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Invited review

Sciatic nerve injury: A simple and subtle model for investigating many aspects of nervous system damage and recovery

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HIGHLIGHTS

- Sciatic nerve injury models many different nervous system pathologies.
- Different functional components of the sciatic nerve are segregated in its branches.
- Selective injury to the nerve components results in neuropathic pain states.
- Technologies exist to accurately reproduce different degrees of injury.
- Many methodologies to assess damage and promote recovery are described.

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ABSTRACT

Sciatic nerve injury has been used for over a century to investigate the process of nerve damage, to assess the absolute and relative capacity of the central and peripheral nervous systems to recover after axotomy, and to understand the development of chronic pain in many pathologies. Here we provide a historical review of the contributions of this experimental model to our current understanding of fundamental questions in the neurosciences, and an assessment of its continuing capacity to address these and future problems. We describe the different degrees of nerve injury – neurapraxia, axonotmesis, neurotmesis – together with the consequences of selective damage to the different functional and anatomic components of this nerve. The varied techniques used to model different degrees of nerve injury and their relationship to the development of neuropathic pain states are considered. We also provide a detailed anatomical description of the sciatic nerve from the spinal cord to the peripheral branches in the leg. A standardized protocol for carrying out sciatic nerve axotomy is proposed, with guides to assist in the accurate and reliable dissection of the peripheral and central branches of the nerve. Functional, histological, and biochemical criteria for the validation of the injury are described. Thus, this paper provides a review of the principal features of sciatic nerve injury, presents detailed neuroanatomical descriptions of the rat's inferior limb and spine, compares different modes of injury, offers material for training purposes, and summarizes the immediate and longterm consequences of damage to the sciatic nerve.

Contents

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1. Introduction

1.1. Historical perspectives

The use of sciatic nerve axotomy (SNA)[2] as an experimental model in neuroscience dates back at least to the turn of the 20th Century, when Santiago Ramón y Cajal described its use in his 1906 Nobel prize acceptance speech (Ramón y Cajal, 1906). His seminal contribution to the study of nervous system injury, the two volume *Estudios sobre la Degeneración y Regeneración del Sistema Nervioso* (Ramón y Cajal, 1928) published in 1913 and 1914, made frequent reference to the use of sciatic nerve lesions by others, suggesting that the technique was already widely practiced by neurophysiologists and neuroanatomists in the mid to late 19th Century (Anderson, 1902; Fraidakis, 2010; Garcia-Poblete et al., 2003; Lobato, 2008). Through clever application of the model and rigorous description of the results, Cajal made substantial contributions to the defense of neurotropic theory and nerve continuity in regeneration.

Cajal experimented with degrees of injury to the sciatic nerve, but it was not until the end of the Second World War that Sir Herbert Seddon published his ternary classification of nerve damage severity based on his observation of hundreds of trauma cases (Seddon, 1942, 1943). In increasing order of damage, he defined *neurapraxia*, a rapidly reversible compression injury; *axonotmesis*, loss of axon continuity with preservation of the nerve sheath; and *neurotmesis*, where the nerve itself is transected. It is of no small significance that this classification is still current 70 years later.

Subsequently, Sunderland refined this system into five categories based on the histopathology, rather than the degree of injury, and added electrodiagnostic and clinical criteria that related the categories to the possibility of regeneration with or without surgical intervention (Sunderland, 1951). In Sunderland's classification the first and fifth degrees of injury correspond to Seddon's neurapraxia and neurotmesis, respectively. Thus the principal refinement was to subcategorize axonotmesis into three degrees of injury with progressively worse prognosis for spontaneous recovery; surgical intervention was considered by the third and recommended by the fourth degree. In 1988, Mackinnon and Dellon proposed a sixth degree (Mackinnon and Dellon, 1988) for cases where different parts of the nerve had suffered a combination of the previous five grades of injuries, resulting in a mixed syndrome.

[2] Sciatic nerve axotomy.

The idea that the degree of injury might be of profound clinical importance had been mooted by the physicians Weir Mitchell, Morehouse and Keen (Richards, 1967a) during the American Civil War of 1861–1865. They described the development of an intractable burning pain after gunshot injuries to nerves and blood vessels (Weir Mitchell et al., 1864) that they later termed causalgia, from the Greeks words for heat and pain (Richards, 1967b). Weir Mitchell, who had studied in Paris under the renowned physiologist Claude Bernard, subsequently experimented on the sciatic nerve of rabbits (and human cadavers) in an attempt to better understand the damage caused by trauma (Weir Mitchell, 1872), showing that the tough sheath of the sciatic nerve made it particularly resistant to injury. His observations also led him to conclude that the nerve maintained functional and anatomical segregation of the axons:

> *"The toughness and general elasticity of nerve trunks sometimes serve a useful purpose in cases of ball wound, and I have repeatedly seen nerves escape total destruction from missiles simply because they were thrust aside, instead of being divided. . . . On the other hand, injuries of nerves in connection with bone or near to joints are likely to be severe and lasting, because at these points and in these positions the nerve trunk is more firmly anchored than elsewhere. . .*
> *. . . When a spinal nerve emerges from the intervertebral canal it is motor and sensory, by the union of the anterior and posterior roots, which represent motion and sensation respectively. Whether or not these fibres become at once scattered so that every part of the area of the nerve contains an equal share of the nerve tubes, both of sense and motion, is not at present very clear. Such, however, is the popular medical belief, though there is a good deal of reason to think that the nerve filaments of either function remain in bundles; because, as we shall see later, it is very common to find that a nerve trunk, injured by a missile, has suffered in its sensory or motor functions alone, which could scarcely be accounted for upon any other supposition than that last mentioned. Any other explanation must presuppose some greater susceptibility to injury in one set of fibres than in another."* (Weir Mitchell, 1872) pp. 25–26.

Thus, by the end of the 19th Century, the SNA had been established as a fundamental experimental model in the two major fields that would continue to motivate its use over the following century – nerve regeneration and neuropathic pain. In both fields, recognition of the importance of the degree of nerve damage has driven the development of multiple technologies to replicate the consequences of different clinically relevant injuries. In the last two decades of the 20th Century, several important innovations were introduced to reliably induce neuropathic pain (see Section 1.3) and the technologies to evaluate and ameliorate the consequences of nerve damage are becoming ever more sophisticated.