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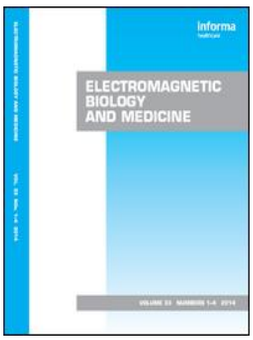

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Extremely low-frequency electromagnetic fields: A possible non-invasive therapeutic tool for spinal cord injury rehabilitation

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ABSTRACT

Traumatic insults to the spinal cord induce both immediate mechanical damage and subsequent tissue degeneration. The latter involves a range of events namely cellular disturbance, homeostatic imbalance, ionic and neurotransmitters derangement that ultimately result in loss of sensorimotor functions. The targets for improving function after spinal cord injury (SCI) are mainly directed toward limiting these secondary injury events. Extremely low-frequency electromagnetic field (ELF-EMF) is a possible non-invasive therapeutic intervention for SCI rehabilitation which has the potential to constrain the secondary injury-induced events. In the present review, we discuss the effects of ELF-EMF on experimental and clinical SCI as well as on biological system.

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Extremely low-frequency electromagnetic field; recovery; regeneration; secondary injury; spinal cord injury

Introduction

Sir Ludwig Guttmann (Sperryn, 1976), the great pioneer in the field of spinal cord injury (SCI) rehabilitation, reported that SCI, for certain, is one of the greatest disasters to human beings. It is one of the most debilitating pathologies, leading to huge rehabilitation challenges (Campagnolo et al., 2000; Wu and Ren, 2009). It is not only incapacitating to the affected individual but also impinge on quality of life of the affected family (Lin et al., 2004). SCI leads to serious disability in movement but may also cause dysfunctions of many organs, including the respiratory, gastrointestinal, urinary and autonomic nervous system, as well as skin, bone and joints, depending upon the level and severity of injury. The involvement of multiple organ system could be one of the causes for high mortality rate during both acute and chronic stages of SCI (Chiu et al., 2010). Worldwide, an estimated 2.5 million people live with SCI, with more than 13×10^4 new injuries reported annually (Thuret et al., 2006).

Pathophysiology of SCI

SCI leads to an immediate hind limb paralysis, lack of reflexes and loss of sensation below the level of injury and bowel and bladder dysfunction with significant residual complications of marked chronic pain and osteoporosis (Basso et al., 1996; Christensen and Hulsebosch, 1997). Pathophysiology of SCI is contributed by both primary (acute) and secondary mechanisms (chronic) of injury.

Primary injury

Initial mechanical trauma includes direct compression of spinal cord tissue by fractured and displaced bone fragments, disc material and ligaments injuring both the central nervous system and peripheral nervous system. Blood vessels are damaged, axons disrupted and neural cell (neuronal) membranes broken. Microhemorrhages occur within minutes in the central gray matter and spread out radially and axially over the next few hours. Within minutes, the spinal cord swells to occupy the entire diameter of the spinal canal at the injury level (McDonald and Sadowsky, 2002).

Secondary injury

The secondary injury begins minutes after the primary injury and is a progressive degeneration that can last from several months to years (Park et al., 2004). It comprises a battery of vascular, biochemical and cellular disturbances that result in the formation of glial scar at the injury site. This scar is not only a mechanical, but also a chemical barrier, secreting a number of molecules that inhibit axonal growth, including chondroitin sulfate proteoglycans (Yiu and He, 2006). However, it also provides several beneficial functions after SCI, such as limiting damage by re-establishing the blood–brain barrier and by preventing an overshooting

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inflammatory response (Faulkner et al., 2004; Okada et al., 2006; Sofroniew, 2005). The summary of events occurring during secondary injury is enumerated in Figure 1 (Adapted and modified, Hausmann, 2003).

Although SCI initiates a secondary phase of progressive degeneration, it also initiates a number of neuroprotective and regenerative responses in the central nervous system (Hagg and Oudega, 2006). Regenerating axons can be observed within the first 24 h after injury (Kerschensteiner et al., 2005), a process called abortive sprouting (Schwab and Bartholdi, 1996). However, this regenerative process leads to minimal functional improvement. Functional plasticity and local circuit formation/adaptation in the spinal cord may contribute to the spontaneous behavioral improvement seen in rodents as well as in humans after incomplete SCI (Bareyre et al., 2004; Edgerton et al., 2004; Frigon and Rossignol, 2006).

Treatment strategies for SCI

Over the last few years, research work has been done using *in vitro* and *in vivo* approaches on improving SCI repair, functional restoration and recovery, accounting to a partial success, but only a limited success is achieved so far (Joo et al., 2012). The therapies proposed generally fall under one of two classifications: (i) those that block cues that inhibit regeneration and (ii) those that provide or enhance growth-promoting cues. Many combinatorial and singular therapies employ both approaches and thereby target at halting the spread of secondary tissue damage, curbing inflammation, reducing glial scar formation, neutralizing inhibitory factors, stimulating nerve fibers to regrow, nourishing surviving nerve cells, promoting physical fiber growth across the injury area, directionally guiding physical growth and enabling connection establishment (Bunge, 2008).

Epidural stimulation and locomotor training are among the most recent recommended combinatorial therapies proposed for recovery from SCI in experimental animals (Gad et al., 2014; Gerasimenko et al., 2008) and patients (Angeli et al., 2014; Dietz and Fouad, 2014; Harkema et al., 2011). However, the challenge of this technique is its invasiveness of surgically implanted electrodes epidurally or even penetration into the "healthy" parts of the spinal cord (Dietz and Fouad, 2014). Thus, non-invasive spinal electromagnetic stimulation which is better than epidural in several ways and tested on SCI patients has been recommended by the same group of scientists (Gad et al., 2015; Gerasimenko et al., 2010). Further, there are reports which highlight the potential of electromagnetic fields (EMFs) (Gerasimenko et al., 2010).

Electromagnetic fields (EMF)

An EMF, a property of space, is caused by the motion of an electric charge. A changing magnetic field (MF) produces an electric field (EF), as the English physicist Michael Faraday discovered in work that forms the basis of electric power generation. Conversely, a changing EF produces a MF, as the Scottish physicist James Clerk Maxwell deduced. The EF and MF travel together through space as waves of electromagnetic radiation, with the changing fields mutually sustaining each other. The mutual interaction of EF and MF produces EMF which is considered as having its own existence in space apart from the charges or currents (a stream of moving charges) with which it may be related. Under certain

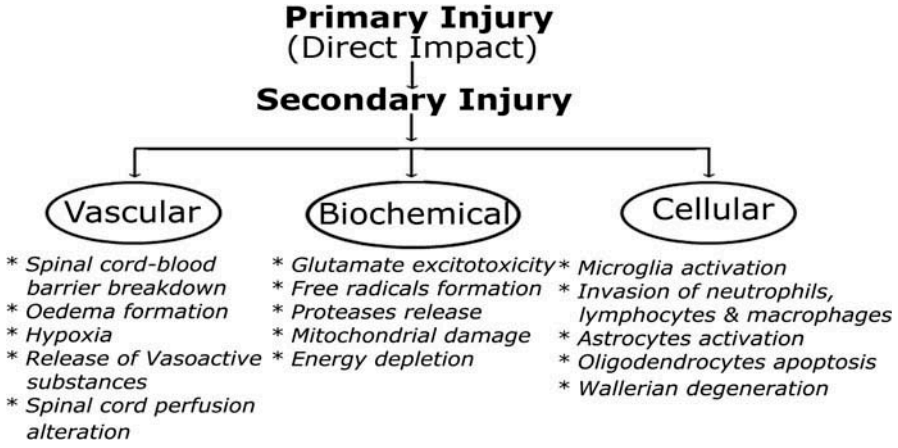

Figure 1. Summary of events following spinal cord injury.

circumstances, this EMF can be described as a wave transporting electromagnetic energy. Examples of electromagnetic waves travelling through space independent of matter are radio and television waves, microwaves, infrared rays, visible light, ultraviolet light, X-rays and gamma rays. Particularly nowadays, due to close integration of wireless communications into our daily lives, EMFs are all around us.

There are two main forms of EMFs: radiofrequency (RF)-EMF and extremely low frequency (ELF)-EMF. The frequencies of RF-EMF (100 kHz to 300 GHz) are considerably higher than ELF-EMF (0–100 Hz). The main uses of RF-EMF are in broadcasting information, whereas, it is the ELF-EMF which is of biological significance. The Earth's natural geomagnetic field strength varies from ~60 μT at the magnetic poles to ~30 μT at the equator (Spencer et al., 2010). In the present review, studies are included which have used 0–100 Hz frequency with micro-tesla to tesla EMF intensity.

Effect of ELF-EMF on Biological System

Life on earth evolved in a sea of natural EMF. However, over the past century, this natural environment has changed with a huge and fast growing spectrum of man-made EMF. In eukaryotes, narrow fluid channels surrounding each cell play an important role in cell–cell signaling. These channels (150A° wide) act as windows on the electrochemical world surrounding each cell. They also act as routes for hormones, antibodies, neurotransmitters and chemicals to reach their binding sites on cell membrane (Adey, 1992). Since they offer much lower electrical impedance than cell membranes, they are also preferred pathways for intrinsic and environmental EMF. Although this intercellular space forms only about 10% of the conducting cross-section of typical tissue, it carries at least 90% of any imposed or intrinsic current and directs it along the cell membrane surface. The ELF and RF-EMF, if amplitude modulated in the range of 0–100 Hz, produces tissue gradients in the range 10-'-10–1V/cm. This has been shown to mediate certain essential physiological functions in marine vertebrates, birds and mammals (Adey, 1981).

The ELF-EMF, which is produced by alternating current between 30 and 300 Hz, is mainly generated by power distribution networks, industrial machinery and electric appliances (WHO, 2007). General public is thereby exposed continuously to ELF-EMF on a daily basis in industrialized nations. Therefore, the biological effects of ELF-EMF have been a subject of exploration for a long period of time. A great deal of research has been focused on the possible relationship between ELF-EMF and their effects on variety of biological processes (Nordenson et al., 1994; Santini et al., 2009; Santoro et al., 1997; Tonini et al., 2001). Biological systems respond to a wide range of EMF. Most of the effects reported so far indicate that the majority of ELF-EMF is tolerated by the living organisms without detectable detrimental effects (Kroupova et al., 2007). The ELF EMF can influence enzyme action, signal transduction, protein synthesis and gene expression, which have important role in cell growth (Kula et al., 1991).

Effect on gene expression and oxidative stress: Proteins are key players in organisms, and it has been assumed that any biological impact of ELF-EMF may be mediated by alterations in protein expression (Phillips et al., 1992); for example, heat-shock proteins have been identified as EMF-responsive genes and/or proteins in certain biological systems (Goodman et al., 2009). Cells respond to ELF-EMF via changes in transcription and translation of heat-shock protein (Carmody et al., 2000; Goodman and Henderson, 1988; Goodman et al., 1994; Lin et al., 1998, 1999).

The hsp70 protein is cyto-protective and has been shown to act as a "chaperone" to refold and restore the function of cellular proteins after damage by injury or inflammation (Morimoto, 1998). Goodman et al. (2009) showed that ELF-EMF (60 Hz, 80 mG, 1h × 2/day for 15 days) significantly facilitates the regeneration of tail and head within 3 days of exposure after complete transection of Planaria *Dugesia dorotocethala* from the middle. These ELF-EMF-exposed heads and tails also exhibited an elevation in the level of hsp70 protein, an activation of an extracellular signal-regulated kinase (ERK) cascade and an increase in serum response factor-element (SRF-SRE) binding that are generally associated with repair processes. Li et al. (2005) in human breast cancer cell line MCF-7 performed a proteomics approach to investigate the changes of protein expression profile induced by ELF-EMF exposure (0.4 mT, 50 Hz × 24 h). Three proteins that decreased their expression were RNA-binding protein regulatory sub-units, proteasome sub-unit β-7 precursors and translational controlled tumor protein. Sulpizio et al. (2011) investigated protein expression post ELF-EMF (50 Hz, 1 mT) at different times in human SH-SY5Y neuroblastoma cells. There were nine new proteins resolved in the sample after 15 days of treatment, and these were either involved in a cellular defense mechanism and/or in cellular organization and proliferation. The authors also showed that the exposure altered the cell proliferation and cell viability.

In addition, the exposed cells showed a higher and more widespread expression level of α-tubulin, especially in the periphery of cell clusters, compared to control cells, suggesting that the exposure induces a

spatial orientation of cells. The authors hypothesized that EMF exposure triggers a shift toward more invasive phenotype (Chen and Xu, 2013). Recently, Patruno et al. (2015) showed that short exposure (1 h or 24 h) of ELF-EMF (50 Hz, 1 mT) to HaCaT cells (keratinocyte cell line) modulates distinct patterns of gene expression which are involved in cell proliferation and in the cell cycle. They found that an increase of the canonical pathway of mTOR regulation (PI3K/Akt) and activation of ERK signaling pathways related to pivotal biological processes and function in wound healing. This raises a possibility that ELF-EMF may serve as a potential tool for manipulating neuronal death and/or survival (Oda and Koike, 2004). With regard to their effects on signal transduction in non-neuronal cells, both positive and negative results have been reported (Uckun et al., 1995; Woods et al., 2000).

Metabolic processes which generate oxidants and antioxidants can also be influenced by ELF-EMF. Increased EMF exposure can modify the cellular balance by generating reactive oxygen species. Physical processes at atomic level is the basis of reactions between bio-molecules and EMF, as the field can magnetically affect chemical bonds between adjacent atoms and alter the energy levels and spin orientation of electrons. It thereby modulates the redox status of cell, leading to reactive oxygen species generation which induces DNA damage, thus acting as a cancer initiator in different cell types (Lai and Singh, 2004; Wolf et al., 2005). Absence of genotoxicity in cells exposed to ELF-EMF has also been shown, suggesting that excessive oxidative stress may not be induced due to ELF-EMF exposure (Amara et al., 2007). The WHORA-2007 has classified the *in vitro* studies regarding the evaluation of reactive oxygen species into a high-priority line of inquiry in the research field of biological effect of EMF. *In vitro* study of human breast epithelial MCF10A cell have shown that ELF-EMF exposure did not increase intracellular reactive oxygen species, superoxide dismutase activity and GSH/GSSG ratio (Hong et al., 2012). Similarly, low-level EMF exposure (45 μT) suppressed hydrogen peroxide production in fibrosarcoma cells, whereas superoxide dismutase level increased (Martino and Castello, 2011). There are three different types of literature available namely positive, negative and no effects on oxidative stress/free radical formation by ELF-EMF exposure depending upon the exposure time, model, magnetic force, parameters studied and type of exposure (acute/chronic/intermittent).

Bioinitiative report, 2014 (www.bioinitiative.org), mentioned that the relation of oxidative stress with ELF-EMF and their role on neurological/behavioral effects has not been carefully considered taking into the account of other physiological factors (e.g. sex, age, stress, etc.) that can influence the response of ELF-EMF. Falone et al. (2008) studied the effect of age on ELF-EMF (50 Hz, 0.1 mT for 10 days)-mediated oxidative stress. They observed an increase in antioxidative enzymes and defense against oxidative damage in brains of young rats, whereas that of old rat showed a decrease. Janac et al. (2012) reported age-dependent effects of ELF-EMF on locomotor activity in the Gerbils. Sun et al. (2010) reported that, after *in ovo* exposure to ELF-EMF, chicks showed memory deficit only when they were under stress. A short-term EMF exposure increases the lipid peroxidation in brain while long-term exposure decreases it (Ciejka et al., 2011). Exposure to 2.45 GHz microwave increases the apoptotic activity and DNA damage of cell, whereas the EMF exposure of 100 Hz relieves this effect (Kumar et al., 2011).

Brain-derived neurotrophic factor (BDNF) plays an important role in the adaptive responses to oxidative stress and can prevent reactive oxygen species-mediated neuronal cell death (Mattson et al., 2002). Magnetic stimulation also activates the BDNF-TrkB signaling pathway including the MAPK/ERK and PI3K/Akt pathways, to upregulate expression of the downstream effector molecules and synaptic protein markers SYN, GAP43 and PSD95 (Ma et al., 2013), thereby promoting the BDNF role in survival, development, differentiation and regeneration of neurons (Ciejka et al., 2011). An exposure of neurons to 1 mT ELF-EMF causes a significant increase in the mRNA and protein expression of both BDNF ligand and its receptor TrkB (Ciejka et al., 2011). Tasset et al. (2013) showed that ELF-EMF activates the antioxidant pathways *in vivo*. ELF-EMF (50 Hz, 0.7 mT) can modulate the Nrf2 transcriptor factor in a Huntington's disease via an increase in cytoplasm and nucleus Nrf2 levels. It was therefore concluded that it modulates Nrf2 expression and translocation and that may explain the neuroprotective effect as well as its antioxidant and cell protection capacity.

Effect on survival of neurons and neurotransmitters/neuropeptides: There is evidence that the neuroprotective effect of exposure to ELF-EMF may be due to their effect on levels of neurotrophic factors and cell survival. EMF exposure exerts a strong effect on reducing apoptosis in several cell systems (Fanelli et al., 1999) and help in healing process (Milgram et al., 2004). Oda and Koike (2004) showed that ELF-EMF exposure suppresses neuronal apoptosis and promotes survival of mammalian neurons in the central nervous system. The survival-promoting effect of

ELF-EMF is greater than that of neurotrophic factor, BDNF, and comparable to membrane depolarization with elevated K^+ (Oda and Koike, 2004). Since ELF-EMF is mediated through induced currents, higher induced currents are more efficient in suppressing the cell death and promoting survival. These effects are mediated by an increase in Ca^{2+} influx, since its inhibition attenuates EMF anti-apoptotic effect. ELF-EMF enhances neuronal differentiation of cortical neural stem cells *in vitro* through upregulation of Ca v1-channel expression and activity (Kim et al., 2013; Piacentini et al., 2008). The entry of Ca^{2+} through these channels influences the transcription of certain classes of genes that are involved in cell survival and differentiation (e.g. ELF-EMF promotes neural differentiation of bone marrow stromal cells possibly via upregulation of Prdx3 and ferritin expression within these cells) (Kim et al., 2013). *In vitro* study by Wang et al. (2010) showed that EMF (0.23–0.28T) can reproduce the effect of promising class of non-dopaminergic PD drug (ZM241385) in a non-invasive manner. This work on rat PC12 cell line via altering the Ca^{2+} flux increased ATP level and decreased cAMP, nitric oxide, p44/42 MAPK phosphorylation and iron intake. Raus et al. (2012, 2013) also reported that ELF-EMF (50 Hz, 05 mT – 7 days) is neuroprotective *in vivo*. In Gerbils, global cerebral ischemia-induced motor hyperactivity was reduced significantly when these animals were exposed to ELF-EMF continuously. It was further supported by histological evidences where ELF-EMF prevented the cell loss in CA1 region of hippocampus and activated the astrocytes and microglia cells after ischemia (Raus et al., 2013). Thus, ELF-EMF shows neuroprotective efficiency both *in vitro* and *in vivo*.

Neurotransmitters/neuropeptides are endogenous chemicals that enable neurotransmission and play a major role in shaping everyday life and functions. Imbalances in these chemicals have been related to pathogenesis of many diseases namely Parkinson's, depression, insomnia, attention-deficit hyperactivity disorder, anxiety, memory loss, dramatic changes in weight and addictions. Medications that directly react with serotonin and nor-epinephrine are prescribed to patients with diseases such as depression and anxiety disorders (Leo and Lacasse, 2008). There are several studies which show the beneficial role of ELF-EMF on neurotransmitters/neuropeptides with varying etiology, which are discussed in a different section of this review (Arias-Carrion, 2008; Bao et al., 2006; Ben-Shachar et al., 1997; Kanno et al., 2004; Keck et al., 2000; Kumar et al., 2013; Lai et al., 1993; Poirrier et al., 2004; Shin et al., 2007; Sieron et al., 2004). ELF-EMF exposure (10 Hz, 1.8–3.8 mT 1 h/day × 14) does not influence the level of the examined biogenic amines (dopamine, 5-HT) and metabolites but increased their turnover in corpus striatum and frontal cortex of adult male Wistar rats by changing receptor reactivity (Janac et al., 2009) of monoaminergic systems and related behaviors or their agonists and antagonists (Sieron et al., 2004). Bao et al. (2006) showed that an increase in endogenous beta-endorphin, substance P and 5-HT by ELF-EMF exposure (55.6 Hz, 8.1 mT) is associated with analgesic effects in rats. However, Masuda et al. (2011) observed that exposure to ELF-EMF (50 Hz, 1 mT) does not affect the physiological functions mediated by 5-HT1B receptor subtype. Acute treatment with repetitive transcranial magnetic stimulation (TMS) in rodents modulates monoamine content and turnover, but there is no effect on its levels or metabolites after chronic stimulation (Arias-Carrion, 2008). Acute repetitive TMS reduces dopamine in the frontal cortex and increases in the dorsal striatum (Ben-Shachar et al., 1997), ventral tegmental area, nucleus accumbens and hippocampus (Arias-Carrion, 2008). Reductions in arginine vasopressin release and increase in taurine, aspartate and serine are reported in the hypothalamic paraventricular nucleus after EMF exposure (Keck et al., 2000). There are reports which show the role of ELF-EMF on glutamate transmission via N-methyl-D-aspartate (NMDA) receptors as well as its metabolism (Frilot et al., 2014; Kim et al., 2014; Li et al., 2014; Wieraszko et al., 2005).

Effect of ELF-EMF on pain: There have been growing evidence that ELF-EMF has analgesic effects in animals (Martin and Persinger, 2004; Shupak et al., 2004a), and it alleviates pain caused by psoriasis, tendonitis and rheumatoid arthritis (Johnson et al., 2004; Nindl et al., 2000; Thomas et al., 2001). Shupak et al. (2004a) observed increased latencies to the hot plate test (analgesia) in mice exposed to ELF-EMF (100 μT × 30 min). They also reported a decrease in pain following a brief EMF exposure (30 min) in humans (Shupak et al., 2004b). Martin and Persinger (2004) exposed rats for 30 min to a burst-firing ELF-EMF and showed an increase in pain threshold for a period of 4 h after a single exposure. Bao et al. (2006) also observed an analgesia following exposure to ELF-EMF (8.1 mT, 55.6 Hz, 6h/day × 4). They also observed analgesia at day 5, along with elevated levels of 5-HT, β-endorphin and substance P in the brain. However, after a repeated exposure for 14 days, no further increase was evident in behavior as well as in levels of neurochemicals. Various mechanisms for pain modification by EMF have been postulated in the literature, of which opioid-mediated analgesic effect is most acceptable

(Bao et al., 2006). The administration of naloxone abolished or attenuated the analgesic effects of ELF-EMF, confirming the opioid-mediated effects of EMF. Thus, opioid-mediated factors are keys to magnetic anti-nociception research (Kavaliers and Ossenkopp, 1993; Papi et al., 1992). Exposure to ELF-EMF (50 Hz, 17.96 μT, 2h/d × 15, 30 days) decreases tonic pain in intact rats and mice (Mathur et al., 2006; Shupak et al., 2004a), which is opioid mediated since naloxone (opioid antagonist) pretreatment reversed the effect.

Opioid receptor activation may lead to inhibition of neurotransmitter release and/or slow cell firing rate, thereby inducing analgesic effect. Upon activation of δ and μ receptor activation, G-protein subunits interact with multiple cellular effector systems, inhibit adenyl cyclase and voltage-gated Ca^{2+} channels and stimulate G protein-activated inward rectifying K^{+} channels and phospholipase C, thereby inhibiting neuronal activity (Del Seppia et al., 2007). Consistent inhibitory effects of acute exposures to various EMFs on analgesia have also been suggested (Del Sepia et al., 2007). In response to ELF-EMF (10 Hz, 1.8–3.8 mT/day × 14), increased turnover rates of dopamine and 5-HT were also observed (Sieron et al., 2004). This indicates that the effect of EMF on pain is also mediated by several neurochemicals at the supraspinal level. Dopamine and 5-HT plays an important role in the activity of the descending pain pathway. Increased levels of serotonin through the raphe nucleus activate the GABA-ergic neurons of the PAG causing increased inhibition of the dorsal horn neurons which respond to painful stimuli. Thus, ELF-EMF may alleviate pain behavior by supraspinal inhibition of pain responses. In contrary, TMS treatment (60 Hz, 2 and 6 mT, 2 h twice/day × 5) in rats leads to a significant reduction in the nociceptive threshold as compared to sham-treated rats. A slow recovery to normal mechanic threshold was observed after removal of TMS (Ambriz-Tututi et al., 2012).

Effect of EMF on regeneration: EMF stimulation creates intense, rapid EFs that can penetrate soft tissue and bone to reach the nervous system structures. The magnetic pulses produce EF and if the induced current is of sufficient amplitude and duration such that depolarization occurs, neural tissue is stimulated. Thus, MF stimulation improves the microenvironment of the nerve regeneration by stimulating neurotrophic factor release, increasing c-fos gene expression and glial cell migration at the lesion site and decreasing cell apoptosis after neural injury (Grissom, 1995). Wilson and Jagadeesh (1976) first demonstrated that EMF exposure can enhance nerve regeneration in rats. Since then, in last few decades, weak EMFs have been predominantly used to enhance growth and regeneration of the nervous tissue following nerve injuries in experimental conditions. Broad-frequency spectrum of EMF seems to be more essential for the nerve regeneration promotion than their intensity (Bassett, 1993).

In vitro, EMF exposure enhanced neurite outgrowth from cultured spinal cord and peripheral ganglia and *in vivo*, it stimulated regeneration of the sciatic nerve as measured by recovery of function, nerve fiber diameter and number of regenerating fibers in rats (Ito and Bassett, 1983; Raji and Bowden, 1983; Sisken et al., 1990). Bervar (2005) has shown that combining exposure of pulse EMF and sinusoidal EMF promotes earlier onset of functional recovery and more efficient attainment of the functional recovery plateau due to their effect on peripheral nerve regeneration and systemic effect on neuronal cell bodies. ELF-EMF exposure also facilitates adult hippocampal neurogenesis *in vivo* as revealed by neural differentiation markers (Cuccurazzu et al., 2010) and synaptic plasticity in hippocampal neurons in cultures through BDNF-TrkB signaling pathways (Ma et al., 2013).

The exact mechanism of EMF action to promote regeneration is still not known, though several possible candidates have been discovered. Among them, calcium ion, G protein signaling and protein kinase C are most obvious. Besides these observations, EMF stimulation increases neurotrophic factor secretion, their receptor upregulation and modulation of several neurotransmitter levels which collectively suppress the apoptosis and promote cell survival as described previously. Together, all these processes support neuro-regeneration.

ELF-EMF as therapeutic alternative for SCI

SCI is a multifactorial syndrome though its onset is mediated by mechanical trauma. Major factors that can contribute to its etiology are inflammation, oxidative stress/free radical formation, glutamate and serotonin excitotoxicity, mitochondrial dysfunction, gliosis and cell death, leading to the formation of scar. Thereby, there is a need for a therapy that has multiple targets. It is evident from the above discussed review of literature that ELF-EMF has this potential. Thus, it seems to be most suitable possible alternative treatment for SCI rehabilitation.

A number of studies have been conducted on various SCI models. Pulsed EMF has been shown to improve locomotion, restore muscle contraction properties, limit muscle degeneration and spare white matter, leading to smaller lesion volume following SCI (Ahmed and Wieraszko, 2008; Ahmed et al., 2011; Cho et al., 2013; Crowe et al., 2003). Functional magnetic stimulation improves the quality of life of the SCI patients and animal

model by better autonomic control of bladder and bowel; respiratory and coughing capabilities; colon emptying and gastrointestinal liquid transit time (Ahmed et al., 2011; Crowe et al., 2003; Shen and Zhao, 2010). ELF-EMF also leads to an alteration in the expression of genes, leading to osteoblast proliferation and regeneration in SCI (Manjhi et al., 2013) and non-SCI osteoporosis model of aves and rodent (Chang and Hong-Shong Chang, 2003; Diniz et al., 2002a, 2002b; Shen and Zhao, 2010). There was also attenuation of SCI-induced tonic pain and general body conditions following chronic exposure of ELF-EMF (Das et al., 2012; Kumar et al., 2010, 2013; Manjhi et al., 2013). Among several neurotransmitters/chemicals involved in locomotion, 5-HT has a pivotal role since its application to the lower thoracic–upper lumbar spinal cord produces alternating rhythmic activity in the hind limbs (Grillner, 2003). In complete SCI rats, ELF-EMF exposure restored supraspinal (Kumar et al., 2013) and spinal (Poirrier et al., 2004) 5-HT concentration which contributed toward improvement in locomotion as shown by BBB score. Further, the level of 5-HT was restored secondary to resumption of its normal metabolism and regeneration of critical number of descending fiber's which has a significant role in improvement of locomotion (Kumar et al., 2013; Poirrier et al., 2004).

There is a decrease in tonic pain responses after SCI which is restored to eualgesic state by ELF-EMF exposure (Kumar et al., 2013). This is generally associated with an alteration in pain-related neurotransmitters (5-HT, GABA, NE, dopamine, glutamate and glycine) in the cortex, fore brain structures and in brain stem. There was a decrease in 5-HT concentration throughout the brain; an increase in the concentration of GABA and noradrenalin in brain stem and no significant change in the concentrations of dopamine, glutamate and glycine after 8 weeks of SCI. ELF-EMF exposure increased 5-HT concentration in all parts of the brain, which, in turn, assisted in restoration of the nociceptive responses. Correlation between the recovery and magnetically induced increase in the release of major excitatory neurotransmitter (glutamate) from injured tissue is also reported in *in vitro* experiment (Leydeker et al., 2013).

Mechanism of action of ELF-EMF in SCI

ELF-EMF have been shown to ameliorate SCI-induced locomotor deficits, osteoporosis, tonic pain and general body conditions (Ahmed and Wieraszko, 2008, 2011; Crowe et al., 2003; Das et al., 2012; Hunanyan et al., 2012; Kumar et al., 2010, 2013; Leydeker et al., 2013; Manjhi et al., 2013; Pal et al., 2013). This recovery may be either due to reduction in secondary damage or promotion of neuro-regeneration and neurochemicals. EMF exposure leads to a reduction in the secondary damage-induced inhibitory environment and thereby a reduction in the lesion volume. This creates milieu that is conducive for the growth of new synaptic connections. ELF-EMF exposure per se also directly facilitates nerve regeneration, neurochemical/neurotransmitter levels, angiogenesis, osteogenesis and increase in neurotrophic factors at the lesion site after SCI and non-SCI studies (Delle Monache et al., 2008; Kumar et al., 2013; Manjhi et al., 2013; Mert et al., 2006; McKay et al., 2007; Leydeker et al., 2013).

Das et al. (2012) have shown that exposure to ELF-EMF reduces the hemi-section SCI-induced hyperalgesia exhibited in response to both thermal and direct nociceptive afferent stimulation of the tail. The underlying mechanism for restoration of eualgesic state appears to be twofold: 1, MF bio-interaction per se on pain processes and/or 2, its facilitation of neurogenesis. The former gains support from the widely observed analgesic responses after exposure to EMF in several species to a variety of noxious stimuli involving multiple pathways (Del Seppia et al., 1995; Kavaliers and Ossenkopp, 1993; Mathur et al., 2006), while the latter is possibly indicated by the restoration of threshold of simple vocalization and locomotion. The threshold of simple vocalization is a brain stem-mediated reflex involving supra-lesion structures, whereas locomotion involves the intrinsic network involving central pattern generators for control of timing and pattern of muscle activity, which are present in lumbar spinal segments (Kiehn, 2006).

Damaged corticospinal tract axons destined for the lumbo-sacral spinal cord sprout on to propriospinal tract neurons above the lesion (Bareyre et al., 2004) and expand their arborization among lumbar motor neurons. Thus, the propriospinal axons spontaneously form a new functional intraspinal circuit that relays input from the brain to its original spinal target. EMF has been reported to reduce corticospinal inhibition so that there is facilitation of the recovery process and modified plasticity of the sensory cortex (Belci et al., 2004; Thomas and Gorassini, 2005). EMF also promotes recovery by amending the non-neural contents of the endoneurium, thereby reducing the size of the endoneurial space (Kerns and Lucchinetti, 1992), and by generation of ionic currents promoting elongation of growth cone (Ito and Bassett, 1983; Sisken et al., 1993). Therefore, EMF supports the development of functional integration gradually with the ascending neural pathways on the injured side by restoring the connectivity and reducing the secondary injury. Further, EMF exposure promotes

osteogenesis and probably recovery from SCI via increase in nicotinamide adenine dinucleotide (NAD)-specific isocitrate dehydrogenase activity and acetyl cholinesterase at the motor end plate, sparing of white matter and by increasing the number of surviving motor neurons re-establishing connections (Crowe et al., 2003), maturation of bone trabecula, bone volume, bone formation and decrease in lesion volume (Aaron et al., 1990; Mert et al., 2006; Tsai et al., 2007). It induces the differentiation of cartilage cells and enhances alkaline phosphatase activity in rat osteoblasts (Lee and Mcleod, 2000).

Hunanyan et al. (2012) have documented that repetitive spinal EMF stimulation induced a long-lasting facilitation of synaptic transmission to glutamatergic lumbar motor neurons and hind limb muscles from dorsal corticospinal tract and lateral white matter spinal tracts in chronic hemi-sectioned rats. This long-term potentiation (LTP)-like facilitation of responses were mediated by NMDA receptors at lumbar inputs after repetitive EMF and lasted beyond the stimulation period (Hunanyan et al., 2012). Consistent with this observation, it has been shown that activation of NMDA receptors had a marked, positive effect on locomotion in chronic spinal cats, and blockage of NMDA receptors abolished the responses (Giroux et al., 2003). Repetitive TMS is a non-invasive technique that induces changes in cortical excitability at the site of stimulation and at distant sites through descending corticospinal outputs. Modulation of excitability at the directly targeted brain region depends on the TMS parameters and can result in either transient facilitation or suppression.

Repetitive TMS in SCI patients has been suggested as a potential important tool in the promotion of motor recovery. It has been reported to reduce central pain, decrease in depression, and spasticity after SCI (Andre-Obadia et al., 2006; Defrin et al., 2007; Fregni et al., 2006; Kang et al., 2009; Lazzaro et al., 2002; Lefaucheur et al., 2004; Tazoe and Perez, 2015). The functional effects of repetitive TMS are through stimulation of corticospinal tracts that results in excitation at the spinal cord level (Benito et al., 2012). Long-lasting analgesic effect of repetitive TMS has also been observed in patients with trigeminal neuralgia and post-stroke pain-related syndrome (Khedr et al., 2005). Magnetic brain stimulation also increases the American Spinal Injury Association (ASIA) sensory and motor scores in patients after SCI (Belci et al., 2004). Evidence has shown that the effects of TMS depend on the activity in NMDA receptors (Ridding and Ziemann, 2010), which is similar to the mechanisms involved in LTP and depression of neurotransmission, suggesting it to be a possible therapeutic strategy for SCI patients. Generally, high-frequency rTMS (>5Hz) increases corticospinal and primary motor cortex (M1) excitability (Maeda et al., 2000; Valero-Cabre et al., 2001), whereas low-frequency rTMS (<1Hz) decreases it. Thus, both types of stimulation can result in changes in the excitability of spinal neuronal circuits. There is also an activation of immediate-early gene activation in specific brain regions of rats following repetitive TMS (Ji et al., 1998). In SCI rats, repetitive TMS has been shown to produce motor potentials in hind limbs. This is due to activation of extra pyramidal sub-cortical motor pathways located in ventral and ventrolateral white matter that are preserved after dorsal horn spinal cord lesions (Kamida et al., 1998; Metz et al., 2000; Simpson and Baskin, 1987).

Repetitive TMS has been used to map the cortical representation of muscles (Levy et al., 1990) and create recruitment curves of motor evoked potentials for increasing facilitation in subjects with SCI. Other attributes of cortical control over muscles in subjects with SCI that can be revealed by TMS are central conduction time of the cortico-spinal tract (Chang and Lien, 1991) and the inhibitory circuitry that determines cortical output (Davey et al., 1994). Chronic neuropathic pain after SCI is associated with structural and functional changes of both gray and white matter, which involve a number of brain structures related to pain perception and modulation (Moreno-Duarte et al., 2014; Yoon et al., 2013). Most studies that investigated the effects of repetitive TMS on neuropathic pain mainly target the motor cortical area corresponding to the painful zone (Defrin et al., 2007). In patients with facial pain, repetitive TMS showed more improvement in the hand motor cortical area than in patients with upper limb pain (Lefaucheur et al., 2004). Lefaucheur et al. (2004) explained this discrepancy between the sites of repetitive TMS (hand cortical area) and the painful zone (face rather than upper limb) by two mechanisms: 1, the face area may shift toward the hand area in patients with a facial lesion and 2, the fast rate of applied repetitive TMS over hand area might modulate some output from the nearby face cortical representation. Garcia-Larrea et al. (1999) proposed the "thalamus to pain-related structure pathway" as a mechanism of pain relief induced by motor cortex stimulation. The activity of projections from the primary motor cortex to the thalamic nuclei is modulated by motor cortical electrical or magnetic stimulation entailing a cascade of synaptic events in pain-related structures including the anterior cingulate and upper brainstem. Thus, thalamo-cortical tract plays an important role in the pain reduction

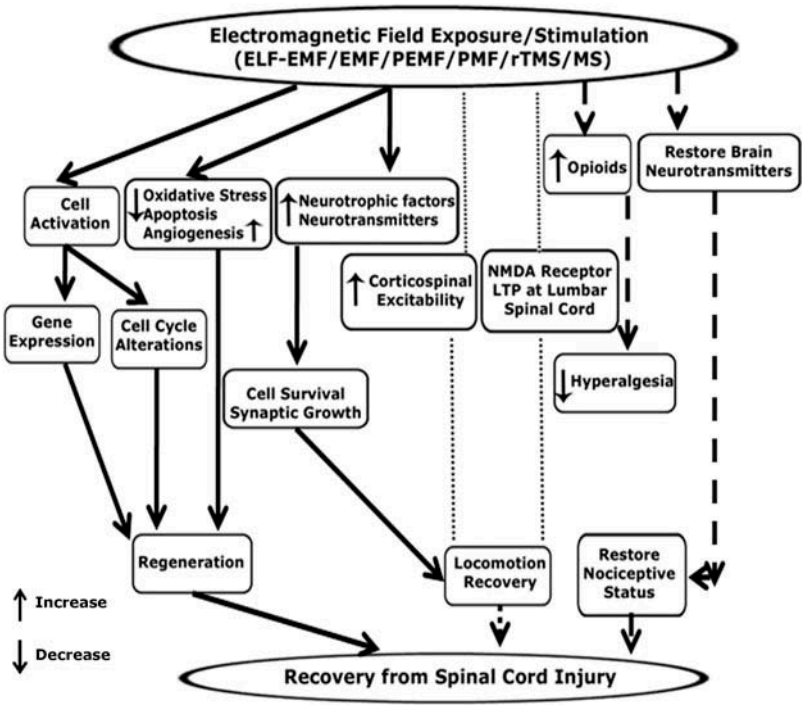

Figure 2. Schematic representation of effect of electromagnetic field on spinal cord injury-induced events.

induced by repetitive TMS of the primary motor cortex (Goto et al., 2008). Yilmaz et al. (2014) used 10 Hz high-frequency TMS over the leg representation of the M1 with chronic complete and incomplete SCI. Patients participated in 10 days of real TMS over the vertex for 10 days or sham TMS over the same region. After real and sham TMS, the visual analog scale (VAS) scores decreased.

However, only real TMS resulted in sustained reduction of the VAS for 6 weeks. Further studies systematically exploring the effects induced by repeated sessions of high-frequency repetitive TMS on corticospinal tract excitability in SCI are necessary to provide further mechanistic insights and assess the clinical benefits and ability to offer therapeutic benefit to patients with SCI (Nardone et al., 2015; Tazoe and Perez, 2015).

The consequences of a SCI are devastating and the complexity demands a multifactorial repair strategy. ELF-EMF is a non-invasive possible potent rehabilitative tool for treatment of SCI. It can easily penetrate biological tissues painlessly, can be easily applied by placing external coils and is clearly bioreactive. The FDA-approved electromagnetic devices are now routinely used in the clinic to aid in non-union bone fractures. It is also used in the management of unexplained, agonizing chronic pain syndromes and osteoporosis. Recently, reports of its beneficial effects in spinal cord injuries, neurogenic bowel and bladder dysfunction have started trickling in the literature. Several studies suggest the potential of ELF-EMF in supporting regeneration as well as in reducing the secondary injury, thereby facilitating functional recovery of locomotion and pain attenuation after SCI (Figure 2). The mechanistic studies suggest its action via modulating antioxidant system, gene expression, neurotransmitter levels, ion permeability and synaptic strength However, despite the large number of studies performed so far, the exact mechanism of EMF is still unknown. Further research is needed to evaluate the role of ELF-EMF parameters (low frequency, low magnitude) in clinically relevant SCI model and patients. The use of EMF is limited within animal studies and experimental situations; thus the use of EMF as a therapeutic strategy in broad-spectrum condition still needs to be appreciated.

Declaration of Interest

The authors report no conflicts of interest.

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