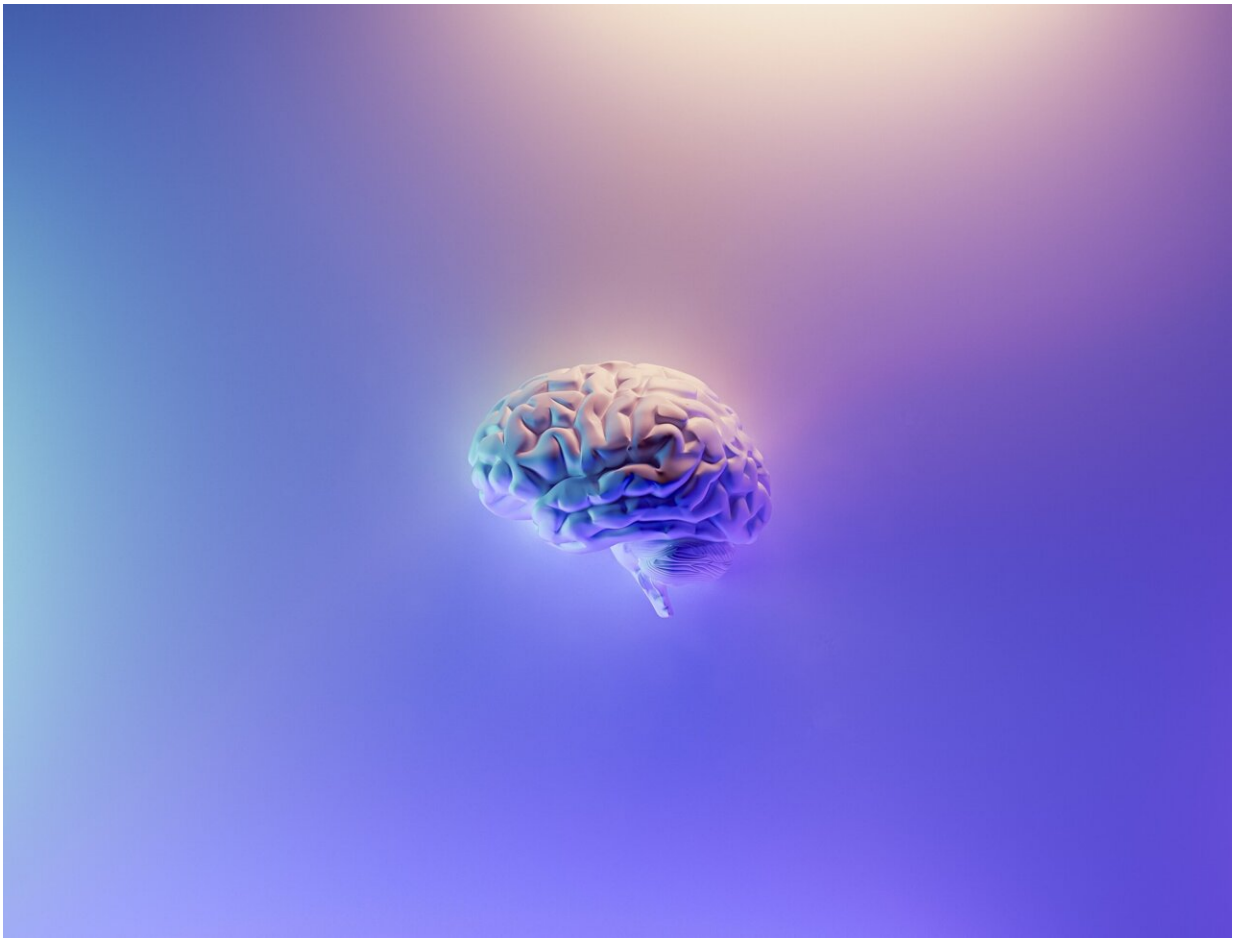
Developing drugs to reduce brain impairment after stroke

March 17 2014, by Frederic Meunier



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Stroke claims five million lives worldwide each year and is the second

biggest killer after ischaemic heart disease. Of those who survive, a significant number (around five million) live with neurological deficits that profoundly affect their quality of life.

Current treatment for ischaemic stroke, which results from a blood clot, aren't very effective. But research published by my colleagues and I today in the journal *Nature Communications* shows an emerging drug treatment is effective in mice and could one day reduce the neurological impact in people who've suffered an ischaemic stroke.

By 2020, the World Health Organization predicts that worldwide, the number of years lost to disability resulting from stroke will reach 61 million. The economic burden is similarly massive, costing Australia $49.3 billion a year. So finding better treatments is crucial.

Brain inflammation after stroke

Quick treatment is one way to enhance the prospect of recovering from a stroke.

If patients are treated within around three hours of the stroke, the stroke-inducing clots can be broken down relatively efficiently using a substance called tissue plasminogen activator (tPA). This allows the blood to start flowing again, supplying the brain with the oxygen required to keep the tissue alive.

But after the clot is removed and blood starts flowing, the body produces an unwanted neuroimmune response. This occurs because the damaged brain tissue contains elevated levels of molecules known as proinflammatory cytokines, which regulate the body's response to infection, inflammation and trauma.

These cytokines are able to recruit many other immune cells to the area,

leading to further cell death.

Limiting the initial release of these cytokines should therefore help to decrease the excessive local inflammatory response, leading to a decrease in tissue damage and better patient outcomes.

Targeting a critical molecule

A key cytokine involved in this process is tumour necrosis factor-α (TNF-α). In previous work, we showed that the secretion of TNF-α is dependent on a molecule named phosphoinositide 3-kinase delta (PI3Kδ). For our latest study, we hypothesised that PI3Kδ could be similarly involved in stroke.

In collaboration with Garrie Arumugam from the University of Queensland, researchers at Monash University and international colleagues in London and Hamburg, we induced strokes in mice to demonstrate that – as expected – PI3Kδ controlled the release of TNF-α from immune cells of the central nervous system.

This suggested to us that by inhibiting PI3Kδ activity, we would be able to prevent the rise in TNF-α secretion and therefore limit inflammation of the brain and cell death.

Two separate lines of evidence indicated this was the case: mice genetically modified to have inhibited PI3Kδ activity had only limited TNF-α release, and mice that were given the PI3Kδ-inhibiting drug CAL-101 showed similar effects.

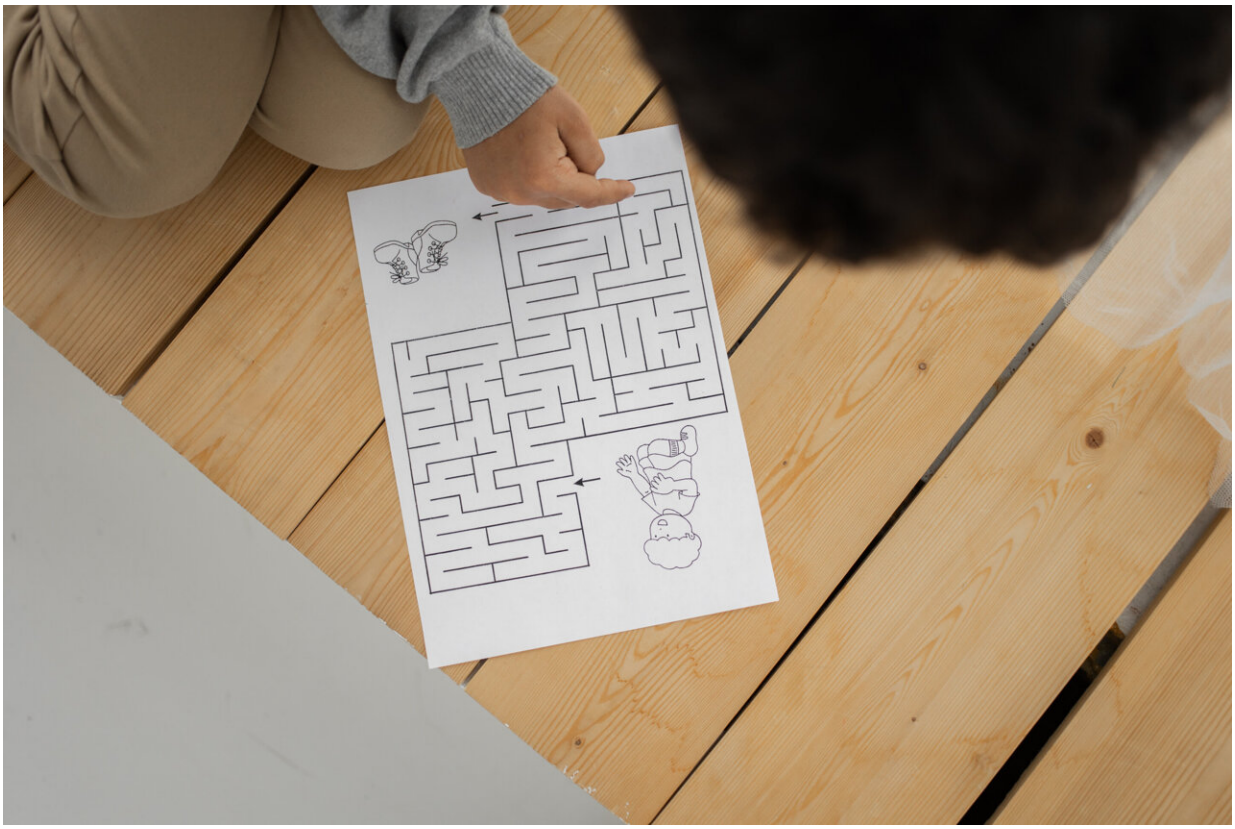
Further, blocking PI3Kδ activity (through genetic manipulation or medication) decreased blood clot-induced brain damage and resulted in improved performance on neurological tests.

These results indicate that we successfully identified a pathway critical to post-treatment inflammation of the brain, and that we could limit the damage by blocking PI3Kδ, a key molecule within that pathway.

While the genetic manipulation played a role in identifying the signalling pathway involved, it is the efficacy of CAL-101 that is particularly exciting and relevant to stroke therapy. Not only was the drug effective in improving post-stroke recovery, but its effects could be seen when given up to three hours after the clot was removed and blood started flowing.

Since initial stroke treatment is typically initiated by medically trained staff, CAL-101 (or a related molecule) could potentially be injected alongside tPA to reduce inflammation of the brain and improve patient outcomes.

Taking it to the clinic



Credit: Monstera Production from Pexels

The next obvious question is whether CAL-101 or a similar derivative may ultimately be used to improve stroke treatment in humans.

Our study was conducted in mice, and translating findings in animal models to the development of clinical therapies can be very difficult – clinical trials of drugs fail frequently due to safety or efficacy concerns.

In positive news, however, CAL-101 (also known as GS-1101 or idelalisib) has recently undergone phase three clinical trials in the United States for the treatment of certain forms of lymphoma and the results look promising.

CAL-101 is therefore a very promising molecule. Not only does it treat lymphomas, it has the potential to alleviate the complications that arise following initial stroke treatment. We're now also looking into other medical conditions that could be improved by reducing inflammation of the brain with CAL-101 or a similar compound.

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