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Chapter 7

PALLIATIVE STRATEGIES FOR SPINAL CORD INJURY

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Abstract

We have developed a number of translational strategies to address some of the symptoms following spinal cord injury (SCI). We first described a method for epidural stimulation of the spinal cord to induce locomotion that was based on *in vitro* work in developing animals to identify the appropriate parameters required, then advanced to the use of these parameters in adult spinal animals, which ultimately resulted in a patented method for epidural stimulation to induce locomotion in the human patient with a SCI. We then turned our attention to brainstem stimulation of the Mesencephalic Locomotor Region and Pedunculopontine nucleus that resulted in identifying parameters of stimulation for inducing locomotion following brainstem stimulation, and is now being used to compensate for locomotor deficits in patients with Parkinson's disease using deep brain stimulation. We also developed a method for compensating for the muscle atrophy and hyper-reflexia induced by SCI using motorized bicycle exercise training (MBET). Studies in spinal rats found that muscle mass and hyper-reflexia could be normalized using passive exercise through MBET, which led to the development of MBET for human patients with SCI. Recently, we found that the time course of the onset following SCI for hyper-reflexia differs from that of spasticity, and described the use of MBET to address both symptoms. We developed a novel pharmacological intervention based on the idea that electrical coupling is dysregulated after SCI, which can be compensated for by the use of modafinil, with salutary effects to the H-reflex and the stretch reflex, measures of hyper-reflexia and spasticity, respectively. We suggest that a multi-therapeutic approach using all of these methods is required to compensate for some of the symptoms of SCI.

Keywords: Deep brain stimulation, electrical coupling, gap junctions, hyper-reflexia, modafinil, motorized bicycle exercise training, pedunculopontine nucleus, spasticity.

Introduction

Our long-term strategy is directed at attempting to address the symptoms produced by spinal cord injury (SCI) using a variety of palliative therapies in order to alleviate these devastating deficits sooner rather than later. The potential for regenerative methods to compensate for SCI is still out of reach, but we can certainly use the wealth of knowledge and experience at our disposal to address more proximal needs. There is little question that the field of physical therapy has matured to the point that considerable restitution of function can be expected for a patient with an incomplete SCI, if well-designed regimens are instituted early and maintained until salutary effects are observed [1]. Typically, we undertook basic studies on animals that were translated into human application, and those results in some cases pointed to further studies on animals, which were then applied to humans, resulting in a circular model of translational research. We first addressed the issue of attempting to drive locomotion following stimulation of the spinal cord, especially given that spinal pattern generators are known to be present in the spinal enlargements and contain the flexion-extension sequences necessary for stepping. We also addressed the use of brainstem stimulation to induce locomotion given the early description of the Mesencephalic Locomotor Region (MLR), with the hope that such stimulation could be used to compensate for loss of descending locomotor control. We also addressed the issues of muscle atrophy, hyper-reflexia, and spasticity by developing a passive exercise therapy that normalized reflexes and measures of spasticity. Recently, we discovered dysregulation of the coherence of muscle contraction in SCI, and used a pharmacological agent that increases electrical coupling in order to attempt to compensate for this deficit. In each case, the basic research findings have been translated into human testing. The Jackson T. Stephens Spine and Neuroscience Institute is thus developing a SCI Mobilization Program using the full spectrum of therapies to treat patients with a SCI.

1. Stimulation of the Spinal Cord

Years ago, Forssberg proposed that the locomotor deficits in PD represented a regression to a neonatal state [2] based on the observation that festinating gait in Parkinson's disease (PD) is similar to the digitigrade step cycle of the newborn. We reasoned that the same might be the case after SCI, i.e. that the spinal cord below the level of the lesion is deafferented from central control and reverts to an earlier state [3]. The early patterns of activity appear to be retained with age, which gives rise to additional patterns rather than replacing those patterns with new ones across development [4]. Since spinal pattern generators are present at birth that contain the flexion-extension sequences necessary to drive stepping [5], we needed to know what parameters of stimulation would be required to drive stepping in the neonatal spinal cord. Thus, we developed the *in vitro* brainstem-spinal cord preparation in the 0-4 day old rat [6]. These studies were the first to show that 1) chemical stimulation of the brainstem or spinal cord bath could be used to drive locomotion [7, 8], and 2) that stimulation of the spinal cord in the neonate rat required the use of long duration (0.5-1 msec) pulses delivered at low frequencies (0.5-20 Hz) [6-9]. Figure 1A shows that stimulation of the spinal cord in the neonatal *in vitro* brainstem-spinal cord preparation induced not only alternating hind limb movements along with electromyographic (EMG) alternation of agonists on the left and right

sides, but also other characteristics of an advanced step cycle in eliciting alternation of antagonists in the same limb and a proximodistal delay in patterning [6, 8, 9]. We then translated these parameters of stimulation applied epidurally over the lumbar enlargement to the adult, acutely transected cat [10].

Figure 1B shows that epidural stimulation of the pre-enlargement and enlargement segments of the lumbar cord, using the same parameters of stimulation used in the neonatal *in vitro* brainstem-spinal cord preparation, induced locomotion on a treadmill within 4 hours after mid-thoracic transection of the spinal cord in the adult cat [10].

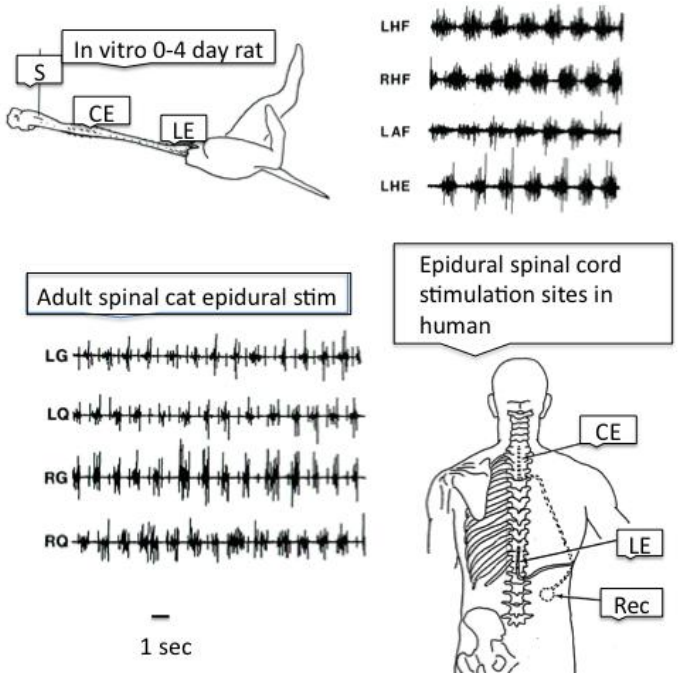

Figure 1. Stimulation of the spinal cord. Top panel. Left side. Drawing of 0-4 day neonatal rat in vitro brainstem-spinal cord preparation showing stimulation site (S) and location of cervical enlargement (CE) and lumbar enlargement (LE) in relation to attached legs. Right side. EMG recordings in vitro of left (LHF) and right (RHF) hip flexors (alternation of agonists in opposite limbs), and left ankle flexor (LAF) and left hip extensor (LHE) (alternation between antagonist in the same limb and proximodistal delay). Bottom panel. Left side. Epidural stimulation 4 hr after spinal transection in the adult cat using the same parameters as in the *in vitro* neonatal preparation. Note alternation of left hip flexor (LG) and extensor (LQ), and of right hip flexor (RG) and extensor (RQ). Right side. Epidural spinal cord stimulation sites in the human cervical (CE) or lumbar (LE) enlargement with subcutaneously attached receiver for transdermal reception of stimulus parameters. Calibration bar- 1 sec for top and bottom panels.

The use of epidural stimulation of the spinal cord in humans had been used for many years for the treatment of chronic pain. Transcutaneous electrical nerve stimulation (TENS) is still being used for such treatment and involves the implantation of epidural stimulating electrodes over the cervical spinal cord in patients with chronic pain. These units use short duration (~0.1 msec), high frequency (>100 Hz) pulses to disrupt pain signaling. We proposed the use of similar units for implantation epidurally in patients with a SCI over the cervical or lumbar pre-enlargement and enlargement segments, but using long duration, low frequency pulses, and

secured a patent for such a method and device [11]. Figure 1C shows the proposed site of implantation for the electrodes, which are driven by a subcutaneous receiver that is activated by an external transmitter. A similar method was later used by others to induce stepping in a patient implanted with a similar device and used similar parameters of stimulation [12]. The patient was classified as ASIA C, having some sensation below the level of the injury. The results showed that the pattern and duration of locomotion was improved by epidural stimulation. Recently, epidural stimulation (using shorter duration and higher frequency stimulation) was used to drive standing by stimulating more caudally in the lumbar enlargement, and also some locomotor movements were induced, in an ASIA B paraplegic patient [13]. Different parameters of stimulation are required to induce changes in posture (standing) than in stepping, in keeping with work showing that standing and treadmill training in spinal animals is possible, but animals must be trained in each activity separately [14]. Nevertheless, the technology of epidural stimulation is receiving renewed attention because it shows promise for compensating some of the deficits induced by SCI. We reasoned that the effects of spinal stimulation would be improved if we could also compensate for other deficits, especially muscle atrophy, hyper-reflexia and spasticity, all of which impede progress in regaining locomotor function. These avenues are discussed below; however, we also approached the potential use of brainstem, instead of spinal cord, stimulation to induce locomotion.

2. Stimulation of the Brainstem

Low amplitude (10-100 μA), long duration (0.5-1.0 sec) pulses delivered at 40-60 Hz to a region in the posterior midbrain were reported to induce locomotion in the precollicular-postmammillary transected cat [15]. The region around the lateral cuneiform nucleus was named the "Mesencephalic Locomotor Region (MLR)". Later work showed that other sites in the posterior midbrain could also be stimulated to induce locomotion, such as points in the inferior colliculus, in the cuneiform, and in the pedunculopontine nucleus (PPN), among others [16-18]. We directed our efforts at the PPN since we could identify the stimulation sites by processing the tissue for choline acetyltransferase (ChAT) immunocytochemistry [18], or NADPH diaphorase histochemistry [19], which selectively labels cholinergic PPN neurons. The lowest threshold sites were found dorsal to the brachium conjunctivum, in the lateral cuneiform nucleus, but in a region that contained cholinergic neurons of the PPN. These studies were the first to report that neuroactive agents injected into the PPN to induce locomotion [20]. We also recorded from locomotion-related PPN neurons, and some cells were active in relation to left-right alternation, while others were related to the duration of the stepping episode [19]. Later studies localized their stimulation sites to the cuneiform nucleus dorsal to the brachium conjunctivum, but did not label PPN cells in the stimulated animals [21]. This led to the erroneous localization of the PPN as within, but not dorsal to the brachium conjunctivum. Cholinergic PPN neurons are present dorsal to the brachium conjunctivum, in the region these authors reported positive effects on locomotion [18, 19]. There is little doubt that there are multiple regions in the posterior midbrain that when stimulated can induce locomotion in the decerebrate animal. The fact that the PPN is involved in sleep-wake control and arousal led us to conclude that this was not a locomotion-specific region. One concern was the fact that locomotion was never instantaneous, but took several seconds to ensue, so that we proposed that this region "recruited" locomotion, rather than

induced it. We did not know why 40-60 Hz stimulation, but not lower or higher frequencies, was required to elicit stepping. In reports of deep brain stimulation (DBS) of the PPN, only one study has used stimulation frequencies in this range, and to good effect [22]. Recent studies from our labs have found that all PPN neurons, regardless of transmitter type, cholinergic, glutamatergic or gabaergic, exhibit P/Q-type high threshold calcium channels that oscillate at gamma band frequencies [23, 24]. These results help explain why it is necessary to stimulate the PPN at 40-60 Hz to induce locomotion in the decerebrate animal, basically because that is the preferred firing frequency of the maximally activated PPN cell.

The considerable attention paid to this system over the years ultimately led to the use of DBS to treat the locomotor deficits induced by PD. Early studies focused on patients with parkinson's disease who presented severe axial symptoms and gait disorders not responsive to L-Dopa treatment [25]. Early attempts used ventriculography and intracranial recordings to verify the stimulation sites, while later studies modified the electrode trajectories and visualization methods for assessing location [26, 27]. All of the treated patients showed improvements in walking, postural stability and oromandibular movements, although not all groups report such positive results [22, 28]. A number of issues remain to be clarified before this therapy can be used consistently across groups, namely, a) current practice in DBS is to stimulate using 50-100 μsec pulses, which may preferentially be activating intrinsic axons and fibers of passage rather than neurons; b) current practice in DBS is to use frequencies >100 Hz, which, when applied to PPN, may actually tend to inactivate these neurons; and c) the practice of applying continuous DBS throughout the day may not result in creating a continuous facilitation, and it is difficult to extrapolate from animal studies using periodic stimulation to the potential effects of continuous DBS. Overall, better localization of stimulating leads in the human requires consultation with one of the few studies of three-dimensional reconstruction of the PPN [29]. In addition, the use of DBS electrodes of 1.2 mm in diameter may produce undesired effects [30]. As the field matures to allow more exact localization and determination of effects of stimulation, PPN DBS may prove to be a viable strategy for the treatment of at least some of the locomotor deficits in PD.

3. Passive Exercise

Hyper-reflexia- Some of the deficits resulting from SCI are hyper-reflexia and spasticity below the level of the lesion. The H-reflex or Hoffman reflex has been used to quantify hyper-reflexia [31], and several investigators have utilized frequency-dependent depression of the H-reflex to examine changes in spinal cord circuitry after SCI [32-35]. Thompson found that there was no difference in low frequency-dependent depression between rats at 6 days post-injury and control animals, but reported a significant decrease in low frequency-dependent depression 28 and 60 days post-injury [35]. This suggests a time course of transition to hyper-reflexia occurring between 6 and 28 days that correlated with findings after chronic spinal cord hemisection in the rat using the monosynaptic reflex [36].

Human studies have reported absent H-reflexes 24 hours after injury that recovered to normal amplitudes within several days post-injury [37]. Other researchers showed normal low frequency-dependent depression in acute patients with SCI (defined as less than 2 weeks post-injury), and reduction in low frequency-dependent depression for patients with a chronic SCI (greater than 1 year) [38]. Schindler-Ivens and Shields observed H-reflex frequency-

dependent depression in an acute patient over a time course of 44 weeks in addition to examining a group of acute and chronic patients [39]. They found that the H-reflex of the acute group (within 6 weeks of the injury) showed a pattern of suppression similar to the able-bodied group. They also reported that the one patient examined over 6-44 weeks post-injury, showed reduction in frequency-dependent depression between 6-18 weeks post-injury, which continued to change until 44 weeks. That is, the onset of hyper-reflexia in the human is delayed beyond a period of "spinal shock", suggesting that slow changes occur after SCI that lead to hyper-reflexia and spasticity.

We studied the time course that animals with a complete transection of the spinal cord transitioned to a state of hyper-reflexia, and found that this transition in the rat occurred between 7 and 14 days after transection [40]. Figure 2 (upper panels) shows the H-reflex measured at 0.2, 1, 5 and 10 Hz in transected rats 7 and 14 days following transection representing that hyper-reflexia is present 14 days after injury. We also reported the ability of long-term passive exercise therapy, in the form of motorized bicycle exercise training (MBET), instituted prior to the onset of hyper-reflexia, restored frequency-dependent depression of the H-reflex in adult rats with complete spinal cord transection [34, 41]. One area of interest is a comparison of the modulation of spinal cord circuitry using passive exercise prior to the onset of hyper-reflexia (acute phase of injury) compared with initiation of exercise after the onset of hyper-reflexia (chronic phase of injury). The literature is limited when examining exercise paradigms that compare exercise initiated during the acute versus the chronic phase of injury.

We used passive exercise to modulate the H-reflex in complete transected animals that began exercise after hyper-reflexia had been established (after 30 days post-transection), therefore demonstrating a form of rescue from hyper-reflexia. [42]. However, we hypothesized that the amount of exercise required to prevent hyper-reflexia, when initiated prior to its onset, would differ compared to the amount of exercise required to rescue from hyper-reflexia. We also determined if spinal cord circuitry would retain its modulation when exercise was stopped. Therefore, the duration of savings on modulation of frequency-dependent depression of the H-reflex was examined [40]. Our results concluded that exercise provided greater benefit to the plasticity of spinal cord circuitry if it was initiated prior to the onset of hyper-reflexia. However, longer durations of passive exercise were still effective in ultimately normalizing reflexes if exercise was initiated after the onset of hyper-reflexia. Only short-term savings were observed when MBET was discontinued after normalizing the H-reflex [40].

The mechanisms underlying the development of hyper-reflexia and spasticity after SCI are currently unknown [43]. In addition, the mechanisms influenced by passive exercise to induce reflex changes are also unknown. Two potential mechanisms that have been studied related to exercise training include changes in insulin-like growth factor-1 (IGF-1) and brain derived neurotrophic factor (BDNF).

Recent attention has focused on the role of insulin-like growth factor-1 (IGF-1) in the recovery of locomotion after incomplete injury and the effects of exercise in complete injuries [44, 45]. An additional mechanism has focused on changes to BDNF following exercise. After several days of voluntary wheel running, normal rats were tested and found to have increased levels of BDNF mRNA in the hippocampus, cerebellum and cortex [46]. Other authors have investigated mRNA changes in BDNF after exercise in the lumbar spinal cord following SCI

[47]. Treadmill training facilitated normalization of the peripheral BDNF levels and normalized sensory changes observed in incomplete spinal cord injuries in the rat [48].

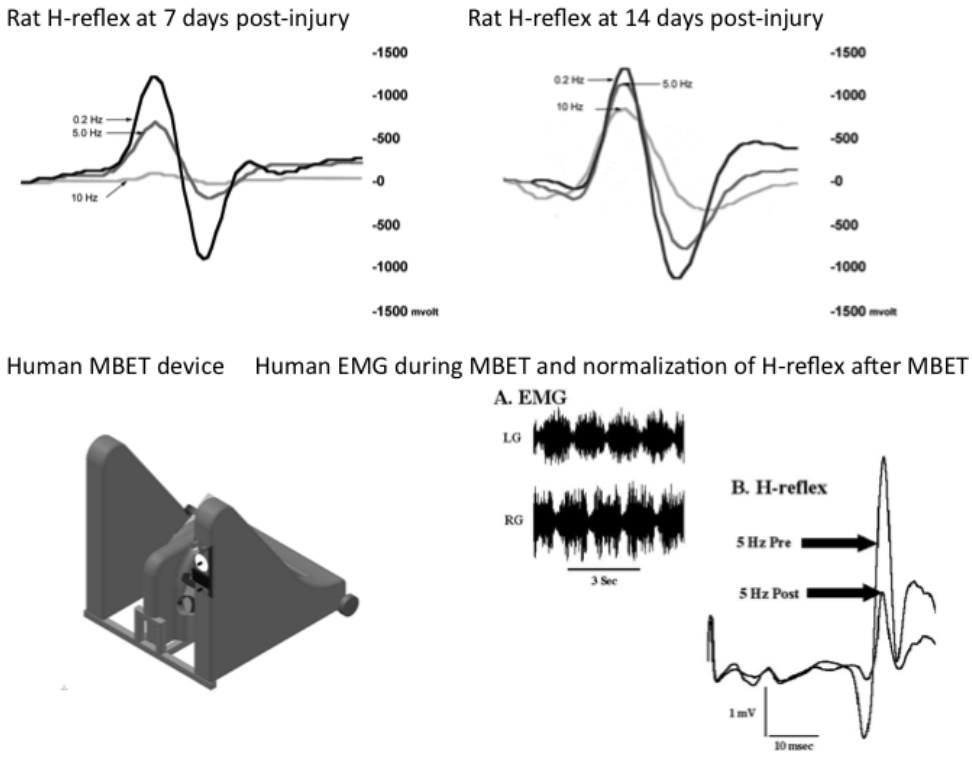

Figure 2. Passive exercise. Top panel. H-reflex in the spinal rat. Left side. H-reflex in the transected adult rat recorded 7 days post-injury. Stimulation at 0.2, 5 and 10 Hz showed normal frequency-dependent depression (note decreased amplitude at 10 Hz). Right side. H-reflex recorded 14 days after transection showing decreased frequency-dependent depression. Note the higher amplitude of the H-reflex at 5 and 10 Hz, compared to 7 days (left side). Bottom panel. Human MBET and H-reflex changes resulting from MBET. Left side. Blueprint of MBET device for humans showing body with wings to help align the hip, knee, and ankle joints. Right side. Electromyograms (EMGs) (top left) and H-reflex (bottom right) from human SCI subject. A. The EMGs of the left (LG) and right (RG) gastrocnemius muscles are shown during MBET cycling at 40 RPM (note calibration bar of 3 sec). The recordings showed consistent alternation of agonists in different limbs in response to muscle stretching induced by the MBET. B. The H-reflex recording shows the averaged H-reflex at 5Hz stimulation rate before (5 Hz Pre) and after (5 Hz Post) 12 weeks of MBET. Note the reduction in H-reflex amplitude after passive exercise training in this ASIA B subject. M-wave is evident at ~12 msec latency. Calibration bars for the H-reflex, vertical 1 mV, horizontal 10 msec.

We then developed and patented a MBET device for the treatment of symptoms related to SCI in the human [49]. The device, as the name implies, passively pedals the subject, allows any wheelchair to attach, provides pedals that allow the shoes to be strapped in place with Velcro, and has wings that maintain the hip, knee, and ankle joints aligned. The patients sit in their own wheelchairs, which are adjusted to ensure stretch reflexes of the thigh and leg muscles. A torque sensor in the pedals shuts off cycling to prevent rotation through a spasm. A convenient emergency shut-off switch also helps prevent injury. Testing in a patient

classified as ASIA B 1 year after SCI showed that 8-10 weeks of daily MBET were required to normalize the H-reflex, that MBET was effective even 1 year after injury, and that cessation of MBET led to a restoration of hyper-reflexia with 3 weeks [50]. Figure 2B shows that 8-10 weeks of MBET normalized hyper-reflexia in a patient with a SCI, which showed little savings after discontinuation of MBET.

Spasticity- Spasticity is a common disorder following spinal cord injury (SCI) that can impair function and quality of life [51]. While there has been progress in understanding the spinal pathophysiology involved in the plastic changes that occur post-injury, the exact mechanisms remain unknown [43, 52]. In addition, quantifying spasticity continues to be a challenge. One group reviewed a number of neurophysiological methods for spasticity assessment citing their advantages and limitations [53]. Because there is no gold standard in spasticity measurement, these authors concluded that a combined neurophysiological and biomechanical approach might be used to provide a more complete assessment [53].

The frequency-dependent depression or post-activation depression of the H-reflex as described earlier provides valuable insight into post-SCI plasticity of the monosynaptic reflex arc involved in the stretch reflex (SR). However, a number of differences in the H-reflex and mechanical SR have been documented [54], including fundamental differences in spinal motoneuron excitatory post-synaptic potentials (EPSPs) that are evoked by stretch versus a single synchronous discharge that produces the H-reflex [55]. Finally, polysynaptic reflexes composed of group II afferents have been suggested to play a major role in spasticity following SCI [56], and these contributions would not be fully assessed by the H-reflex.

The noninvasive measurement of EMG and torque response to a movement perturbation has been reported in the human [57, 58]. Thompson et al developed a device to quantify the SR in rats and documented the velocity-dependent response in normal rats [59], and in rats with a contusion injury of the spinal cord [60]. Furthermore, Thompson documented the time course of the response post-injury. However, the SR response to a complete transection injury had not been reported, and evidence from human studies indicates that responses differ based on completeness of injury [61, 62].

In order to overcome the limitations inherent in comparing non-normalized EMG recordings over time, a new protocol was developed that examined the wind-up response to repeated stretches. In a wind-up protocol, the EMG response to the first stretch is used to normalize subsequent responses. Wind-up behavior is characterized by temporal facilitation that results in increased duration and amplitude of the reflex responses. This has been demonstrated both for flexor reflexes [63], and also in the SR in the human following SCI [64]. It has been suggested that the mechanism for this prolonged reflex response is due to alterations in intrinsic motoneuronal properties, namely persistent inward currents (PICs) [65]. In reduced preparations, PICs demonstrate the ability to amplify and prolong the response to brief inputs [66, 67], and their re-emergence is linked to the onset of hyper-reflexia [68, 69]. We developed an actuator that is capable of producing controlled stretches at various frequencies to provide a measure of changes in spasticity. Additionally, we modified our H-reflex recording technique to be minimally invasive by using percutaneous stimulation [70]. The ability to carry out these measures longitudinally allows for the assessment of the effects of passive exercise and pharmacological interventions as abnormal symptoms develop and are reversed.

We thus measured the H-reflex and the SR in groups of rats subjected to spinal transections and various forms of treatment [71]. Using changes in SR wind-up to track the

effects of transection, we found that the SR became hyperactive much later than the H-reflex, with the wind-up of plantarflexion torque and gastrocnemius EMG emerging 7 weeks after transection [71], compared to 14 days for the H-reflex [40].

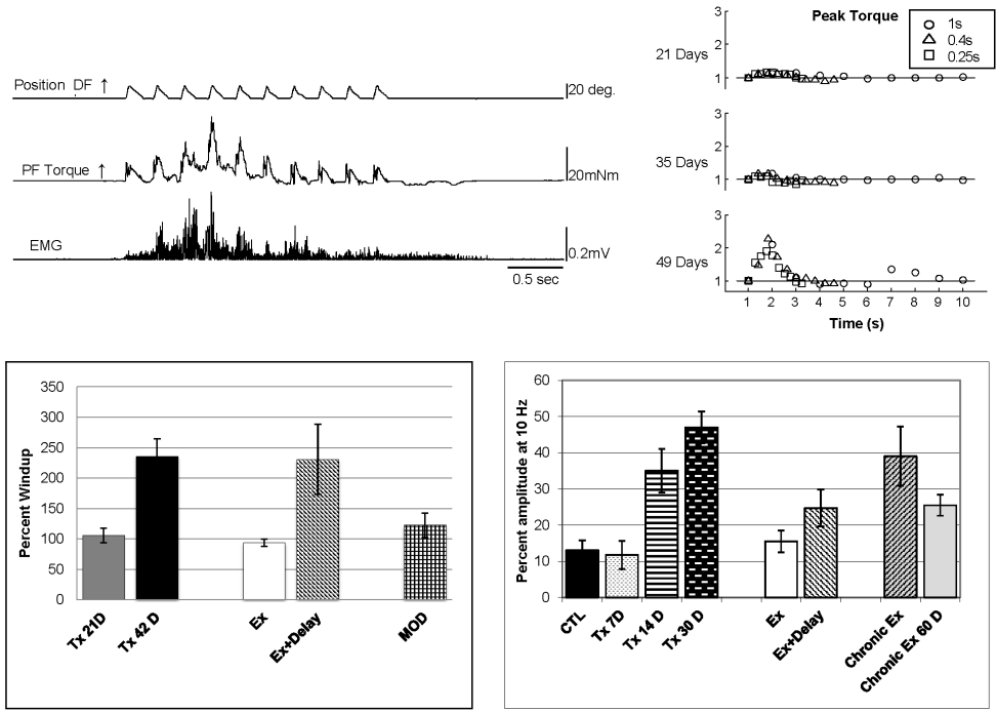

Figure 3. Hyper-reflexia and spasticity. Top Panel, Stretch reflex (SR) windup in the spinal rat. Left side, SR recordings showing the windup protocol at a 0.25s interval. Representative data is shown at 49 days post spinal cord transection (Tx) for a Tx only animal. Ankle position, ankle torque and rectified gastrocnemius EMG are plotted across time. Tx animals showed considerable windup of both the EMG and torque response to repeated stretch. Right side, peak plantarflexion torque is plotted for various frequencies of repeated stretch (1s, 0.4s, and 0.25s) and across time. The windup response was slow to evolve with established windup at all frequencies occurring by 49 days post Tx. Bottom panel. Summary data for SR and H-reflex changes in the rat following various interventions. Left side, Windup of the SR shown as a percent of the first stretch. Tx only animals showed windup at 42 days post Tx. Exercise and Modafinil (MOD) interventions both eliminated windup. The effects were short-lived with windup returning following delay or cessation of exercise. Right side, H-reflex frequency dependent depression at 10 Hz. Lack of depression was evident by 14 days and well established by 30 days (Tx 30D). Animals initiated on exercise acutely demonstrated a return to control levels with 30 days of exercise (Acute Ex) while chronic animals required 60 days of exercise (Chronic Ex compared to Chronic Ex 60D). Retention or savings were realized to a modest extent following cessation of exercise (Acute Ex+ Delay).

The upper panels of Figure 3 show the emergence of the stretch reflex windup after complete spinal injury in the rat. Passive exercise, however, prevented wind-up of the SR if continued for 45 days after transection. These studies suggest that both hyper-reflexia and spasticity are amenable to MBET therapy as seen in the lower panels of Figure 3. This figure also demonstrates the lack of savings of the modulation of the stretch reflex once passive exercise has been discontinued.

4. Modulation of Gap Junctions

Oscillatory activity mediated by electrical coupling via gap junctions has been demonstrated in a number of regions including the neocortex [72, 73], hippocampus [74], olfactory bulb [75], amygdala [76], inferior olive [77, 78], and locus coeruleus [79]. In addition, electrical coupling is evident in the reticular activating system (RAS) [80], respiratory brainstem regions [81], and spinal cord [82, 83]. Gap junction blockers have been reported to depress rhythmogenesis in the RAS [80], respiratory pre-Botzinger complex [84], the retrotrapezoid nucleus [85], and the nucleus of the tractus solitarius [86]. Although few studies on chewing and swallowing have been carried out using gap junction blockers, there is little doubt that gap junctions are present in the trigeminal nucleus [87], and hypoglossal [88] neurons are electrically coupled.

As far as locomotion is concerned, electrical coupling has been found to modulate swimming in tadpoles [89]. It is known that mammalian motoneurons are extensively coupled during development, but coupling decreases by 14 days postnatally in the rat [90]. There are a number of interneurons that were found to be electrically coupled in the ventromedial region of the spinal cord and appear related to locomotor control [91]. How do spinal cord gap junctions influence motor coordination? Electrical synapses may contribute to the generation and maintenance of synchronized neuronal bursting firing patterns [92]. Others demonstrated that motor patterns in the neonatal rat spinal cord were observed during blockade of chemical synapses, probably through the synchronization of bursting through gap junctions [93]. They suggested, "Gap junction-mediated neuronal coordination contributes to the basic function and organization of spinal motor systems." These authors also suggested the existence of numerous independent rhythms in distinct motor pools. However, the modulation of gap junction communication in the adult spinal system and the adult system after injury are poorly understood.

Hyper-reflexia and spasticity are present following a multitude of upper motor neuron disorders. Pharmacological agents such as Baclofen, Diazepam, Tizanidine, Dantrolene, and others have been used in human subjects in an attempt to decrease spasticity following SCI. However, some of these drugs have some undesirable side effects on patients and some have no effects on hyper-reflexia [94]. The effects of modafinil (MOD) on hyper-reflexia and spasticity have not been investigated extensively, despite the fact that we found it is effective in treating patients with neglect after stroke injury [95]. Moreover, recent reports suggest MOD may be useful in the treatment of spasticity arising from cerebral palsy [96, 97]. Why would a stimulant used as an antinarcoleptic agent have salutary effects on spasticity? The mechanism of action of MOD was unknown until recently, but was credited with increasing glutamate, acetylcholine, noradrenaline and serotonin release, and decreasing GABA release [98]. However, MOD was recently found to increase electrical coupling between nerve cells in the inferior olivary nucleus, cortical interneurons, and thalamic reticular neurons [99]. Following pharmacological blockade of connexin permeability, MOD restored electrotonic coupling within 30 min. The effects of MOD were counteracted by the gap junction blocker mefloquine.

These authors proposed that MOD may be acting in a wide variety of cerebral areas by increasing electrotonic coupling in such a way that the high input resistance typical of GABAergic neurons is reduced. This "shunting effect" of MOD may activate the entire

thalamocortical system by slightly diminishing inhibitory networks and, at the same time, increasing synchronous activation of both interneurons and non-inhibitory neurons. We confirmed that MOD increased electrical coupling in cell groups in the RAS, thus accounting for its stimulant effects on arousal [100, 101].

Results from our labs indicate that oral administration of modafinil (MOD, 4mg/kg, p.o.) over a period of 30 days, was able to prevent the loss of frequency-dependent depression of the H-reflex [102]. Follow-up experiments were able to show that MOD had similar reductions in the windup of the SR [70] (see also Figure 3). These results for the first time suggest that pharmacological intervention with an agent that increases electrical coupling may be useful in reducing hyper-reflexia. These data indicate that MOD was as effective as passive exercise in normalizing low frequency-dependent depression of the H-reflex and the SR. These results also suggest the possibility that at least some of the changes occurring between 1 and 2 weeks after transection involve changes in gap junction function [102]. It is not known if MOD directly affects electrical coupling in the adult transected rat, but if it does, it may do so by influencing motoneurons, locomotion-related interneurons, or perhaps even GABAergic spinal interneurons, as it does in the brain [99, 100].

While a number of new questions are raised by this study, our results do strongly suggest that MOD may represent a valuable therapeutic adjunct to the treatment of SCI, and supports previous results in cerebral palsy, but suggest that some of the gains made may have been due to direct effects on spinal circuitry rather than cerebral in origin.

These data demonstrate that a) SR habituation becomes abnormal much later after transection than the H-reflex, b) MBET nevertheless could normalize the SR, and c) MOD was also able to prevent the changes in the SR in the absence of MBET.

These findings suggest that, although the mechanisms behind hyper-reflexia and spasticity undergo changes with different time courses, the SR is responsive to MBET and MOD in a manner similar to the H-reflex. Are passive exercise (MBET) and MOD addressing the same underlying mechanism? The answer is not known.

We do not yet know if passive exercise has its salutary effects by modulating electrical coupling and Cx-36, along with other mechanisms. The fact that the onset of hyper-reflexia (H-reflex) and exaggerated SR are different suggests that they are mediated by different mechanisms. Other studies have shown differences in these two measures in regard to sensitivity to GABAergic presynaptic inhibition [54], temporal dispersion of the afferent volley [55], and post activation depression [103].

However, both measures are normalized in response to MBET and to MOD, suggesting related mechanisms. Much work needs to be undertaken before we can answer these questions, but these need not await the application of these novel therapeutic avenues to the patient with a SCI.

Conclusion

We describe a number of proven therapeutic interventions that can be implemented in SCI patients to alleviate such deficits as locomotor, hyper-reflexia, and spasticity. The use of epidural stimulation of the spinal cord is gaining acceptance, while that of brainstem DBS is already in a number of clinical trials.

The potential for the use MBET and modafinil to decrease the deleterious effects of hyper-reflexia and spasticity is clear despite lack of information on the exact mechanism of action. In the future, a multi-therapeutic approach will provide the most likely salutary effects by treating several of the symptoms at the same time.

Acknowledgments

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