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Editorial comment

On two papers showing the effects of testosterone on recovery from sciatic nerve crush

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The use of sex hormones as potential neurosteroids capable of enhancing neuronal repair and functional recovery is gaining some momentum in the experimental literature. Two very interesting papers are presented in this issue of *Restorative Neurology and Neuroscience* outlining the effects of testosterone treatment upon anatomical and functional recovery after sciatic nerve crush injuries. The article by Brown, Khan and Jones reports that testosterone treatment can accelerate recovery from lower limb paralysis caused by sciatic nerve crush. These investigators looked at recovery of post-operative locomotion over seven weeks of testing as measured by the "Sciatic Functional Index". On this measure, the investigators observed that between three and five weeks after injury, the testosterone-treated rats had better outcome scores than controls, and reaching significance at four weeks; however, beyond five weeks post-operatively, the differences between the treated and untreated injury groups disappeared. Histological examination using HRP labeling revealed that, by the end of the experiment, the sciatic nerve had regenerated in both groups. The authors concluded that the administration of testosterone via Silastic implants accelerated both nerve regeneration and behavioral recovery beginning in the early stages of the injury process. They propose that the upregulation of cytoskeletal protein β_{II} plays a role in the process of regeneration and repair.

In a companion paper from a different laboratory, Swallow and colleagues performed a similar nerve crush injury and used three weeks of daily *injections* of testosterone to accelerate sciatic nerve regeneration and to enhance functional recovery. These investigators also measured gait, response to thermal stimuli, and skin pinch (nocioception) to determine the outcome of the testosterone treatments. Swallow and colleagues found that the testosterone treatments accelerated the sciatic nerve regeneration by over 22 %, but this increase in regeneration did not improve functional recovery.

The results of the two studies serve to highlight some of the problems facing investigators as they seek to determine the effects of various pharmacological agents on neural and functional recovery. One of the key questions concerns the development of a standardized series of outcome measures for specific types of injuries, allowing different studies to be compared to one another. What might be needed is something along the lines of the Glasgow Coma Scale equivalent for rats or even a standardized way of measuring and statistically analyzing gait that could be applied across the different laboratories. Here, the issue concerns the actual "definition" and measurement of "functional recovery".

Both papers had measures of anatomical and behavioral outcomes in response to treatment, but very often "neural plasticity" is measured primarily in terms of molecular or physiological variables. In the Swallow et al. report, testosterone was shown to accelerate sciatic nerve regeneration by more than 22 %, but without measurable behavioral outcomes. Had they not done any behavior, it might have been concluded that testosterone was a useful agent in promoting recovery…depending of course, on a rather limited definition of recovery; i.e. nerve regeneration.

A second factor that is important here concerns the delivery of putative agents thought to promote recovery. One study used chronic injection of testosterone, the other applied chronic treatment by Silastic implant. How does one assess the efficacy of these two approaches? If replications of studies are attempted, the replications should be as complete as possible to permit direct comparisons.

Despite the differences, the two papers highlight the growing interest in examining the role of "gonadal" hormones in brain damage and repair. Increasingly, evidence

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shows that hormones like estrogen, progesterone and testosterone have multiple, systemic effects as neurotrophic agents, anti-oxidants and anti-inflammatory agents acting both peripherally and in the brain itself. Given the current lack of effective treatments for traumatic brain damage, the further study of these neurosteroids is warranted.

Suggested reading

Stein, D.G. and Hoffman, S.W. Brain injury, functional recovery after. In: G. Adelman and B.H. Smith (Eds). *Encyclopedia of Neuroscience*, 2nd edition (CD-ROM), Elsevier Science, Amsterdam, 1997.