New Thoughts on Nerve Regeneration

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Thank you very much for asking me to present a lecture on "New Thoughts on Nerve Regeneration" in this afternoon. When your president, Dr. Soin asked me to present this subject, she said that I could say anything on the subject so long as it is new. New ideas are not necessarily true but sometimes they are worthwhile to try. I was asked three questions and tried to find answers for some of the problems in neural injury and repair and they form the basis of this presentation.

1. Is immediate return of function possible after complete division of a nerve from a tidy injury? This return of function would be very similar to the immediate restoration of an electricity failure.

2. When immediate restoration of function is not possible, can we accelerate the recovery by stimulating the nerve cell to produce more cytoplasm at a faster rate after nerve continuity has been restored, rather then wait for months for a sciatic or high median or ulnar nerve injury to recover?

3. Can neural damage that we now consider as irreversible be reversed? For example, the cerebral palsy spinal cord injury and the avulsion of nerve roots from the cord in a brachial plexus lesion.

Nerve injury and repair are slightly different from healing of a fracture or skin wound. It is basically an injury to a number of cell processes, the axons which grow back to their end organs after Wallerian degeneration. Why does Wallerian degeneration in the proximal nerve segment stop at the next node of Ranvier and not proceed further up the axon? Is there any natural mechanism to prevent such a thing happening in the entire proximal segment after nerve injury? Does Wallerian degeneration occur in the distal segment because no immediate action has been taken to re-establish anatomical continuity at cell membrane level to prevent cytoplasmic loss? If these postulates are true, we should be able to re-establish molecular and biological continuity for the immediate return of nerve function and prevent Wallerian degeneration in some instances. The answer of the above questions must be found at the molecular and cellular level, for the axon is a long cell process and it functions in many ways like other cells in the body. Therefore, what is known about a cell at the molecular biology level, it must be applied to the nerve cell and axon to understand nerve degeneration and regeneration, otherwise we will be left behind in spite of the tremendous advances in molecular and cell biology.

Every cell has a potential difference across it and electrical conductivity of a nerve depends on this potential difference across the cell membrane of the axon. The cell membrane is a two molecular bilipid layers. It is fluid and not solid and can therefore, be made to flow from one point to another in the manner of forming, enlarging or joining soap bubbles. One of the properties of the bilipid layer is that it can break and reform if we bring the lalyers sufficiently close togther. The fusion of bilipid layers takes place in every day life in cell vesicles. Integrity of the cell membrane is necessary after nerve injury otherwise cytoplasmic and electrolyte loss from the axon will occur. I feel that the proximal axon segment is sealed off by a mechanism of cell membrane closure at the next node of Ranvier after nerve injury. The distal axon which is not continuous with the parent cell therefore, degenerates and this is the basis of Wallerian degeneration.

If we can get the immediate continuity of the cell membrane in a tidy nerve injury before cytoplasmic and electrolyte loss, return of nerve function is possible if the potential difference can be restored to the pre-injury level. Instead of splicing the nerve, we must therefore, splice the axons at cell molecular biology level after the tidy nerve injury for recovery of function.

If immediate reconnection at molecular cell biology level is not possible, Wallerian degeneration and regeneration has to follow. The regeneration depends on increased cytoplasmic production by the parent cell. If this can be accelerated by biostimulation, the nerve recovery can be accelerated to a few days or weeks rather than the usual waiting for months.

It is also important to look at the supporting cells of a peripheral nerve in regeneration and repair for a peripheral nerve is a composite structure and not an only collection of axons. The Schwann cells, basement membrane, collagen and blood vessels form part of the nerve and they must therefore be taken into account in the repair process. Moreover, similarly intrinsic and extrinsic factors which affect the nerve cell, axon and the supporting cells must be looked into. They may be chemical, physical, electrical, endocrine and other factors.

Finally, I would like to touch on foetal neural tissue transplantation for this has a lot of potential in nerve, plexus and spinal cord repair and recovery. It appears that working on foetal neural transplantation is nearly 100 years old. In addition, early work has shown that the foetal neural tissue transplants survive, grow, differ and develop a cytoarchitecture. They form connections with the host cells and alter the functional status as a result of the transplant. Various animal models have been developed to study the foetal tissue transplantation. Dunn[1] in 1917 published her results of grafting cerebral cortex from embryonic rats into cavities of litter mate hosts. She noted to the survival of grafts whenever they were juxtaposed to the choroid plexus of the lateral ventricles. In 1957, Flerko and Szentagothai[2] in a neuroendocrinal experiment discovered the usefulness of the ventricular system as a site for promoting graft survival and growth. Endocrinologically active tissue was placed in the third ventricle where it showed excellent survival. Halasz[3] et al pursued these experiments and provided the first evidence of functional interaction between grafted tissue and host brain by reversing endocrine deficits produced in hypophysectomised rats. In 1945, May[4] showed that anterior chamber of the eyes provided an excellent environment for the neural grafting. He also showed that co-grafts of the cerebral tissue and peripheral nerve resulted in growth of axons from central nerves into the degenerating peripheral axons.

The identification of monoamine neurotransmitters within the nerve cell bodies and their terminal axons with the help of formaldehyde vapour to analyse grafted neurons has revolutionised our understanding of the neural plasticity and regeneration (Bjorklund et al).[5]

It is therefore, important that we apply the principles of foetal neural transplantation to the spinal cord regeneration, the regeneration of the avulsed nerve roots from the spinal cord in brachial plexus lesions and in the near future do foetal neural tissue transplantation to the brain of a cerebral palsy child to improve hand function.

I have taken into account two important areas of advances, the molecular and cell biology research and the research in foetal tissue transplantation. If these two areas of research are not used or taken into account, we will be left behind in our ideas and methods of nerve repair and regeneration.

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