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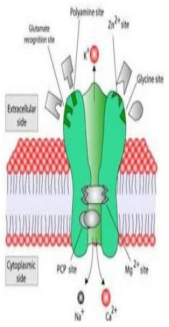
Drugs with Anti-Stroke Potential and Less Side Effects



During the 1990s, a class of drugs was identified as showing promise is the area of stroke. NMDA receptor antagonists were found to limit damage to the brain in animal models of stroke. However, the drugs were not tested in a clinical setting because of their side effects which included disorientation and hallucinations. Researchers have now found a potential path around this obstacle. The research has been published in *Neuron*.

"We have found neuroprotective compounds that can limit damage to the brain during ischaemia associated with stroke and other brain injuries, but have minimal side effects," says senior author Stephen Traynelis, PhD, professor of pharmacology at Emory University School of Medicine.

These neuroprotective compounds are most active when the pH is lowered by biochemical processes associated with injury of the surrounding issue. This is the mechanism of action that could be useful in several conditions such as stroke, traumatic brain injury and subarachnoid haemorrhage.

The researchers found that in a mouse model of ischaemic stroke, a NMDA receptor antagonist called 93-31 reduced the volume of damaged brain tissue by more than half. It also did not lead to the side effects associated with other NMBA receptor antagonists.

The drugs phencyclidine (also called PCP) and ketamine are NMDA receptor antagonists and block all subtypes of NMDA receptors. This is what is believed to account for their psychoactive side effects. NMDA receptors are found on the surface of brain cells and play an important role in processes such as memory formation.

In patients affected by stroke or traumatic injury, the environment in the brain tissue becomes acidic because of a lack of oxygen and the build-up of metabolites such as lactic acid. Also, NMDA receptors get overstimulated by an increase in the neurotransmitter glutamate.

93-31 is ten times more potent at pH 6.9, typical for ischaemic tissue with an insufficient brain supply, than at pH 7.6 which is close to the value for healthy brain tissue. According to the researchers, NMDA receptor antagonists, if used in the right dose, can be active in the injured areas of the brain.

Researchers tested 93-31 on mice trained to press a lever when levels of PCP declined. When 93-31 was substituted with PCP, the mice did not perceive 93-31's subjective effects to be similar enough to PCPs and did not respond the same way. Doses of 93-31 that had a positive effect in the stroke model did not impair coordination or motor function. The mice were still able to hold onto a turning rode compared with mice who were dosed with other NMDA receptor antagonists.

While 93-31's pharmaceutical profile may not be optimal for further development, a related drug candidate, an analogue of the compound identified in this research, is being developed as a preventive measure for people who experience subarachnoid haemorrhage. Safety studies are being conducted and an Investigational New Drug Application is expected to be filed with the FDA later in 2015.

Source: Emory Health Sciences

Image Credit: Emory Health Sciences

Published on : Fri, 6 Mar 2015