Could Neurotrophins Replace Treadmill Training as Locomotor Therapy Following Spinal Cord Injury? Focus on “Neurotrophic Factors Promote and Enhance Locomotor Recovery in Untrained Spinalized Cats”

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How to repair the injured spinal cord is a question that scientists have struggled with for decades. The answer is of course still a mystery. But ask people on the street for their opinion and they will likely offer something like “stem cells” as the solution. I find it amusing (and honestly, a bit annoying) that family and friends continue to ask me if there is anything new with stem cells. My usual response is that I am not a stem cell researcher (I don’t even think I have ever seen a stem cell in person) but I would be happy to talk about treadmill training therapy for spinal cord injury. But herein lies the problem. One can argue that there have not been any “new discoveries” in this field and that the basic ideas underlying treadmill training for spinal cord injury have not changed since they were introduced by Serge Rossingol and Reggie Edgerton over 20 yr ago (Barbeau and Rossignol 1987; Lovely et al. 1986). To be sure, progress has been made (e.g., enhancing the effectiveness of treadmill training using drugs, robotic devices, and functional electrical stimulation) and there has even been a recent surge of media interest in body-weight–supported treadmill training (e.g., Kluger 2007), although the fundamental ideas have not changed; spinal repair (and thus functional recovery) is an activity-dependent process. Providing optimal sensory cues to the spinal circuitry reinforces the ability of these spinal circuits to generate locomotion. In this issue of Journal of Neurophysiology (p. 1988–1996), Boyce and colleagues provide evidence that, in effect, challenges this way of thinking (Boyce et al. 2007). Their findings suggest that activity may not be essential, but that neurotrophin delivery alone may be sufficient to stimulate plasticity in the spinal cord.

Boyle and colleagues investigated the effect of delivering neurotrophins to the spinal cords of complete spinal transected cats. Fibroblasts that secreted brain-derived neurotrophic factor and neurotrophin-3 were transplanted into the lesion site. To determine whether the neurotrophins affected locomotor recovery, the investigators assessed the ability of the spinal cats to perform quadrupedal stepping on a treadmill. Additional experimental groups were used to compare the effects of neurotrophin treatment to daily treadmill training and also to determine whether a neurotrophin treatment + treadmill training combination would enhance locomotor recovery. The investigators found that indeed neurotrophin treatment significantly enhanced locomotor performance. The surprising result was how effective the neurotrophin treatment was at improving stepping. The spinal cats that received neurotrophin treatment performed as well as the spinal cats that received daily treadmill training. The neurotrophin-treated spinal cats also regained weight-bearing stepping earlier than did the treadmill-trained spinal cats. Further evidence for a neurotrophin-enhanced recovery was that the combination of neurotrophin treatment + treadmill training resulted in the best stepping performance.

As an ardent believer in treadmill training therapy and activity-based therapies in general, naturally my reaction to these results was one of skepticism. How could neurotrophin treatment, in the absence of any activity imposed on the spinal circuitry, produce this level of locomotor recovery? In these types of studies, the methods used to measure recovery are critical and so the first thought was that perhaps the locomotor assessments were flawed in some way. As it turns out, the assessment and subsequent analyses used by Boyce and colleagues were solid. First of all, they collected data over a 12-wk postsurgical period, which is more than a sufficient amount of time to capture the plateau in recovery (de Leon et al. 1998). Rather than relying on gross measures of stepping, they performed detailed kinematic analyses of the hindlimb step cycle and interlimb coordination. Moreover, they compared stepping performance in the same animal before and after spinal cord transection, thus providing a true measure of recovery (Belanger et al. 1996). They even chose to examine quadrupedal stepping on a treadmill, which is difficult to test in spinal cats but is a more natural form of gait than bipedal hindlimb stepping (which has traditionally been used in spinal locomotion experiments). Some may be concerned with the number of animals in the study (n = 16) and, certainly, it will be wise for other scientists to confirm their findings. Still, the Boyce et al. study is one of the largest spinal cat locomotor studies ever to have been performed and this is impressive, considering how difficult it is to perform long-term locomotor studies in large spinal mammals.

If we accept that neurotrophins enhanced locomotor recovery in the absence of treadmill training, the obvious question is how were the neurotrophins able to do this? Some insight into the mechanisms was provided by Boyce and colleagues when they failed to find any axonal growth through the transplants. This suggested that the effect of the neurotrophins was to enhance plasticity within existing circuits of the lumbar spinal cord. In the brain, exercise is known to induce neurotrophin expression, which in turn promotes neural plasticity (Cotman and Berchtold 2002). Recent evidence suggests that neurotrophins may also mediate the effects of treadmill training on synaptic plasticity in the injured spinal cord (Ying et al. 2005). The findings of the Boyce et al. study suggest that it may be possible to bypass treadmill training altogether and directly...
stimulate plasticity by delivering neurotrophins. At this point, it is premature to think that one could simply replace treadmill training therapy with neurotrophin therapy. However, if indeed neurotrophins turn out to be powerful stimulators of spinal plasticity, we may very well consider the Boyce et al. study as the study that changed our beliefs regarding the role of activity in recovery following spinal cord injury.

REFERENCES


