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Editorial

# The Electric Fields and Neural Stem Cells in the Treatment of Neural Injury

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## EDITORIAL

Nearly 1 of every 50 people (approximately 6 million) in the United States lives with at least some degree of paralysis. Paralysis occurs as the result of various nervous system injuries and/or neurological diseases. The research of treatment of paralysis is significant for the society. The application of electric fields (Efs) as a therapeutic strategy for the treatment of damaged nerves has been explored since the early twentieth century [1], with primary success to date being observed in amphibian, avian and mammalian models of neural injury.

Efs used in neural injuries, especially in spinal cord injury, have been studied for decades. In animal models of spinal cord injury, researchers found that artificially applied direct current electrical fields(DCEfs) increased the growth of axons after the transection of spinal cord in the larval lamprey *Petromyzonmarinus* [2] and in guinea pigs after transection of dorsal column axons [3]. The above studies suggest Efs play a critical role in the regeneration of neural injury. Evidence has showed that DCEfs induced neurite growth toward the cathode in Xenpus spinal neurons [4] and rat spiral ganglion neurons [5]. Pan and Borgens (2010, 2012) found that neurite growth in chick sympathetic neurons and dorsal root ganglion (DRG) was directed by DCEfs [6,7]. Neurites in both chick sympathetic neurons and DRG that were not perpendicular to the DCEfs rapidly began absorbing within minutes of exposure, and finished the absorption of the processes into the cell body within 1-3 hours. Over the next 3 hours, significant new neurite growth occurred, and was patterned perpendicular to the DCEfs. Another finding in these two studies was that the neurite orientation diminished after Efs were tuned off [6,7], supporting neurite outgrowth may be Ef-dependent. In addition to DCEfs, alternating current electrical fields (ACEfs) stimulation also affected neuronal growth and caused an increase in neurite length and better viability in PC12 cells [8]. Oscillating field stimulator (OFS), which delivers 500-600μV/mm of direct current and switch polarity every 15 minutes, can improve recovery of spinal cord injury in dogs [9]. OFS has also been used in a Phase 1 clinical trial, in which OFS was implanted into spinal cord injury patients and found improved recovery [10]. The results of Phase 1 clinical trial of OFS were found that oscillating electric field benefited spinal cord injury patients, indicating the efficacy and safety of the application of Efs. Asymmetrical alternating electrical fields (AACEfs), in which each component of the waveform, including the duration of positive and negative stimulation time as well as the relative intensity of both polarities can be adjusted, were first reported by Pan et al. in 2012 [11]. In this study, the effects of AACEfs on chick sympathetic neurons were investigated. The authors found that AACEfs induced a rapid retraction of neurites that prior to exposure were parallel/ tangential to the lines of force. The latter was determined to be less than 15° from perpendicular to the long axis of the experimental chamber (or alternately, perpendicular to the lines of force of the imposed AACEfs). These neurites retract rapidly beginning less than 5 min after exposure and began to regrow / re-extending to a preferred orientation perpendicular to the lines of force of the given AACEfs. The research by Pan et al. (2012) indicates that AACEfs direct neurite outgrowth of neurons and may be a potential therapy for neural injury. Those above in vivo and in vitro studies have built up a great support that Efs, including DCEfs, ACEfs, OFSand AACEfs, can benefit nerve system recovery after neural injuries.

Neural stem cell transplantation as a promising therapeutic strategy for promoting tissue repair after neurological diseases has been widely studied in both the central and peripheral nervous systems. Since NSCs were first isolated, neural stem cell transplantation has been broadly used in many neurological disease models, e.g. Parkinson's disease, fimbria-fornix lesions, and spinal cord injury [12-14]. In peripheral nervous injury, NSC transplantation can induce remyelination and axon regeneration [15,16]. Many studies have shown that NSC migration, proliferation and differentiation are regulated by both external and cell-intrinsic signals, including signalling molecules [17], growth factors [18], neurotransmitters [19], transcription factors [20,21], epigenetic regulators [22,23], as well as Efs [24, 25]. Among these factors, Efs are being studied more and more during the last decades [4,8,24,26]. Efs may guide NSCs to migrate to their appropriate destination and then induce NSCs to differentiate into different neural cells. The applied DCEfs of physiological magnitudes (up to 500 mV/mm)can guide neural stem cells that are derived from adult rats [24], human embryonic stem cells [26], and fetal rats [27] to migrate towards the negative pole. Biphasic electric current, a pulsed alternating current stimulation, has been reported to increase the proliferation of

NSCs and promote the NSC differentiation into neurons [28]. In the study of biphasic electric current, the authors found that NSC proliferation and differentiation were related to the magnitude of the electric current and the duration time of stimulation [28]. Matos & Cicerone (2010) studied the effects of ACEfs with different frequency (0.1-10 Hz) and strength (2, 4, and 16V/m) on NSC differentiation [20]. They found high frequency (1Hz) induced more astrocyte differentiation over neuronal differentiation and marked peak in NSC viability, but high field strength (16V/m) was more associated with neuronal differentiation, indicating NSC differentiation is related to frequency and strength of ACEfs. Based on the above literature, the characteristic of Efs (e.g. field strength and frequency/pulse) can influence NSC migration, proliferation and differentiation. AACEfs were found to direct mouse NSC migration in an unpublished study. In this study, three different formats of the AACEfs were used. In these three formats of AACEfs, the current outputs and the positive polarity duration time were same, but the negative polarity duration time and the latency, which is prior to reversal of polarity, were different. The format of AACEfs, which had the shortest polarity duration time and latency, had the optimal effect on NSC migration and NSCs migrated towards negative pole dramatically compared to other two formats of AACEfs. One of the important advantages of AACEfs is that their waveform components can be adjusted optimally based on the request of NSC status, such as migration, proliferation or differentiation.

Therefore, adjustable waveform components of the applied Efs should be a better strategy for researchers to investigate the therapy of neural injury. The combined research of AACEf and NSC would serve as a positive impact for a therapy to treat neural injuries.

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