Review

The use of treadmill training to recover locomotor ability in patients with spinal cord injury

Russell Thomas Frood*

Faculty of Biological Science, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, UK.
* Corresponding author: Email: um07rtf@leeds.ac.uk

Spinal cord injury (SCI) affects over 1000 people a year in the UK and has severe consequences for their independence and quality of life. Treatments to address SCI focus on techniques that aim to restore some degree of walking or locomotor activity. One such technique is treadmill training of SCI patients. This paper reviews the use of treadmill training in the recovery of locomotor ability in patients with SCI. Outcomes from treadmill training are variable; for patients with incomplete SCI (where some degree of connection between the brain and the spinal cord is spared from injury), treadmill training only enabled limited full weight-bearing locomotion. In patients suffering a complete SCI (where communication between the brain and spinal cord is lost), no weight-bearing locomotion at all was achieved with training. However, treadmill training does influence the activity of the leg muscles in the acute patients, observed by recordings made from the muscles (electromyography). The improvements achieved by treadmill training are not significantly different from other techniques such as overground training and functional electrical stimulation. The most effective way of restoring locomotion is through complete repair; however, regeneration techniques are still being developed. For regeneration to take place, the neurons within the spinal cord that are important in generating rhythmic movements (the central pattern generator (CPG) circuits) still need to be functioning, as these circuits have been shown to decline through long periods of inactivation. Treadmill training has therefore an important role in keeping neurons active until regenerative techniques become viable. Furthermore, in spinalized rats, it has been shown that by combining treadmill training with pharmaceutical and electrical stimulation therapies, greater improvements are seen. This suggests that the treatment of spinal cord injury should not be limited to one method. Techniques that repair the damage are the ultimate goal and it is important that patients keep active in order to increase chances of recovery.

Key words: spinal cord injury, treadmill training, rehabilitation, locomotion.

Submitted July 2010; accepted on 20 January 2011

Introduction

Independent locomotion, though not fundamental for human survival, is still important in terms of physical and psychological health.1 With over 1000 people a year in the UK sustaining spinal cord injuries (SCI) resulting in paraplegia or tetraplegia, successful treatment of these conditions is much sought after.2

Current research on restoring locomotor function in SCI patients focuses on either restoration of lost connections or uses the adaptive properties of the spinal cord to train the patient to walk.3 Treadmill training can take two forms: robotic control or manual limb assistance. Patients will have either their entire or a percentage of their weight supported during training to allow for proper extension of the legs. The training is designed to closely resemble normal locomotion to allow the spinal cord to relate to the sensory stimulation that is required for stepping movements.

This paper is going to review the use of treadmill training in the treatment for recovery of locomotion in SCI patients.

What is SCI and what are the effects?

SCI consists of primary and secondary phases which can affect the biophysical layout of the spinal cord.4 The primary phase is the mechanical impact, compression,
laceration or transection of the cord. The secondary phase consists of neurogenic shock, haemorrhage, excitotoxicity, disruption of electrolyte balance, apoptosis and calcium-mediated injury (Fig.1).

Limb spasticity is associated with SCI and this is problematic when trying to restore locomotion. The cause is the loss of inhibitory signals below the lesion due to lower expression of KCC2 membrane potassium-chloride transporter resulting in higher intracellular chloride ion concentrations. A low concentration is required for effective inhibition of neurons via GABAA and glycine receptors. The change in ion concentration leads to these receptors exhibiting excitatory properties.

Unlike the peripheral nervous system, the central nervous system has a limited capacity to regenerate after damage due to a number of biological mechanisms which follow central nervous system (CNS) injury. First, the environment is not permissive; axon guidance signals are absent in the basal lamina after axon degeneration. There is likely to be a glial scar which not only forms a physical barrier but also releases chondroitine sulphate proteoglycans; chemo-repellent molecules which make the glial scar impassable by a developing growth cone. Other chemo-repellents present on myelin such as Nogo, myelin-associated glycoprotein and oligodendrocyte myelin glycoprotein also inhibit the growth cone. The neuron is likely to die due to retrograde degeneration from the breakdown of the axon. Oligodendrocytes are also likely to die due to apoptosis leading to a lack of myelination of developing axons and a loss of myelin around axons away from the site of injury. Therefore, to make correct connections in the spinal cord after injury, four main obstacles have to be addressed: keeping the cells alive or replacing them, making a permissive environment for axon growth, providing correct signalling to the desired target and allowing remyelination of the axon.

Clinically, SCI can be classified as complete, where the cord is fully transacted, or incomplete, where the cord is only partially damaged. A detailed classification is provided by the American Spinal Injury Association (ASIA) scale (Table 1). The injury can also be described as acute (less than a year old) or chronic (more than a year old).

Can the spinal cord support locomotion after SCI?

Locomotion is achieved through interactions of the nervous system and skeletal muscles occurring in rhythmic sequence. The leg muscles show varying temporal activity and level of activity depending on the type of locomotion (Fig. 2).

The ability of the body to achieve these rhythmic patterns for locomotion is attributed to isolated circuits known as central pattern generators (CPGs). These cause alternating stimulation of extensor and flexor muscles. However, both the organization and components of these circuits remain unclear. Studies on the activity of neurons in isolated spinal cords of rats have identified populations of neurons that may form part of the CPGs. The populations of neurons identified were situated near the central canal (medial lamina VII and lamina X), dorsal horns and the medial region of the ventral horns of the lumbar region. Research using genetic animal models has also identified neurons that play a role in the CPG activity in similar areas suggesting that V0–V3 lumbar interneurons, interneurons expressing ephA4 and HB9 expressing interneurons are the constituent parts of the CPG.

Support for the presence of CPGs in humans comes from both SCI patients and healthy subjects. Calancie et al. described a patient who had suffered an injury to the cervical spine 17 years prior, leading to paralysis of the limbs. It was observed that when the patient was supine with legs...
extended, he showed involuntary stepping movements.\textsuperscript{16} Gurfinkel \textit{et al.}\textsuperscript{17} demonstrated in healthy subjects that stimulation via a tonic afferent input can lead to stepping movements. The same was also achieved in patients with complete SCI.\textsuperscript{18} Investigations conducted on decerebrated rats have shown by varying the intensity of stimulation of the mesencephalic locomotor region, the gait could be changed from a walk to a run.\textsuperscript{19} This suggests that the input is regulatory and that there is a programmed response to this single tonic input which results in locomotion.\textsuperscript{19} This further suggests that these systems need input to allow adaptation, e.g., walking over uneven surfaces and changing stride length. Maegele \textit{et al.}\textsuperscript{20} showed that voluntary control is not key in locomotion function, but that proprioception and hip loading phases experienced during locomotion are required.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Normalized electromyograph (EMG) data for the major leg muscles during normal gait, showing the stance, left of the vertical line, and swing phase, on the right of the vertical line. At the same speed, the activity of the muscles is different. SO, soleus; TA, tibialis anterior; VA, vastus medialis; BFL, long head of biceps femoris; GA, gastrocnemius medialis; RF, rectus femoris; GLM, gluteus maximus. Adapted with permission from Prilutsky and Gregor.\textsuperscript{19}}
\end{figure}

\textbf{Is treadmill training an effective course of treatment for SCI patients?}

A hopeful role for treadmill training to improve locomotion after SCI was demonstrated by Lovely \textit{et al.}\textsuperscript{21} with investigations on spinal transected cats.\textsuperscript{21} The cats improved their ability to demonstrate weight-bearing stepping on their hind legs. However, the paper also shows that untrained cats demonstrated improved locomotion over time, showing some degree of spontaneous recovery.\textsuperscript{22} Consideration of the age of the animal is required as younger animals show a greater ability to recover locomotor ability.\textsuperscript{23}

Caution is necessary when relating data from animals to humans since SCI in humans can take numerous forms and therefore affect the spinal cord in many different ways. In animal models, contusion injuries are used to study incomplete SCI providing a model that can be accurately repeated to allow comprehensive study of SCI.\textsuperscript{24} Transected models are used to represent patients with complete SCI; however, it is rare for a patient to suffer an injury that fully transects the spinal cord. Furthermore, in transected animals, because the dura has to be cut, this leads to mechanisms of repair that are not usually seen in human SCI patients.\textsuperscript{25}

In humans, Wernig \textit{et al.}\textsuperscript{26} demonstrated that in acute incomplete SCI, treadmill training led to 33 out of 36 patients who were wheelchair bound to become ambulatory compared with 12 out of 24 patients from a retrospective study using conventional methods of treatment. However, the conventional methods were not clearly defined. Interestingly, some of the patients who improved locomotor ability still had low voluntary muscle activity. This suggests that recovery of locomotion via treadmill training is due to plasticity in the spinal cord caused by repetitive movements. The study does give evidence that treadmill training can improve the locomotor ability of patients, and this conclusion is supported by other studies.\textsuperscript{27–31}

Dobkin \textit{et al.}\textsuperscript{32} compared the effectiveness of body weight-supported treadmill training (BWSTT) with a control group which were trained using an overground mobility programme using parallel bars or braces. Overground training uses similar principles as treadmill training whereby therapists assist the movement of the patient’s legs to aid in stepping movements; however, the patient is actively moving and not relying on the physical cues of the treadmill to initiate stepping. The study was carried out on acute SCI patients who were unable to walk without any physical
assistance and both groups had the same amount of training. The patients who could not demonstrate any stepping ability in the control group had standing training; however, it has been demonstrated in animals that standing and stepping are independent skills and that by improving one it does not necessarily improve the other. Therefore, the control group may have been at a disadvantage. In both groups, patients who showed no motor function below the lesion did not improve overground walking. There was no significant difference between the two training methods in treating patients with ASIA C or D classification of SCI, both showing improvements. The study therefore suggests that it is not the type of training used but the targets set and the routines that are beneficial. The study also discounted patients taking spasticity medicines, potentially ruling out patients with more severe injuries and consequently not giving the full picture. The study focused on acute rehabilitation (before 56 days post-injury) and therefore does not assess the benefits of BWSTT on patients who have a chronic (more than 1 year post-injury) SCI.

It has been shown that spinal cord interneurons that are involved in locomotion are lost or have an impaired function a year after complete SCI and that treadmill training does not have an effect on neuronal activity in these patients (Fig. 3). This suggests that a year after SCI, the CPG apparatus starts to degenerate and that the CPGs need to be kept active to stop this from occurring. However, improvements in locomotor function have been reported after BWSTT in chronic incomplete SCI patients. This is most likely due to the fact that patients with incomplete SCI have some spared supraspinal input and some ability to move their legs which would keep the CPGs active. BWSTT treadmill training had significantly better improvements compared with conventional treatment. Again, it has to be taken into consideration that the conventional training method is not fully described in the methods. To fully evaluate if BWSTT is better than overground training, and the improvements are not all creditable to the frequency and intensity of training, a randomized parallel comparison study is required.

So far this study has used the term BWSTT to mean treadmill training that has been assisted manually by physiotherapists. Robotic-assisted treadmill training also shows improvements in SCI patients’ locomotor ability. However, a study by Wirz et al. showed that only 2 out of 20 patients with ASIA C or D grade SCI showed locomotor improvements. Patients who were non-ambulatory before the study did not regain locomotor ability but all patients improved their walking speed and endurance while being supported on the treadmill. The number of patients who showed improvements seems low when compared with the study by Wernig et al. using manually assisted BWSTT. This would suggest that manually assisted BWSTT is more effective. However, it is not possible to make a direct comparison between the two studies as variables such as the methods and the differences between patients need to be taken into consideration. Nooijen et al. found no significant difference in the improvements seen between the two methods in

Figure 3. The electromyographs (EMGs) for four different leg muscles of a chronic SCI patient before (A) and after training for 3 months (B). There was no significant difference before or after training between the EMGs of the different muscles. TA, tibialis anterior; BF, biceps femoris; RF, rectus femoris; GM, gluteus maximus. Taken from Dietz and Muller.
patients with chronic incomplete SCI. This is supported by a preliminary study by Field-Fote et al.\textsuperscript{39}

Even if there is no difference between the functional outcomes of the two different types of BWSTT, robotic aids may allow training to be carried out more easily and require less human resources. In one study, patients felt that they could achieve longer training sessions when using robotic BWSTT compared with the physiotherapy-assisted alternative.\textsuperscript{40} However, the patient has to actively train, not just allow the machine to do the work, for improvements to be seen.\textsuperscript{26} Therefore, longer training sessions may not generate faster results or greater improvements as the patient may be spending more time passively training.\textsuperscript{26,41}

One of the disadvantages of robotic-assisted BWSTT is the machines are expensive and therefore not viable for all clinics. However, there is work on non-motorized exoskeletons that aim to improve the gait of patients with incomplete SCI.\textsuperscript{42} The exoskeleton uses springs that are charged by the treadmill that aid in the swing phase of locomotion. This opens up the possibility of using able to offer BWSTT to patients in areas that do not have physiotherapists and cannot afford expensive equipment. Technically, the treadmill does not have to be electrically powered; it would be possible to extend the treadmill track and have a second person walking behind the SCI patient to power the treadmill. This would mean it would be possible to make a training device that was relatively inexpensive to run and could therefore offer added help to patients in countries that are unable to provide adequate rehabilitation to SCI patients.

Treadmill training can improve locomotor ability; by understanding the mechanisms involved in locomotion recovery, it may be possible to tailor treatment to make it more effective and specific to the patient’s needs.

**How does treadmill training achieve these improvements in locomotion?**

Step training helps reorganize the spinal cord connections and uses the spinal cord’s plasticity and memory to learn the movement of locomotion.\textsuperscript{43} However, when examining the electromyography of SCI patients, muscle activity was correlated more to load than muscle stretch.\textsuperscript{28,43}

Brain-derived neurotrophic factor (BDNF) is up-regulated in rat models of SCI after treadmill training.\textsuperscript{44} This is supported by the idea that plasticity in the spinal cord occurs via a transmembrane tyrosine kinase receptor (tkr) of BDNF.\textsuperscript{45} Fibroblasts, modified to secrete BDNF and NT-3, transplanted into the spinal cord improved locomotion.\textsuperscript{46} Thus, higher levels of neurotrophic factors (NTF) may increase neuron survival and lead to improved locomotion which links to the idea that acute SCI patients have better responses to training than chronic SCI patients.

Treadmill training also influences the electrophysiological properties of motor neurons, decreasing the after hyperpolarization phase which correlates with recovery of locomotion function.\textsuperscript{47} This is most likely due to the greater ability of the motor neurons to achieve doublet firing providing enough force to achieve locomotion.\textsuperscript{47} In mice with hemisectioned spinal cords, axon number was greater within 100 μm of the lesion in the treadmill-trained mice compared with non-trained mice.\textsuperscript{48} This suggests that treadmill training is able to promote new connections with the spinal cord. Since the study did not clearly show any newly formed axons traversing the lesion, axon sprouting may underlie this functional reorganization of the spinal cord to aid in the re-learning of locomotion. In spinal transected rats, step training elicited a decrease in active neurons associated with a recovery of locomotor ability.\textsuperscript{49} This suggests that the increase in axon number reported by Goldschmit et al.\textsuperscript{48} after training is pruned to make the pathways more efficient.\textsuperscript{48,49}

Training can have an effect on many different aspects of the chemical and electrophysiological functioning of the spinal cord. Therefore, it may be possible to achieve the same levels of recovery through alternative methods which focus on these individual aspects.

**Disadvantages of treadmill training**

One problem with training the spinal cord is that it has limited ‘memory’. Spinal transected cats lost their ability to walk after a period of 12 weeks without training. However, when training was reinitiated, the skill was learnt quicker.\textsuperscript{50} Furthermore, the length of time between when the injury occurred and the start of training affects the outcome and ability of the patient to walk following training.\textsuperscript{34,51}

Even after training, patients can only achieve distances of metres with the aid of walking devices. Therefore, treadmill training may be more of a temporary solution rather than a treatment. Moreover, if the level of the lesion involves the circuitry of the CPG, it is unlikely that treadmill training would have any effect.

Treadmill training is not effective in aiding patients with complete SCI to walk over ground. However, the training is still beneficial. Behrman and Harkema\textsuperscript{52} presented a case study of a patient who had an ASIA A classified SCI who after 83 BWSTT sessions was able to support 90% of their weight.\textsuperscript{52}

Having reviewed the treadmill technique, this paper now addresses some alternative therapies for improving locomotor abilities.

**Functional electrical stimulation approaches to improving locomotor activity following SCI**

Functional electrical stimulation (FES) aims to provide electrical signals to denervated nerves to produce functionally
useful movements via the contraction of key muscles. FES improves locomotion in patients with incomplete SCI while in complete SCI patients, it strengthens the muscles and joints as well as being incorporated into standing and walking training.\textsuperscript{53,54} However, is FES better than treadmill training in terms of functional outcomes? Nooijen et al.\textsuperscript{58} showed that there was no significant difference between patients, with incomplete SCI, who were trained with body-weight-supported FES or BWSTT. However, there was no discrimination in the study between chronic and acute patients. As far as this study can find, there is no research comparing the use of the two training regimes in patients with complete SCI. However, when trying to compare FES with other methods, it has to be remembered that FES involves a degree of overground training as the patient uses the FES and walking aids to walk over ground. Therefore, it is possible to combine treadmill training and FES.\textsuperscript{55,56}

**Pharmaceutical approaches to improving locomotor activity following SCI**

Specific neurotransmitters have been implicated in the modulation of locomotion, with the suggestion that different neurotransmitters have precise roles in the acute and chronic phases of SCI. By targeting specific receptors and channels of these key neurotransmitters, it may be possible to create new therapeutic strategies for the recovery of locomotor ability.

Noradrenaline, when applied to an isolated spinal cord of a rat can cause variable results, sometimes initiating a locomotor-type rhythm. It has been suggested that its primary role is in maintaining locomotor activity.\textsuperscript{57} In acute spinalized cats, application of noradrenaline agonists at the L3 and L4 region allows them to walk with body weight support before 7 days post-injury, unlike untreated spinalized cats.\textsuperscript{58,59} This suggests that the use of noradrenaline agonists would enable earlier and more beneficial treadmill training.

However, the use of clonidine, an a2-noradrenergic agonist, had negative effects on the locomotor ability of partially transected spinal cats.\textsuperscript{60} These differences may be due to effects of clonidine on just the postsynaptic adrenergic receptors in complete transection, whereas in partial transection, it also acts on the presynaptic receptors which inhibits release of noradrenaline that aids in functional recovery.\textsuperscript{50,61} Since patients rarely fully transect their spinal cord, it could be assumed that clonidine would have a negative effect on a patient’s recovery. Indeed in two complete SCI patients, clonidine caused leg flaccidity associated with a decrease in the activity of the gastrocnemius muscle.\textsuperscript{62} However, Stewart et al.\textsuperscript{62} suggests that the effects of clonidine vary depending on the severity of the injury and it may be beneficial to patients with incomplete SCI when training.

Serotonin has also been identified to play a role in locomotion. In rats, brainstem-stimulated stepping can be blocked by the administration of serotonin antagonists, while in spinalized rats, serotonin agonists elicited improvements in locomotor function.\textsuperscript{63,64} Raphe grafts providing longer term application of serotonin to the spinal cord also improved function in spinalized rats.\textsuperscript{65} What is interesting is the graft has to be placed at the site of the CPG rather than the site of the lesion. This reiterates the importance of the CPG in recovery after SCI. However, there are species differences in response to treatment. In cats, serotonin agonists only modulated locomotion in chronic SCI while contusion model rats treated with serotonin agonists, combined and on their own, did not improve their locomotion.\textsuperscript{66} This suggests that serotonin agonists may not be beneficial to patients.

No studies could be found that used serotonin agonists in humans, but the combination of BWSTT and the serotonin antagonist cyproheptadine improved patients’ locomotor ability to varying degrees.\textsuperscript{67} This could be down to the antispasmodic properties of the drug while variation may correlate with how much of the 5HT apparatus was spared in the spinal cord. Norman et al.\textsuperscript{68} reported that cyproheptadine helped patients with chronic incomplete SCI improve their maximum walking speed and reduced their need for assistance when treadmill training. Furthermore, clonidine and cyproheptadine had different effects on locomotion, suggesting that the combination of the two would further benefit the patient.\textsuperscript{68,69}

Other pharmaceuticals have also been implicated in affecting locomotion in animal models.\textsuperscript{60,70–76} However, little research is available regarding their use in humans, most likely to the limited effects and the side effects.

The use of the aforementioned drugs has disadvantages. In the case of clonidine, there is a short therapeutic window that is also influenced by the severity of the injury. Different drugs may be useful depending on the different time periods after injury. The drugs have relatively short-lasting effects that would require numerous injections to sustain. Therefore, for them to be effective as a treatment, they have to be combined with a training regime to make full use of the drug-induced improvements. Preliminary reports have shown that the use of both drugs and training produces greater and faster improvements than training by itself.\textsuperscript{52} This suggests that BWSTT treadmill training is not as effective as a drug treatment combined with training. The use of this treatment would require a significant amount of medical supervision and as previously mentioned, the robotic-assisted gait BWSTT allows patients to train without having to have physiotherapists or medical staff present. Also, the use of treadmill training without pharmaceuticals would mean that side effects would not be an issue.
Courtine et al.\textsuperscript{77} went a step further by using FES, serotonin agonists and treadmill training in spinalized rats, allowing them to perform full body weight-bearing treadmill locomotion, resembling normal gait. It also reported that the combination of treatments showed a greater improvement than individual treatments.\textsuperscript{77} The use of this treatment in patients is just about to be researched in the same laboratory in UCLA and may help understand the best way to rehabilitate patients with complete SCI. However, in humans, it has been proposed that because there is a greater reliance on supraspinal inputs, these inputs need to be strengthened to allow for recovery of locomotor ability.\textsuperscript{78} If this is correct then there is a plateau in the improvement in locomotor ability that these treatments can achieve in SCI patients.

The techniques discussed so far are all related to the adaptation of existing spinal cord circuitry and they show limited ability for improvement of patients with SCI; however, regeneration techniques may be the key to full recovery of locomotor ability.

**Tissue regeneration approaches to improving locomotor activity following SCI**

The most obvious method of treatment of locomotor dysfunction in SCI patients is to repair the damage done; this would undoubtedly be more effective as a treatment than treadmill training. The techniques that are currently being tested are still a long way from being viable for human subjects. As previously mentioned, to allow regeneration in the CNS, neurons have to survive, the environment has to be permissive for axon growth and the growth cones from the axons have to make contact with the correct target. At the moment, these goals are still out of reach in terms of addressing them in humans but there are strategies that have been tested in animal models that show promise. As regeneration of the CNS is such a large topic, this paper is only going to look at two key areas and their prospective roles in locomotion recovery.

The first hurdle is cell survival. NTF aid in the survival of neurons and therefore play an important role in regeneration techniques. In spinal cord-transected cats, implantation of fibroblasts which secrete NTF allowed the cats to show faster recovery of stepping ability than being treadmill trained. What is interesting is that there was no regeneration across the lesion; therefore, the NTF may be working directly on the cells of the CPG.\textsuperscript{46}

The next area that needs to be addressed is the ability of axons to travel to their correct targets. After injury, the axon growth cones are inhibited by chemo-repulsive chemicals and by physical boundaries (for review, see Hou et al.\textsuperscript{79}). Nogo-A antibody promotes growth of axons; however, it does not direct the axons and therefore inappropriate connections can be formed. Furthermore, Nogo-A antibody and treadmill training on spinalized rats had a negative effect on locomotor ability whereas individual treatments had a positive effect.\textsuperscript{80} The results could not be explained by hyperalgesia due to inappropriate connections; therefore, there is another mechanism causing the two treatments to counteract each other. This would be a problem when using this treatment on humans as it would be assumed that SCI patients would still be having rehabilitation.\textsuperscript{80}

The use of regeneration techniques is an exciting area of neuroscience that will play a major role in the management of SCI in the future. However, since the spinal cord consists of many spinal tracts exhibiting some topographic mapping, the major challenge is to line up the correct pathways. Training techniques are still at the forefront of the treatment of locomotor dysfunction in SCI patients, the challenge is to optimize strategies available.

**Conclusion**

Some training types may be more easily applied to different types of SCI. When training patients with complete SCI, it would be more sensible to use robotic treadmill training to improve stepping ability as it can accurately and consistently recreate the normal positioning of the limbs. With over-ground walking, the training may be more reliant on non-ambulatory training or with physiotherapy-assisted BWSTT as the steps cannot be as tightly regulated. It has to be remembered that there are other health risks, such as autonomic dysreflexia, that may also benefit from treadmill training. Even though it may not be any better than any other single forms of training, it may have an added advantage in the health of the patients.

The greatest results seen in the improvement of locomotion are shown after the combination of the different therapies: FES, pharmaceutical and treadmill training. The results shown are based on rats and as previously mentioned, humans are more reliant on supraspinal inputs. Therefore, these techniques are able to improve locomotor ability but do not have the ability to fully recover locomotor function. This is why the use of regeneration techniques is desirable. The techniques show promising results in rats; however, work is just about to start to see if the benefits are the same for humans. The greatest challenge is trying to achieve targeting and therefore correct connections. An interesting point raised by Dietz and Muller is that the loss of interneurons because of chronic SCI below the lesion may impact on the effectiveness of regeneration techniques.\textsuperscript{34} Therefore, since treadmill training affects the neuronal activity in acute complete SCI, the ability of treadmill training to keep the CPGs active may be a viable possibility, until regeneration techniques are feasible.\textsuperscript{34}
Furthermore, by trying to limit the amount of damage done by the secondary injury phase, it may be possible to save some of the connections and therefore give training and rehabilitation techniques a greater chance of succeeding. It had previously been thought that steroids were beneficial in the acute stages of SCI; however, there is growing debate about the beneficial effects of the injection (for systematic review, see Botelho et al.\textsuperscript{81}). Another strategy that has been looked into is the use of AMPA/kainate antagonists on minimizing excitotoxicity.\textsuperscript{82,83} However, for the greatest results, the antagonists would have to be given at ~15 min following SCI, therefore causing issues when trying to create a clinical trial.\textsuperscript{82} Benefits have been reported 4 h after SCI with effects solely in the white matter of the SCI.\textsuperscript{84} Many of the secondary injury phase processes are interlinked, so to effectively minimize the damage done, multiple therapies need to be applied simultaneously. Therefore, a treatment that targets vascular, inflammation and excitotoxicity processes would be the most beneficial.

From the research on this topic, it has become clear that when looking at how to treat locomotion dysfunction in SCI patients, the question that should be asked is not which treatment to use but when a treatment should be used. This suggests that in the acute phase of SCI treatment, the combination of FES, BWSTT and both a noradrenergic agonist and a serotonin antagonist should be given. If research in humans follows that of rats, a serotonin agonist may be more beneficial. The drugs should be tapered off after a few months of training to allow for the maximum effect when they are most needed and stopping the likelihood of any adverse reactions developing. When the patient is able to bear their own weight, they should stop the BWSTT training and carry on with the FES as a neuroprosthesis and as an overground training device. The FES should be removed when the patient is able to cope with everyday tasks and move around with the FES. As the patient has been training, the CPG should still be active, making it possible to repair the spinal cord when regeneration techniques are viable. As previously mentioned, the site of the lesion may dictate how the training is carried out, requiring treatment to be personalized. In patients with complete SCI at the lumbar area, it may be beneficial for BDNF to be administered intrathecally to allow for maximal survival of the CPG components.

In conclusion, BWSTT is not the most beneficial individual treatment, but combining this with drugs and FES, it provides the best option before regeneration techniques become available.

Author biography

R.T.F. recently obtained his degree in Neuroscience in the form of an intercalation year while studying for a degree in Medicine. He was attracted to the course due to an interest in the nervous system and, in particular, clinical conditions arising from the disruption and damage to the nervous system. This led him to decide to write a review on the forms of treatment available for patients with SCI. After completion of his studies he will begin his career as a doctor, in which he hopes to specialize in neurology with an interest in spinal cord injury.

References


