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CLINICAL VIEWPOINT

Development of a Circuit for Oscillating Field Stimulation

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Abstract. Weakly applied electrical fields not only promote growth of damaged axons in the Central Nervous System but also provide them with directional cues to grow in the desired direction rather than random sprouting. The responses of nerve processes are polarized; with faster growth towards cathode and repulsion from the anode after a latent period of 30 minutes. This asymmetric response is the basis of Oscillating Field Stimulation (OFS) that requires the polarity of the field to be reversed every 15 to 30 minutes, thereby ensuring neurite growth regardless of the perceived polarity. However these previously designed stimulators provide limited period of stimulation due to battery life constraints and need to be explanted afterwards. We have proposed a circuit design for an externally powered programmable implantable extra-spinal electrical stimulator (pIEES) for application in an animal model of spinal cord injury. This particular design allows the stimulator not only to provide long term stimulation but can communicate with a host computer for reprogramming if required thus eliminating the need for second surgical procedure for explantation. This can be of value when studying the therapeutic potential of long-term application of weak pulsed electrical field to encourage spinal reconnection in adult rats.

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Abbreviations used: CNS, central nervous system; PNS, peripheral nervous system; OFS, oscillating field stimulation; SCI, spinal cord injury.

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1. Introduction

Advances in neuroscience have shown that adult central nervous system (CNS) has in fact got a limited inherent regenerative ability after injury. After spinal cord injury and subsequent nerve damage, surviving neurons have been shown to sprout and elongate in an effort to bridge the gap created by the injury but fail to do so [1]. Axonal regeneration is the ability to extend the tip of the proximal portion of a severed axon. This tip of the growing axon called growth cone has got the ability to sense cues from the environment and steer the axon to grow in one direction or another. Recent progress in cellular and molecular biology and transplantation techniques has made it possible to induce axonal growth by manipulating the intrinsic processes that limit the CNS regeneration via neutralisation of growth inhibitory factors and promotion of various endogenous growth-promoting factors. Another concept in neural regeneration is of axonal guidance which help the regenerating axons to grow in the desired direction [2]. Regenerative studies done in the peripheral nervous system (PNS) axons have demonstrated that for successful regeneration the growing axons need a guidance channel to follow so that growth can happen in the appropriate direction [3]. In case of PNS this guidance is provided by the Schwann cells which are missing in the CNS. In the absence of such guidance, axonal growth results in a haphazard sprouting [4].

Steady, polarized extra-cellular voltage gradient are a normal environmental component in the early developing nervous system and are required for cranial-to-caudal development [2, 5]. Interfering with these endogenous electrical fields interferes with the morphogenic fields in the embryo thus certifying their role in normal development [6]. These currents have also been found after a wound when tissue regeneration is required [7] suggesting that endogenous currents play some causal role in morphogenesis.

It has been demonstrated that the single nerve processes react within minutes of exposure to an applied DC electric field [8]. The growing nerve fibres respond immediately to voltage gradient and tend to orient themselves parallel with the long axis of the voltage gradient. Another important phenomenon observed was the directional response of the growing nerve fibres within the imposed electrical field. The position of the electrodes determines the direction of neurite growth. Within minutes of exposure, neurites tend to grow three times faster towards the cathode electrode in DC field between 70 and 140 mV/mm. However after a lag period of 30 minutes or so following the exposure to voltage gradient the neurites facing the anode start to regress as if being repelled by the anodal electrode [9]. The observation that neurites grow faster towards the cathode and are repelled by the anode after the imposition of a DC electric field has led to the development of a special stimulatory technique referred to as Oscillating Field Stimulation (OFS) [10]. This asymmetric response requires the polarity of the field to be reversed every 15 to 30 minutes, thereby ensuring neurite growth occurs regardless of the perceived polarity. An implantable device reverses the polarity of the applied field being exposed to the injured axons every 15 minutes. Thus facilitates the cathodal growth before the anodal regression sets in, and leads to a bidirectional axonal growth so that they may grow in the right direction and be able to cross the cleft created by the injury. Two randomised double-blinded clinical trials were conducted in canines with naturally occurring SCI to evaluate the efficacy and biocompatibility of the implantable OFS device [11, 12]. The OFS device was implanted for a period of 14 weeks. The dogs were evaluated for behavioural recovery at 1 week, 6 week and 6 month after injury. Significantly greater neurological improvement was observed in the OFS treated group. The dogs regained the ability to walk, albeit not perfectly. The ascending and descending axons projected to the plane of transection, whereas degeneration of ascending and descending axons was seen in sham-treated control animals. The device also proved to be safe. The FDA approval for the 'human use OFS device' was attained in late 2000 and the first phase-I human clinical trial began in 2001. In this trial, OFS was surgically implanted in 10 patients with acute neurologically complete SCI between C5 and T-10 [10]. Patients also underwent intrave-

nous methylprednisolone therapy according to the NASCIS III protocol prior to the entry into the trial. OFS was implanted within 18 days of sustaining the spinal cord injury (SCI) and left in place for 15 weeks. At the end of this period it was explanted and studied for bio-compatibility. Patients were observed for functional recovery at 6 weeks, 6 months, and 12 months. The net gain in neurological improvement was assessed. Significant neurological improvement from baseline in motor and sensory function was observed in all the patients except for one patient who was lost to follow up. The outcome measures included behavioural assessment of recovery and electrophysiological studies. All patients reported improvement in proprioceptive and exteroceptive sensations. The application of the device was safe and well tolerated by all the patients. Based on the positive data from this phase-I trial, FDA had given approval for 10 additional patients to be enrolled in the study [10]. However, there are no conclusive reports on long term in vivo OFS stimulation. This is mainly because the OFS stimulators that were used in these previously reported studies could only provide a fixed period of stimulation ranging a few weeks because of the inability to produce current for longer periods of time. There is a need to develop an implantable extra spinal stimulator that does not rely on an internal power source and thus can provide ongoing oscillating field stimulation in order to evaluate the optimum duration and therapeutic potential of stimulation for maximal axonal growth and functional reconnection.

2. Hypothesis

It is predicted that if longer periods of oscillating field stimulation can be provided to the acutely injured spinal cord, the degree of axonal regeneration and the associated functional recovery will be much more than shown in the phase I trials of OFS stimulator.

3. Materials and Methods

We have developed a novel microprocessor controlled programmable electrical stimulator circuit that is small enough (5 mm x 18 mm) to be implanted within a subcutaneous pocket near the spinal cord of rats. The design is novel in that power is drawn from an external source using electromagnetic induction and thus requires no battery source, greatly decreasing the size of the unit and the technical/maintenance problems associated with an internal battery source. The various electrical components of the stimulator are composed of platinum and inert silicone polymer, both bio-compatible materials that are known to minimize tissue reaction. The stimulator can be controlled externally using pulse-code modulation of the electromagnetic drive source to select the polarity of the stimulation pulse. The stimulator can energize two electrodes surrounding the damaged portion of the spinal cord and deliver precisely controlled pulses at low current. The amount of current applied will be barely above the detectable threshold, just enough to guide the cells of the injured spinal cord to grow in the direction of the current. Since the current will be of low magnitude, and the stimulus will be localized to the damaged spinal cord, there will be no neuro-muscular contraction response in the animals.

4. Discussion

Devices which rely on an internal battery source for generation of electric current have limited operational duration and need to be explanted after a fixed period of time. Once the battery expires it no longer serves the purpose and is merely a source for inflammatory and foreign body reaction. Our prototype stimulator by not relying on an internal battery for generation of electrical current can cause bidirectional axonal regeneration without a time frame constraint thus providing a better stimulation regime without an interruption. Stimulation can be for as long as is required. Since there is a possibility of ongoing stimulation regime there is no need to explant the device thus minimizing the surgical interventions and the associated risks. By eliminating the need for an internal battery for current generation, we have also limited the technical problems such as wire breakage etc. associated with it.

A major consideration in the design of this postulated stimulator module was the accessibility of the micro-controller to permit reprogramming. The module chosen is small enough for insertion into the subcutaneous pocket yet not so small as to preclude its (hand) manufacture using miniature surface mount components. Our stimulator measures approximately 2.0 cm × 0.6 cm in size. By reducing the physical size of the implantable stimulator we can limit the amount of tissue reaction in the body as well as the extent of invasive surgery required for implantation and which in turn would result in less intra- and post-operative complications.

For the present application of this module, an animal model of spinal cord injury will be created by transecting the spinal cords of rats. During the same surgical procedure the pIEES assembly will be implanted subcutaneously within the test animal (rat) so that the long axis of coil L1 is aligned with the axis of the energizing drive coil. Since the rats will not be mobile therefore the coil will maintain the parallel alignment with drive coil. Nevertheless, it is possible that the pIEES coil would not be optimally oriented at all times during the treatment and in the worst case; the device could cease to function due to lack of power. This would be a momentary event and could be corrected by moving the animal so the coil is again in alignment. With the present system, there is no way of electronically detecting the loss of power and the experimenter must continually monitor the treatment.

A coil of the same dimensions and nominally the same electrical characteristics of the pickup coil L1 connected in parallel with a red LED and mounted on a supporting shaft (3 mm diameter x 200 mm long) could be used to probe the drive coil chamber and provide a visual indication of field strength. During treatment of the animal, the probe can be left within the chamber to alert the operator to any problems with the energizing field.

Currently we are working on in-vitro testing and encapsulation of the device. It is important to encapsulate this module with a biocompatible layer. We plan to deposit a conformal layer of the inert polymer Parylene C (mono chlorine substituted poly- *p*-xylene). This material forms a very tough impermeable layer with excellent barrier resistance. Parylene C coated devices are reported to be stable, exhibit little or no change in response characteristics and are electrically and chemically isolated from the body [13, 14]

The functional loss seen in SCI is due to interruption of electrical impulse conduction through the lesioned axons. Intrinsic circuits below the level of injury remain intact but disconnected from the descending controls of cerebral cortex. Our newly designed microprocessor based stimulator by stimulating indefinitely may provoke long term bidirectional growth response in the sprouting nerve fibres.

Neural repair and regeneration is still in its infancy stages when it comes to replicating various experimental regenerative therapies for human spinal cord injuries. The present application of this type of stimulator is in promoting nerve growth and eventual synaptic connection between the two ends of the transected nerve fibres. If future experiments show positive results then several other applications come to one's mind where long term regenerative stimulation might be of help such as in chronic degenerative conditions in CNS or PNS. Similarly another paradigm would be to combine this technique with another established method of regeneration e.g. growth promoting factors like Nerve Growth Factor (NGF). This combination may result in faster growth rate in the desired direction rather than random growth and better output in functional recovery.

References

1. **Gurgo RD, Bedi KS, Nurcombe V** [2002] Current concepts in central nervous system regeneration. J Clin Neurosci 9: 613-617.
2. **Borgens RB** [2003] Restoring function to the injured human spinal cord. Adv Anat Embryol Cell Biol 171: III-IV.
3. **Fawcett JW, Keynes RJ** [1990] Peripheral nerve regeneration. Ann Rev Neurosci 13: 43-60.
4. **Tatagiba M, Brosamle C, Schwab M**E [1997] Regeneration of injured axons in the adult mammalian central nervous system. Neurosurgery 40: 541-546.
5. **Shi R, Borgens RB** [1995] Three-dimensional gradients of voltage during development of the nervous system as invisible coordinates for the establishment of embryonic pattern. Dev Dyn 202: 101-114.

6. **Hotary KB, Robinson KR** [1994] Endogenous electrical currents and voltage gradients in Xenopus embryos and the consequences of their disruption. Dev Biol 166: 789-800.
7. **Borgens RB, McGinnis ME, Vanable JW Jr, Miles ES** [1984] Stump currents in regenerating salamanders and newts. J Exp Zool 231: 249-256.
8. **Jaffe LF, Poo MM** [1979] Neurites grow faster towards the cathode than the anode in a steady field. J Exp Zool 209: 115-128.
9. **Patel N, Poo MM** [1982] Orientation of neurite growth by extracellular electric fields. J Neurosci 2: 483-496.
10. **Shapiro S, Borgens R, Pascuzzi R, Roos K, Groff M, Purvines S, Rodgers RB, Hagy S, Nelson P [2005] Oscill**ating field stimulation for complete spinal cord injury in humans: A phase 1 trial. J Neurosurg Spine 2: 3-10.
11. **Borgens RB, Toombs JP, Blight AR** [1993] Effects of applied electric fields on clinical cases of complete paraplegia in dogs. J Restorative Neurol Neurosci 5: 305-322.
12. **Borgens RB, Toombs JP, Breur G, Widmer WR, Waters D, Harbath AM, March P, Adams LG** [1999] An imposed oscillating electrical field improves the recovery of function in neurologically complete paraplegic dogs. J Neurotrauma 16: 639-657.
13. **Chang TY, Yadav VG, De Leo S, Mohedas A, Rajalingam B, Chen CL, Selvarasah S, Dokmeci MR, Khademhosseini A** [2007] Cell and protein compatibility of parylene-C surfaces. Langmuir 23: 11718-11725.
14. **Schmidt EM, McIntosh JS, Bak MJ** [1988] Long-term implants of Parylene-C coated microelectrodes. Med Biol Engineering Computing 26: 96-101.