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REVIEW

Developmental history of neurorestoratology

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Abstract: The aim of neurorestoratology is to restore, promote and maintain the integrity of impaired or lost neuronal functions and/or structures, using novel cell-based comprehensive neurorestorative strategies. The purpose of this review is to briefly introduce the developing history of neurorestoratology, which includes neurorestorative strategies, the basis of central nervous system neurorestorable theory, communities in the field of neurorestoratology, and journals related to neurorestoratology.

Keywords: neurorestoration, neurorestorative strategies, CNS neurorestorable theory

Introduction

Neurorestoration took more than 100 years from a method and a branch of neurological science to the establishment of a distinct discipline – neurorestoratology,[1] which is a discipline to study neural regeneration, repair and replacement of damaged components of the nervous system, neuroplasticity, neuroprotection and neuromodulation, vasculogenesis and recovery mechanisms of immune regulation. Its aim is to restore, promote and maintain the integrity of impaired or lost neuronal functions and/or structures, using novel cell-based comprehensive neurorestorative strategies. Prior to neurorestoratology, which was put forward by Huang and Chen and later approved by the International Association of Neurorestoratology as an independent discipline,[1,2] historically, there were other similar sub-disciplines or techniques, such as restorative neurology,[3] restorative neurosurgery,[4] neural repair,[5] neuroprostheses,[6] neurorestorative technique or therapy,[7,8] and restorative neuroscience,[9] among others. All of them share a common connotation for neural functional recovery though they display in different appearance.[10]

History of strategies for neurorestoratology

The strategies of neurorestoratology include tissue and cell transplantation, neurostimulation and neuromodulation, medicine and growth factors, bioengineering and tissue engineering, restorative surgery, and others.

Tissue and cell transplantation

In 2010, Dunnett classified the tissue and cell transplantation developing process into four sections or eras.[11]

1890–1940: the early era

The first cell transplantation into the brain was attempted during this era. Many contemporary themes were initially addressed, such as surgical factors to achieve survival

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of grafted cells and how that should be assessed. Such studies, however, generally exhibited only low levels of viability or successful implantation.[11] Thompson reported the earliest tissue transplantation in animals in 1890 with a graft survival of 7 weeks.[12] Subsequently, Cajal first described the axonal regeneration-promoting effects of peripheral nerve implants in the spinal cord.[13]

1940–1970: the middle era

During this era, the techniques for viable and reliable cell transplantation using embryonic donor tissues implanted into sites with effective vascularization were established in the brain and neuroendocrine systems.[11] It is noteworthy to comment that in all of these studies, the brain of an adult mammal was chosen as the site for transplantation essentially because it has always been considered as an immunologically privileged site.[14–16]

1970–2000: the modern era

Several pioneering studies that combined cell transplantation with the use of improved histochemical and ultrastructural anatomical techniques demonstrated the selectivity, specificity, and regenerative capacity of implanted cells, and the slow acceptance that the adult brain does exhibit considerable potential for plasticity and repair during this era. The findings have witnessed the identification of reliable and efficient transplantation technologies combined with progressively refined methods of molecular, cellular, biochemical, physiological, and functional analysis.[11] A preclinical brain tissue transplantation study was shown to reduce motor abnormalities in animals,[17,18] and a similar study was done by Björklund et al.[19] David and Aguayo found that axons supported by peripheral nerve segments as 'bridges' between the medulla and spinal cord grew approximately 30 mm. The peripheral nervous system glial environment could help central neurons to express regenerative potential.[20] The initial olfactory ensheathing cell (OEC) transplantation studies of histological and functional recovery in animals started in the 1990s. Ramón-Cueto and others reported that the regeneration of injured dorsal root axons into the adult spinal cord was possible after OEC transplantation; and OEC transplants successfully led to functional and structural recovery after complete spinal cord transection in adult rats.[21,22] A study by Franklin et al provided the first in vivo evidence that OECs are able to produce peripheral-type myelin sheaths around demyelinated spinal cord axons of an appropriate diameter.[23] Li et al reported that cut corticospinal axons grew through the transplant and continued to regenerate into the denervated caudal host tract. Rats with complete transactions, in which the transplanted cells had formed a continuous bridge across the lesion, exhibited directed forepaw reaching on the lesioned side.[24] During this era, the first clinical trial of neural tissue transplantation was done.[25,26] In this study, autologous adrenal medullary tissue was transplanted to the striatum in two patients with severe parkinsonism, and some rewarding effects were registered. Subsequently, fetal tissue, including dopamine neuron transplantation was performed, resulting in graft survival and motor function improvement in Parkinson's disease (PD)[27–30] and Huntington's disease (HD) patients.[31–33]

The 21st century: contemporary era

Cell transplantation has been attempted in more central nervous system (CNS) diseases. Over 30 types of cells and tissues have been successfully used in preclinical experiments.[34] A number of cell transplantation clinical studies worldwide were started during this period. The earliest clinical trial of cultured human neuronal cell transplantation into brain parenchyma for patients with stroke was done by Kondziolka et al.[35] The earliest clinical trials or studies of OEC transplantation into spinal cord parenchyma were started for spinal cord injury (SCI) by Huang et al and Rabinovich et al.[36,37] Olfactory mucosa tissue transplantation was done by Lima et al in 2001.[38] Two years later, Mackay-Sim et al followed with OEC from mucosa for SCI.[39] After those pioneering studies, other kind of cells, such as Schwann cells, bone marrow (umbilical cord blood or peripheral blood) mononuclear cells, were used in clinical studies in SCI,[40–47] multiple sclerosis,[48,49] stroke sequelae,[50,51] amyotrophic lateral sclerosis (ALS),[52,53] cerebral palsy, and others.[54–56] Although these studies could not cure the sequela of CNS diseases, they strongly suggest that they have been able to restore some neurological functions. In support of these published works as listed above and our own data, we firstly proposed a CNS neurorestorable theory; that is, neurological functions are able to be restored in degenerative diseases and sequela of damage in the CNS.[10,34,36,52,57]

Neurostimulation/neuromodulation and neuroprosthesis

Brain or spinal cord electrical stimulation

In 1804, Aldini first reported that cortical stimulation evoked horrible facial grimaces.[58,59] The first patient treated using brain stimulation was reported by Bartholow in 1874.[61] Direct electrical stimulation or transcranial direct current stimulation (tDCS) to the cerebral cortex or spinal cord could result in potassium release,[62] antiapoptotic, angiogenic, and

antiinflammatory effects, and synaptic plasticity,[63,64] and induce or promote axon outgrowth[65–67] to restore motor function.[68–70] Brain stimulation (called electroshock) was the first therapeutic application for severe psychosis and then for pain in 1954.[59,71,72] Epidural stimulation of the spinal cord induced stepping-like movements in patients with complete SCI.[73,74] tDCS is a noninvasive technique and is increasingly being used in the treatments of some neurological and psychiatric conditions, eg, chronic pain, epilepsy, depression, motor rehabilitation after stroke, SCI, and PD.[75]

Deep brain stimulation

Initially, deep brain stimulation (DBS) was used as a diagnostic method by Delgado et al[59] and as a treatment method for movement disorders (eg, PD) by Bekhtereva et al.[59] Recent studies have demonstrated the potential for treating epilepsy, depression, and obsessive–compulsive disorder.[59,78,79]

Magnetic stimulation

The magnetic stimulator was reported for stimulating neural elements in 1982.[80] Transcranial magnetic stimulation (TMS) was used in clinics at that time.[81] In recent years, repetitive TMS has been used as a therapeutic tool for a variety of psychiatric and neurological disorders, such as PD,[82] ALS,[83] traumatic brain injury,[84] stroke,[85,86] pain,[87] dystonia,[88] and epilepsy.[89]

Neuroprosthesis

Nashold et al reported electromicturition using a spinal neuroprosthesis implantation for paraplegia in 1971.[90] Recently, real brain–machine interfaces with neuroprosthetic limbs have been shown to help patients with long-term paralysis to recover the natural and intuitive command signals for hand placement, orientation, and reaching, allowing them to perform activities of partial daily living.[91–94]

Growth factors and drugs

Levi-Montalcini and Hamburger discovered that nerve growth factor (NGF) can promote the survival and differentiation of sensory and sympathetic neurons,[95–97] and was first used in a clinical trial by Olson et al in 1991.[98] High-dose methylprednisolone therapy showed neuroprotection for SCI in an animal study in 1982 and stimulated Young et al to carry out a clinical trial on this subject in 1988.[99]

Bioengineering and tissue engineering

Rosenberg et al reported that implanting fibroblasts genetically modified with NGF into rat brains could prevent cholinergic neuron degeneration.[100] Emerich et al found that transplanting polymer-encapsulated fibroblasts genetically modified with human ciliary neurotrophic factor (CNTF) into striatum had a protective effect in an animal model of HD.[101] Bloch et al completed a clinical trial for HD by transplanting these polymer-encapsulated cells engineered with CNTF into the brain.[102] Tuszynski et al reported Phase I clinical trial results of gene therapy with NGF for Alzheimer's disease.[103]

Neurorestorative surgeries

Cordotomy or myelotomy

The first report on cordotomy or myelotomy in an animal study was by Freeman and Wright in 1953, which showed protective effects for injured spinal cords.[104] In 1984, Tachibana et al performed posterior longitudinal myelotomy for patients with cervical acute complete SCI.[105]

Neurotization or nerve bridging

Carlsson and Sundin reported reconstructing nerve bridging to the urinary bladder in a paraplegic child in 1967 and reconstructed nerve bridging to the urinary bladder for another two paraplegic patients in 1980.[106,107] Zhang, Brunelli, and others then improved the surgical technique of neurotization or nerve bridging in clinics for patients with SCI.

Neurorehabilitation

Brackett first mentioned the rehabilitation for soldiers injured in the war in 1918.[108] Ueda summarized the rehabilitation in neural diseases in 1963.[109] Luzhetskaia et al first introduced neurorehabilitation as a therapeutic method for neural diseases and damage in 1974.[110]

Comprehensive cell-based neurorestorative strategies

The study of combined neurorestorative therapies and comprehensive strategies is now recommended in order to help improve benefits for patients or augment neurological functions.[111]

The basis of CNS neurorestorable theory

Based on clinical achievements obtained from cell-based neurorestorative therapy, CNS neurorestorable theory was proposed by Huang et al.[36] Liu and Chambers found intraspinal sprouting of dorsal root axons in cats.[112] Bechtereva and Zontov found a relationship between

certain forms of potentials and the variations in brain excitability.[113] Raisman discovered neuronal plasticity in the septal nuclei of the adult rat.[114] David and Aguayo reported when peripheral nerve segments were used as 'bridges' between the medulla and spinal cord, axons from neurons at both these levels could grow.[20] Bornstein and Raine reported remyelination in CNS tissue.[115] Altman and Das found evidence of postnatal hippocampal neurogenesis in rats.[116] Young and Flamm reported the beneficial effects or neuroprotection of high-dose corticosteroid treatment on both functional recovery and histopathological appearance of injured spinal cords.[117] Later on, it was found that axonal sprouting or regeneration, signal modulation, remyelination, and neurogenesis could restore neurological function after CNS damage.[118–123]

As we know, neurorestoratology is established on the basis of the CNS neurorestorable theory. Currently, we know many mechanisms of functional recovery, which include signaling repair or unmasking, neuromodulation, neuroplasticity, neurorepair or remyelination, neuroprotection, neural circuit or network reconstruction, neurosynapsis, neuroreplacement, axonal sprouting or regeneration, neurogenesis or neuroregeneration, angiogenesis, and immunomodulation.[34,36,38,124]

Generally, the patient's functional restoration may originate from some or all of the mechanisms as listed above. But under many conditions, functional recovery may be from neuromodulation or unmasking, neuroprotection, and then from neural circuit reconstruction, neuroplasticity and neurorepair through neurotrophins, immune or inflammatory modulation, or angiogenesis and local microenvironment change, and only in a few cases from neurogenesis or neuroregeneration, axonal sprouting, or regeneration.[125,126] Neuroreplacement may be an important tool for PD, but may not be a useful method for functional neurorestoration in most other CNS damages or diseases.

In addition, we should point out that overemphasizing the concept of neuroregeneration may be a century directional mistake in this area, because 'neuroregeneration' is not equal to functional recovery. Many people misconstrue that 'neuroregeneration' will bring neurological functional recovery, but actually, it is only one kind of neurorestorative mechanism. Our vision should widen to neurorestoration, instead of solely focusing on 'neuroregeneration'. On the contrary, the concept of neurorestoration surely means neurological functional recovery, which doubtless is the ultimate aim of any physician's treatments. Thus, the scientific term of neurorestoration is more accurate to elucidate and express the real implications of clinical outcome than 'neuroregeneration'.

Community in the field of neurorestoratology

Nowadays, the main associations or societies in or related with neurorestoratology are: the International Association of Neurorestoratology (IANR), American Society for Neural Therapy and Repair (ASNTR), International Conference on Neural Therapy and Repair (INTR), Global College of Neuroprotection and Neuroregeneration (GCNN), International Society of Restorative Neurology (ISRN), International Neuromodulation Society (INS), the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), Cell Transplant Society (CTS), International Conference on Neuroprotective Agenda, Network of European CNS Transplantation and Restoration (NECTAR), and Asia Pacific Symposium on Neural Regeneration (APSNR), among others.

Journals related to neurorestoratology

The main international published journals in the field of neurorestoratology include: Journal of Neurorestoratology, Cell Transplantation, Restorative Neurology and Neuroscience, Neuromodulation, American Journal of Neuroprotection and Neuroregeneration, Stem Cells, Clinical Transplantation, Cytotherapy, Cell Medicine, and Neurorehabilitation Neural Repair.

Summary

Neurorestoratology is an emerging discipline that was put forward on the basis of a CNS neurorestorable theory. Numerous respected pioneers have tried their best to explore a glimmer of light (any possible promoting neurorestorative strategies) in the darkness. Some of them have been trying to spread novel concepts, knowledge, and information by creating societies and journals related to neurorestoration. These important pioneers should be borne in mind forever because of their dedication and great contribution. Today, the CNS neurorestorable door has been successfully opened. The road ahead is still rugged, but we know where we are, and more importantly we know where we will go, because we have already had a roadmap to achieve the goal of longevity and good quality of life for humanity.[127]

Disclosure

The authors report no conflicts of interest in this work.

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