
    - Subsequent re-accessing of events or information from the past, which have been previously encoded and stored in the brain

Hebbian theory: Memory results from synaptic modification

- *"Neurons that wire together fire together"* and *"Out of sync lose their link"*
- The internal representation of an object consists of all the cortical cells are activated by the external stimulus
- This group of simultaneously active neurons is known as a **cell assembly**
- All these cells are reciprocally interconnected

- Hypothesised that internal representation of stimulus is held within STM as long as activity reverberates through the connection of the cell assembly
- Also hypothesised that if activation of cell assembly persisted long enough, consolidation would occur by a 'growth process' that made these reciprocal connections more effective
- After learning, partial activation of the assembly leads to activation of the entire representation of the stimulus

Neural basis of memory

- Learning and memory occur at synapses and result from modification of synaptic transmission
- Synaptic plasticity (ability of the synapse to change in strength in response to use/disuse) is an important neurochemical foundation of learning and memory
- LTP - increase in synapse strength as a result of use

LTP in the hippocampus

Mechanisms of LTP in CA1:

- Activation of AMPA/Kainate receptors by glutamate causes post-synaptic membrane depolarisation
- Mg^{2+} is dissociated from NMDA channels, facilitations of Ca^{2+} entry
- Activation of protein kinases
- Resulting in post-synaptic protein phosphorylation of AMPA receptors
- Recruitment of AMPA receptors to post-synaptic membrane and upregulation of AMPA receptor function

LTD in the hippocampus

- LTD = patterns of electrical stimulation that can weaken synaptic connections

Mechanisms of long-term depression (LTD) in CA1:

- Facilitation of post-synaptic Ca^{2+} entry through NMDA receptors
- Key difference between LTP and LTD - levels of NMDA receptor activation
- LTD - weak depolarisation of post-synaptic neuron, partial blocking of NMDA channels by Mg^{2+}, and only a weak trickle of Ca^{2+} entry
- Activation of protein phosphatases (instead of kinases), resulting in protein dephosphorylation

Dendritic spines

- Dendritic spines are sources of synaptic contact that can be altered by experience
- Structural plasticity of dendritic spines underlies learning, memory and cognition in the cerebral cortex
- Induction of LTP causes enlargement of spine heads and overall increase in the number of spines
- LTD causes spine heads to shrink and reduces the number of spines

Neurodegenerative diseases

- Life expectancy has increased rapidly over the last century which is why there are more cases of neurodegenerative diseases

- Common feature of neurodegenerative diseases:
    - Delayed onset - age is a major risk factor
    - Selective neuronal vulnerability, despite widespread expression of disease-related proteins during the whole lifetime
    - Abnormal protein processing and aggregation
    - Cellular toxic effects involving both cell autonomous and cell-to-cell interaction mechanism
    - Most neurodegenerative diseases have unknown causes
    - Most common form is Alzheimer's disease (AD)

- Prevalence of dementia:
    - Approx. 269,000 Australian currently have dementia
    - ¼ of these are above the age of 85 years
    - Dementia is the 3rd leading cause of death in Australia
    - Most common condition resulting in dementia is AD
    - There is currently no cure for AD and therefore no cure for dementia