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Cure for Paralysis through p45 Protein obtained from Lower Animals

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ABSTRACT

A person with paralysis will have nerve damage. The protein p45 activates nerve regeneration in few animals by stopping myelin the protective coating around nerve fibers from halting nerve regrowth. It is found that humans and primates do not possess the p45 protein; instead they have a protein called p75, which attaches itself to myelin when nerves are damaged and prevents their repair. Using NMR technology it was possible to closely analyze the configurations of the two p75 proteins. By introducing the p45 protein which promotes nerve regeneration, they found it could break up the pairing of the p75 proteins. This reduced the number of p75 pairs that attach to nerve repair inhibitors released from damaged myelin, meaning nerve fibers were able to regenerate. This research implies that we might be able to mimic neuronal repair processes that occur naturally in lower animals.

Key words: *P45, P75, NMR technology, nerve repair.*

INTRODUCTION

Paralysis is loss of the ability to move one or more muscles. It may be associated with loss of feeling and other bodily functions. Paralysis is not usually caused by problems with the muscles themselves, but by problems with the nerves or spinal cord that the brain uses to control muscles. Therefore, a person with paralysis will usually have some form of nerve damage [3].

Classification of paralysis:

Paralysis can either be localized, where a specific section of the body, such as the face or hand, is paralyzed, or it can be generalized, where a larger area of the body is affected. There are also a number of medical terms used to describe different types of paralysis. For example:

- Monoplegia – where one limb is paralyzed
- Hemiplegia – where the arm and leg on one side of the body are paralyzed
- Paraplegia – where both legs and sometimes the pelvis and some of the lower body are paralyzed
- Tetraplegia – where both the arms and legs are paralyzed (also known as quadriplegia) [3].

Causes of paralysis:

The common causes of paralysis are:

- Stroke: A stroke is a serious medical condition that occurs when the blood supply to your brain is disturbed.
- Head injury: A severe head injury can cause brain damage. The brain's surface can tear or bruise as it bumps against the skull, damaging blood vessels and nerves. Paralysis can occur if a part of the brain that controls specific muscles is damaged during a severe head injury
- Spinal cord injury – the spinal cord is a bundle of nerve tracts that runs through the spine and helps control the body's cord can also be damaged. This means the brain may no longer be able to transmit signals to the muscles, causing paralysis.
- Multiple sclerosis

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Sometimes, paralysis can also occur as a result of a number of other conditions such as cerebral palsy and Guillain-Barré syndrome [2].

Diagnosing paralysis:

Diagnosing paralysis is not usually necessary. Tests used to help determine the extent of paralysis include:

- X-Ray
- CT-Scan
- MRI-Scan
- Myelography
- Electromyography [4].

Methodology:

The study initiated by Reeve Foundation and conducted by the University of New Mexico's Center for Development and Disability showed that 1 in 50 people are living with paralysis and out of the sufferers 29% of them are caused by stroke and 24% by accidents. World statistics report approx 5.6 million or 1.9% of population suffer paralysis [1].

New research from the Salk Institute, the research team, including senior author Kuo-Fen Lee, a professor at Salk suggest that a small molecule may be able to convince damaged nerves to grow and effectively rewire circuits. Such a feat could eventually lead to therapies for the thousands of people suffering paralysis. For a damaged nerve to regain function, its long, signal-transmitting extensions known as axons need to grow and establish new connections to other cells.

By studying the configurations of the proteins in solutions using nuclear magnetic resonance (NMR) technology, the researchers found that the growth-promoting p45 could disrupt the p75 pairing.

The protein p45 activates nerve regeneration in few animals by stopping myelin the protective coating around nerve fibers from halting nerve regrowth. Scientists found that humans and primates do not possess the p45 protein, instead have a protein called p75, which attaches itself to myelin when nerves are damaged and prevents their repair. Using NMR technology it was possible to closely analyze the configurations of the two p75 proteins [5].

Treatment:

Heterodimerization of p45–p75 Modulates p75 Signaling: Structural Basis and Mechanism of Action**:** The p75 neurotrophin receptor, a member of the tumor necrosis factor receptor superfamily, is required as a co-receptor for the Nogo receptor (NgR) to mediate the activity of myelin-associated inhibitors such as

Nogo, MAG, and Omgp. It has four extracellular cysteine rich domains, a single transmembrane (TM) domain, and an intracellular domain (ICD) comprising a juxtamembrane and a death domain (DD) [6–10]. Depending on co-receptor partners and cellular contexts, p75 may play seemingly opposing effects in multiple systems. For example, p75 interacts with Trk receptors to promote neurotrophin-dependent nerve growth [9].

Axon regeneration is blocked by the presence of multiple types of nerve growth inhibitors, such as myelin-associated inhibitors from damaged myelins, chondroitin sulphate proteoglycans, and repulsive axon-guidance molecules expressed by reactive glial cells [11–14]. p45 interferes with the function of p75 as a co-receptor for NgR. P45 forms heterodimers with p75 and thereby blocks RhoA activation and inhibition of neurite outgrowth induced by myelin-associated inhibitors. p45 binds p75 through both its transmembrane (TM) domain and DD.

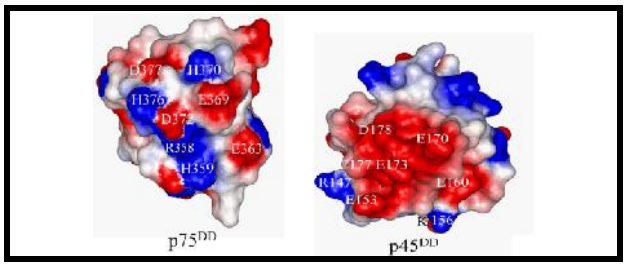

Fig 1: Domains of p45 and p75

p45 is highly homologous in sequence to p75. It is also called neurotrophin receptor homologue 2 (NRH2) [15], neurotrophin receptor alike DD protein (NRADD) [16], or p75-like apoptosis inducing DD protein (PLAIDD) [17]. P45 displays strong sequence similarity to p75 in the TM, juxtamembrane, and DD regions [18].

By introducing the p45 protein which promotes nerve regeneration, researchers found it could break up the pairing of the p75 proteins. The researchers discovered that p45 protein could bind to the exact region in the p75 protein that is responsible for their pairing (**Fig. 2**).

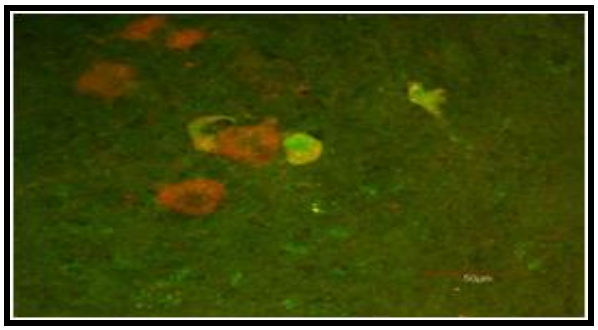

Fig 2: p45 & p75 Pairing

This reduced the number of p75 pairs that attach to nerve repair inhibitors released from damaged myelin, hence nerve fibers were able to regenerate. The presence of p45 (green staining) and p75 (red staining) indicates that motor neurons increase both p45 and p75 expression after sciatic nerve injury in an animal (**Fig. 2**) [5].

CONCLUSION

In conclusion Nerve repair process of some animals 'could be mimicked in humans'. Using NMR technology it became possible to closely analyze the configurations of the two p75 and p45 proteins.

Method of therapy is to introduce more p45 protein to injured neurons, but a smarter tactic might be to introduce a small molecule that jams the link between the two p75 proteins. "Such an agent could possibly get through the blood-brain barrier and to the site of nerve damage and spinal cord injuries".

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