Research Project
By Dr Dhanisha Jhaveri

Dementia Australia™
Research Foundation

Cholinergic regulation of adult hippocampal neurogenesis and cognitive functions

What is the focus of the research?

To investigate the role of a subgroup of cholinergic neurons and assessing the contribution of cholinergic receptors in regulating adult hippocampal neurogenesis and cognitive function.

What is neurogenesis?

The generation of new neurons in the brain.

Neurogenesis slows down as a person ages, but remains an important neuroplasticity mechanism in the adult brain.

The hippocampus plays a crucial role in learning, memory and mood regulation. It is also a key site for neurogenesis throughout adult life. Because this region helps the brain differentiate between memories that are similar, such as where you parked the car today vs. yesterday, it is very important that functional neurogenesis occurs.

Why is it important?

Alzheimer's disease is a neurodegenerative disease that steals memories from people and causes significant heartache for family and friends in the process. It can also affect behaviour, language, judgement, mood, emotion, attention and thinking. There is no cure for this insidious disease and, unfortunately, identifying effective treatments has also proven challenging.

Researchers are now refocusing their efforts and looking to gain a better understanding of the cellular mechanisms happening at the earliest moment of Alzheimer's disease commencement. This information is critical, because it will help establish a potential treatment target. Early in the development of Alzheimer's disease, there is progressive loss in the brain's capacity to generate new neurons in the hippocampus – the region important for learning and memory. There is also degeneration of cells that produce a neurochemical called acetylcholine that is vital for cognitive functions. Dr Jhaveri will investigate how these two cellular processes are linked, how cognitive functions are altered as a result, and whether they can be reversed by stimulating a specific receptor that can boost the production of new neurons.

How will this happen?

Stage 1: study whether the selective lesion of medial septum (MS) cholinergic neurons in mice alters the maturation and integration of new neurons in the hippocampus.

Stage 2: perform a cognitive test on mice to determine the effects of MS cholinergic lesion on neurogenesis-dependent cognitive function.

Stage 3: test if stimulation of M4 using select drugs restores adult neurogenesis after MS cholinergic lesion.

Stage 4: treat mice models to stimulate M4. Test for cognitive deficits or improvements.

Stage 5: examine whether cognitive improvements that occur following stimulation of M4 receptors are mediated via enhanced production and/or function of new neurons.

What are MS Cholinergic Neurons?

Cholinergic neurons are nerve cells that use the neurotransmitter acetylcholine to send messages to parts of the brain, including the hippocampus.

In a healthy brain, these neurons play a vital role in cognition and perception. However, with age in certain neurodegenerative conditions, including Alzheimer's disease, these neurons die, leading to decreases in learning and memory functions.

MS stands for medial septum, hence MS cholinergic neurons live in the medial septum. Their projections to the hippocampus are important for the appropriate functioning of the hippocampal neurons, keeping cognitive processes strong. But when they degenerate, memory is impaired.

How can mice do a cogntive test?

To test spatial learning and memory, mice undergo a test called APA (Active Place Avoidance). It is a cognitively challenging task where mice are placed in a rotating arena with a defined shock zone. The test requires the mice to continuously use and integrate visual cues from their environment to orientate themselves and avoid the shock zone.

What will this mean for people with dementia?

- The potential development of cognition-enhancing pharmaceuticals in their lifetime.
- Hope that something will be able to prevent or slow the progression of Alzheimer's disease.

What will this mean for the research field?

- Evidence for a direct link between MS cholinergic neurons and the regulation of adult hippocampal neurogenesis.
- Answers to whether adult neurogenesis is the primary target of M4-mediated functional improvements.
- An understanding of whether M4 could be used as a target for future drug development.
- The basis for the development of a new approach to harness the therapeutic potential of adult neurogenesis, to delay the onset or slow the progression of dementia.

Who's undertaking the research?

Dr Dhanisha Jhaveri, University of Queensland

Dr Jhaveri is a senior research fellow at Mater Research Foundation and has a joint appointment at the Queensland Brain Institute. She received her PhD from the Tata Institute of Fundamental Research in India and was awarded the Indian National Science Academy Medal for Young Scientist of the Year in 2003.

Her research is focused on investigating the fundamental mechanisms that drive the renewal of neurons in the adult brain, with the goal of harnessing this form of neuroplasticity to relieve the emotional and cognitive burdens associated with neuropsychiatric and neurodegenerative conditions. She has made major discoveries that have transformed our understanding of the regulation and roles of neural stem cells and new neurons in the adult brain.