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At the interface: Convergence of neural regeneration and neural prostheses for restoration of function

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Abstract—The rapid pace of recent advances in development and application of electrical stimulation of the nervous system and in neural regeneration has created opportunities to combine these two approaches to restoration of function. This paper relates the discussion on this topic from a workshop at the International Functional Electrical Stimulation Society. The goals of this workshop were to discuss the current state of interaction between the fields of neural regeneration and neural prostheses and to identify potential areas of future research that would have the greatest impact on achieving the common goal of restoring function after neurological damage. Identified areas include enhancement of axonal regeneration with applied electric fields, development of hybrid neural interfaces combining synthetic silicon and biologically derived elements, and investigation of the role of patterned neural activity in regulating various neuronal processes and neurorehabilitation. Increased communication and cooperation between the two communities and recognition by each field that the other has something to contribute to their efforts are needed to take advantage of these opportunities. In addition, creative grants combining the two approaches and more flexible funding mechanisms to support the convergence of their perspectives are necessary to achieve common objectives.

Key words: *activity-dependent plasticity, FES, neural prostheses, regeneration, rehabilitation, SCI.*

INTRODUCTION

In the field of neural prostheses, electrical activation of the nervous system is used to restore function, to promote plasticity and learning, and to prevent secondary complications (1,2). Recent success in this field has been explosive. After decades of work, researchers have been able to demonstrate safety, efficacy, clinical utility, and cost effectiveness of a number of implants and neural prostheses used to restore function. Reliable miniature implantable electronics and electrodes have also been developed. Yet, the field is still far from being able to achieve restoration of full able-bodied function in the nervous system.

Similarly, exponential growth and discovery have occurred in regeneration research (3–5). There is a much greater understanding of the cascade of cellular events

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that lead to cell death. There are increasing prospects for cell transplantation. The molecular signals that promote and inhibit regeneration are starting to be identified and understood, and antibodies against some of the agents that might retard regeneration are being developed (6). There is a much greater understanding of both the molecular signaling elements in the extracellular space and the molecular receptors on the neurons that are involved in axonal path finding and formation of synapses once those axons reach their target (7). Yet, restoration of function by regeneration in humans with SCI remains theoretical.

The goals of this workshop were to discuss the current state of interaction between the fields of neural regeneration and neural prostheses and to identify potential areas of future research that would have the greatest impact on achieving the common goal of restoring function after neurological damage. The panel was charged with the task of exploring opportunities for collaboration between the rapidly advancing fields of electrical activation of the nervous system and neural regeneration. While these two disciplines have very different approaches to the problem, it is proposed that these approaches are complementary rather than antagonistic.

Workshop organizers and session moderators were Hunter Peckham from the Cleveland VA and Case Western Reserve University and Bill Heetderks from NINDS. Warren M. Grill from Case Western Reserve University and John McDonald from Washington University School of Medicine, St. Louis, were principal discussants, and panel members were Laura Bowman from the Rehabilitation Research and Development Service at the VA, Jeff Kocsis from the West Haven VA and Yale University, and Michael Weinrich from NICHD.

Restoration of Function After Neural Injury

Research has elucidated many of the important concepts of neural injury. It is clearly recognized that apoptosis, or programmed cell death, is a very significant aspect of spinal cord injury (SCI), both in acute injury and in the delayed secondary injury that occurs in the degenerating white matter tracts (8). Also evident is that oligodendrocytes are highly vulnerable not only to this second wave of apoptosis but also to excitotoxic injury (3,9,10). This is particularly salient because each oligodendrocyte myelinates 10 to 20 axons. Therefore, death of just one of these glial cells produces segmental demyelination in a great number of axons. It is widely held that dysmyelination is an important contributing factor to disability in SCI and other CNS injuries. The only available treatment to limit this secondary injury is methylprednisolone, which must be administered within the first 8 hours after spinal cord injury. Its proposed mechanism of action is decreasing inflammation and limiting secondary injury (11,12).

Science has discovered that spontaneous regeneration in the nervous system is the rule rather than the exception. With only partial repair of the nervous system and small anatomical gains, a disproportionate return of function is realized (13). Therefore the goal does not have to be "cure," per se, but rather partial repair and improvement in quality of life. Restoration of function will ultimately require multistage interventions that result in incremental benefits. Clinically relevant animal models need to be studied. Inhibitory factors that limit spontaneous regeneration have been identified and antibodies to block their action are being developed (14).

Another fact that has been highlighted within the past decade is that the nervous system is not static. There are progenitor cells present in the adult brain and spinal cord that can give rise to new cells (15,16), although it is still largely unclear how to stimulate those cells to adequately replace cells lost as a result of injury. However, one of the emerging hypotheses is that patterned activity is a means by which neurogenesis can be stimulated (17). Much has been learned about stem cells in general, and transplantation of cells has been a very useful approach to replacing those lost after injury. However, it is possible that a decade from now instead of transplanting cells, researchers will be harnessing the potential of endogenous cells to replace lost neurons and glia.

After injury, the nervous system is constantly changing as a function of time. Consequently, different strategies that are designed to work at different points in time will have to be employed and coordinated to achieve maximal return of function. For example, a pharmacological treatment like methylprednisolone is designed to prevent secondary injury and must be given during the acute phase. Other treatments, designed to prevent delayed apoptotic degeneration of oligodendrocytes, may be effective in the subchronic stage, and transplantation and neural prosthetic strategies might be employed even later. The key is that each of these interventional strategies is going to be required to achieve optimal recovery of function.

One important outcome to consider when evaluating the potential to repair neural injury is what is most likely to be accomplished. Clearly, it is easier to prevent or limit neuronal injury than to repair the damage once it has

occurred. Glial cell birth is something that happens readily in the nervous system, and many times the objective is to limit this growth, such as in the case of astrocytosis. Therefore, it is reasonable to expect that remyelination is an achievable goal. Many laboratories have demonstrated that remyelination can be accomplished through transplantation. While progress continues to be made in the area of getting transplanted neurons to survive and extend processes over long distances, the transplanted neurons still do not form appropriate functional connections. Functional connectivity remains one of the most challenging tasks in neural repair. A pragmatic approach will be to divide scientific efforts amongst the different regenerative strategies rather than putting all the focus on a single strategy.

How can the success from neural regeneration and electrical stimulation be combined to create a whole that is greater than the sum of its two parts? There are clear opportunities for both scientific and clinical collaboration between the two communities. In particular, at least three major areas for convergence between these two fields are identified. First is the enhancement of neural regeneration by applied electric fields. The second is the development of a hybrid neural interface, an implantable device that not only has a man-made construct, but a biological construct as well. And the third area is investigation of the role of activity in various processes of neural regulation and neurorehabilitation.

Enhancement of Axonal Regeneration with Applied Electrical Fields

There is a great deal of evidence that applying DC electric fields can enhance axonal outgrowth, causing growth toward the cathode with alignment of axons along the lines of current flow (4,18). However, neuroprosthetic research suggests that there may be technical limitations to this approach. Most of the research findings have been obtained with the use of chronic DC currents, known to damage potentially both the electrode and the underlying tissue (19).

In a recently reported set of experiments, the spinal cord of an adult guinea pig was transected at mid-thoracic level and implanted with a guidance channel containing electrodes both on the inside and the outside of the chamber (20). A DC current was passed through the chamber from the inside (cathode) to the outside (anode). The current used was only 0.1 μA, and resulted in a very small electric field (~100 μV/mm). After 1 to 2 months, anterograde and retrograde tracing were performed and the axonal growth with and without the applied DC field was compared. The results indicated that DC fields could promote axonal regeneration following spinal cord injury. However, higher cathodic current levels or anodic currents at any level reportedly prevented the ingrowth of any cells. This was thought to be secondary to the growing concentration of toxic electrode products trapped within the silicon tube.

An understanding of the effects of electric fields on growth cone machinery would be highly relevant in determining the mechanism by which DC fields influence regeneration. The exquisite sensitivity of developing axons in the immature nervous system to chemical gradients appears to be matched by an exquisite sensitivity to voltage potential gradients. Expertise in electrode materials and electrochemistry at the electrode/tissue interface might be useful in preventing the formation of toxic electrode products. In addition, exploring the effects of transient pulsing rather than DC currents could be a worthwhile task. Neuroprosthetic researchers have also developed expertise in implantable electronics for chronic stimulation that might substantially contribute to regeneration research.

Development of Hybrid Neural Interfaces

A second potential point of convergence between neural regeneration and neural prostheses is the development of hybrid neural interfaces, which would combine knowledge of cell culture, cell transplantation, tissue engineering and microfabrication. Hybrid interfaces are implantable synthetic devices with a biological construct that facilitates their integration into the host nervous system. There are at least two possible ways this might be achieved. The first approach involves culturing cells onto the synthetic probe and encouraging outgrowth from those cells to make synaptic connections with the neurons in the host tissue. The second approach is to seed the implant with neurophilic substances that would coerce the host tissue to extend processes to connect with the electrode (20–22).

In an experiment using the first approach, researchers at California Institute of Technology built a micro device containing several wells into which they cultured cholinergic septal neurons (23,24). The probe was then implanted into the rat hippocampus, and the tissue was stained for acetylcholinesterase, the precursor to acetylcholine. The results showed clear neuronal outgrowth from the probe into the host nervous system. Unfortunately, this was achieved on only one of the

implanted probes. Further study indicated that although connections were formed with the host tissue, the implanted cells were no longer connected to the implanted device.

Several important lessons can be gleaned from this experiment. It is possible to culture successfully septal neurons onto a silicon electrode, and when implanted into host tissues, these cells will migrate out of the probe into the more favorable host environment. There is an opportunity to modify the probe environment such that the cultured cells maintain their connection to the device after it is implanted. Experts in regeneration could certainly help the developers of these microelectronic devices formulate appropriate modifications. These could include neuronal phenotype modifications so that the neurons would simply extend processes from the probe rather than leave it completely to reside in the host tissue.

In an experiment using the second approach of fabricating a neurophilic device that would coerce host neurons to grow into it, researchers at Arizona State University developed a polyimide electrode that contained a small well surrounded by electrical contacts (21). The well was loaded with a fluorescent dye and implanted into rat cortex. Analysis performed 4 hours postimplant showed diffusion of the dye into the cortex that extended over some distance indicating the potential for such a system to attract growth of neurons from surrounding tissue to make intimate electrical contact with the electrodes on the polyimide probe. Similarly, a version of the University of Michigan silicon microelectrode containing a well loaded with nerve growth factor was used for neuronal recording after implantation in rat cortex for 10 days. Although it is not clear whether the recordings were any better with the neurotrophic factor than without, the experiment demonstrated the ability to combine electrical recording with delivery of neuroactive substances in chronically implanted devices.

These experiments confirm the potential for successful integration of recording electrodes and substance delivery on the same device. The substance will diffuse from the device when implanted in the brain, and recordings are possible with integrated devices. Potential opportunities for collaboration with the neuroregeneration field include modification of the local environment around the implanted electrode to coerce the host nervous system to extend processes to the implanted electrode. This could involve the surface of the device as well as various diffusible factors to be placed inside the probe wells. Either approach should be taken to control the growth of neurons and glia surrounding the electrode, to mechanically stabilize the implant in brain tissue, and to reduce the effective distance between the recording or stimulating site and the host nervous system, thus leading to greater selectivity.

Activity-Dependent Neural Regulation

Electrical activity in neurons regulates a number of processes within the cells including the stabilization/elimination of synapses (25–28), the patterns of gene expression within individual neurons (29–32), myelination (33,34), and the preservation of neurons following injury and perhaps neural genesis (15,17,35,36). Electrically induced activation or inhibition of the nervous system might help modulate synaptogenesis and synaptic strength for the purpose of restoring function.

The efficacy or strength of individual synapses can vary and this is in part regulated by neural activity, such as long-term potentiation (LTP) and long-term depression (LTD). Thus, neural prostheses can be used to control the level of activity in a neuron and possibly control the connectivity and strength of connections within the nervous system.

The mechanisms for activity-dependent development and plasticity are, in part, regulated by activity-dependent gene expression. Electrical activity causes an influx of calcium at the synaptic level. This calcium influx leads to a retrograde signal that specifies production of new gene products that are delivered back to the synaptic terminal to change its properties (32). Similarly, that electrical activity can affect gene expression within the cell body itself by indirectly influencing a class of genes called the immediate early genes. Increased activity in the neuron leads to an increase in intracellular calcium, which in turn activates second messenger cascades to stimulate transcription of the early immediate genes. These genes are then translated to produce a class of proteins that in turn act on another group of genes called the late response genes. It is these late response genes that are believed to be involved in neuronal growth and neuronal plasticity. Thus, through control of electrical activity, a kind of genetic neuroprosthesis might be developed.

Activity-Dependent Rehabilitation

Development is arguably the best model of regeneration, and during development, it is very clear that optimal levels of patterned activities are essential for synapse stabilization/elimination, myelination, new cell birth, neural cell survival, axonal guidance, and molecular

expression and release (see previous paragraph). After SCI, neural activity below the level of the lesion is dramatically reduced. It is probable that more can be done clinically to optimize the spontaneous regeneration observed experimentally by applying patterned sensory feedback to enhance neural activity. This can be accomplished by use of electrically stimulated stationary bicycling, partial-weight supported walking, or passive limb movements (13). These various approaches represent an attempt to activate endogenous pattern generators.

There are many potential benefits to an activity-dependent rehabilitation program (13). Primary benefits include an increase in muscle mass, which reduces skin breakdown, and maintains bone density, thus contributing to the prevention of pathological bone fractures. In addition, activity leads to an increase in blood flow, which can reduce the formation of blood clots. A second level of benefit includes clinically significant reductions in spasticity and perhaps enhanced regeneration.

There is currently a large-scale, multicenter clinical trial underway to investigate the effects of partial weight supported walking on function after SCI. Much of the focus has been on the training effects of this strategy, but it is also possible that the patterned activity may be stimulating spontaneous regeneration via the patterned sensory feedback. However, partial weight bearing is only one small part of a spectrum of behaviors that will have to be elicited to regain function. Locomotion has to be adaptable and partial weight bearing only addresses gravity constraints, not postural constraints. Electrical stimulation of the nervous system offers this effort the potential for postural adaptability that partial weight bearing cannot achieve.

DISCUSSION

One successful interface between neural regeneration and functional stimulation of the brain has already been achieved. A number of Parkinson's patients have gotten significantly better after receiving transplants of dopamine-producing human fetal cells. Dopaminergic neurons were generated in the basal ganglia of the Parkinson's patients, but the neurons were deafferented and not subject to the same dynamic controls that exist under normal conditions. However, over time, a number of these patients became toxic on the dopamine and were treated with deep brain stimulation to counteract the negative effects. This suggests that perhaps regeneration alone is not the answer and illustrates the advantages of electrical stimulation. The high-spatial and temporal resolution of electrical stimulation cannot only be viewed as a tonic for regeneration, but it can also be used to reestablish the necessary command and control systems.

In regeneration research there are essentially three methods to assess outcome: histological, behavioral, and electrophysiological. Ideally, all three methods should be used as they provide important overlapping views into the mechanisms of recovery. There have been cell transplant studies to examine axonal regeneration in transected rat spinal cord in which the anatomical and behavior studies have shown interesting results. However, when electrodes were used to record field potentials, it was clear that within the transection there was nothing conducting up the dorsal columns. The techniques are perhaps more difficult; however, the expertise exists in the neural prostheses field to conduct very definitive electrophysiological analyses. Thus, this would appear to be a crucial area for collaboration.

There are also several testable hypotheses that would best be explored collaboratively. Could electrical stimulation be used in the subchronic time period to limit or prevent delayed apoptosis of oligodendrocytes? Will optimizing neural activity enhance regeneration? Do antispasmodic medications (e.g., baclofen) reduce neural activity and inhibit regeneration? Can electrical stimulation be used to modulate new cell birth and survival? Is activity below the level of the injury suboptimal such that cell birth is reduced rendering adequate replacement of cells impossible, or is activity reduced such that cells are unable to migrate to or survive in the appropriate region? Can electric fields or electrical stimulation be used to modify guidance pathways or migration of cells? In constraint-induced forced use studies, for example, stroke patients who are made to use their impaired arm experience improved functional outcomes (37,38). However, in animal experiments if there is too much use too soon, the injury can be made worse (39,40). Do these results represent examples of the benefits of appropriately timed increased neural activity in the injured cortex? Can similar activity be used to enhance functional outcomes in SCI?

From the research sponsor's perspective in the United States, there is a paucity of good, imaginative grant applications that apply electrical stimulation to new venues such as regeneration. For example, there is an often-used statistic that only 10 percent of cortical spinal neurons need be intact to promote locomotion in cats (41). What if it were possible to regain one percent of the

corticospinal tract using regeneration strategies? It may be an insufficient amount for functional recovery, but what if electrical stimulation could be used to amplify existing neural control signals that have been created by regeneration? The National Institutes of Health (NIH) has received few grant applications looking at this type of possible combination of techniques. There are many opportunities for investigators to write small exploratory grants that do not require pilot data. Many of the NIH institutes support small grants (R03). Many are issuing special requests for exploratory grants (R21). There is an extensive literature using electrical stimulation on the effects of different stimulation parameters and electrodes on different tissues. By establishing good collaborations with experts in transplantation and regeneration, investigators expert in electrical stimulation could team up to conduct very exciting and groundbreaking interdisciplinary research.

CONCLUSION

Many potential interfaces exist between electrical stimulation and regeneration. The potential to use electrical stimulation to limit secondary death and to regulate the efficacy of transplantation should be explored. The potential to stimulate remyelination, progenitor turnover, and survival should also be explored, as should the capability of stimulation to regulate progenitor migration. In addition, the possibility of using electrical activity to modulate axonal regeneration and guidance, as well as spasticity, should be jointly investigated. Collaborative teams should study the potential of electrical stimulation to optimize or drive central pattern generators. If a critical look is taken at all the work done in the last 20 years, it could be argued that regeneration research has been done under the worst settings, i.e., lack of neural stimulation and activity; or under the best settings, i.e., complete transection followed by immediate treatment. Perhaps the next 20 years of work should include a focus on a merger of these complementary approaches to restore function in order to achieve the common goal.

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