

4-Aminopyridine Attenuates Neurogenic Muscle Atrophy After Sciatic Nerve Crush Injury in Mice

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BACKGROUND

Traumatic peripheral nerve injury (TPNI) represents a major health problem that often leads to significant functional impairment and permanent disability from the loss in axonal continuity, neuronal cell death, nerve demyelination, conduction defects, muscle denervation and muscle atrophy. 4-Aminopyridine (4-AP), a broad-spectrum potassium channel blocker and FDA-approved drug, improves neuromuscular function in patients with diverse demyelinating disorders. The neurological benefits of 4-AP are believed to result from increases in action potential duration, calcium influx, neurotransmitter release and synaptic transmission. We have recently repurposed the use of 4-AP and demonstrated that both systemic and local 4-AP administration enhances global functional recovery of the affected limb, promotes remyelination of the nerve and improves the nerve conduction velocity in a mouse model of TPNI. While muscle atrophy occurs very rapidly following nerve injury, the effect 4-AP on muscle atrophy and muscle contractile function is largely unknown. This study was designed to explore the possible beneficial effects of 4-AP treatment in muscle atrophy, intrinsic muscle function, and muscle regeneration following acute sciatic nerve crush injury.

METHODS

• Mouse Model of Sciatic Nerve Crush Injury

Moderate crush injury (30 sec) of right nerve followed by 4-AP treatment for 14 days



• 4-AP Administration

Systemic: 4AP, 10 µg, ip immediately after surgery and once daily

• Walking Track Analysis (SFI, Sciatic Function Index)

• Immunohistochemistry and Western Blotting

• Ex vivo Force Measurements in EDL Muscle

• Results are presented as means ± SEM and considered significant when $P < 0.05$

RESULTS

Figure 1. 4-AP Treatment Prevents EDL Muscle Atrophy (n = 3-6/group)

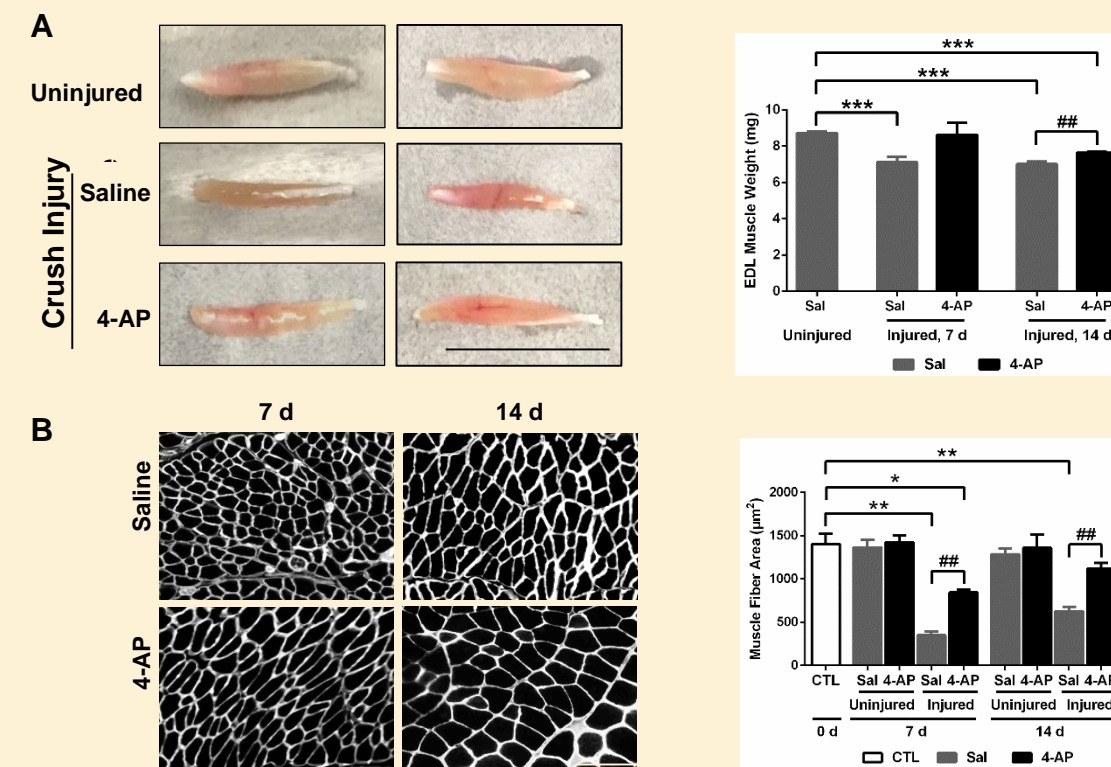


Figure 2. 4-AP Improves TA Muscle Histology with More Centralized Nuclei and Better Muscle Fiber Distribution (n = 3 /group)

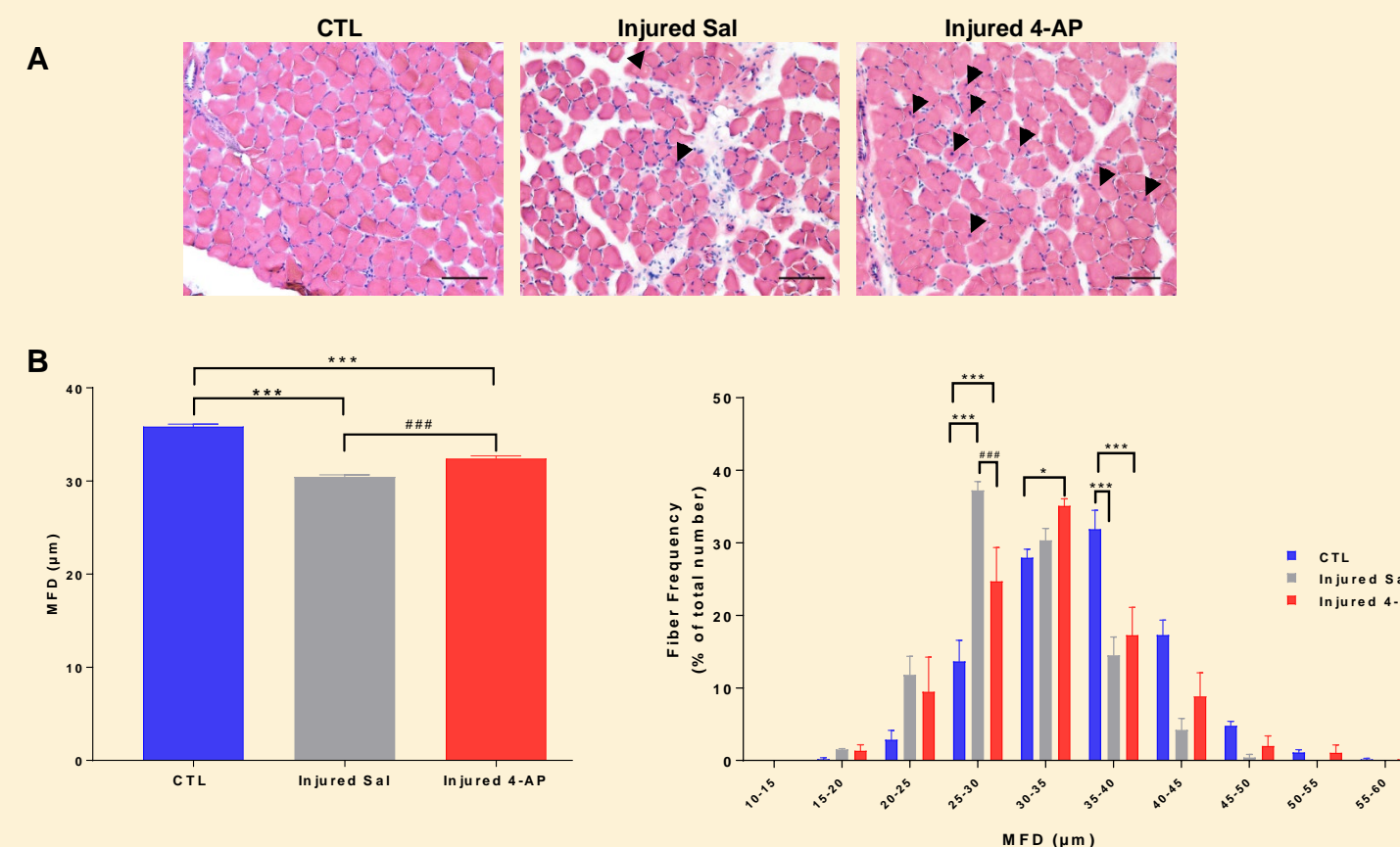
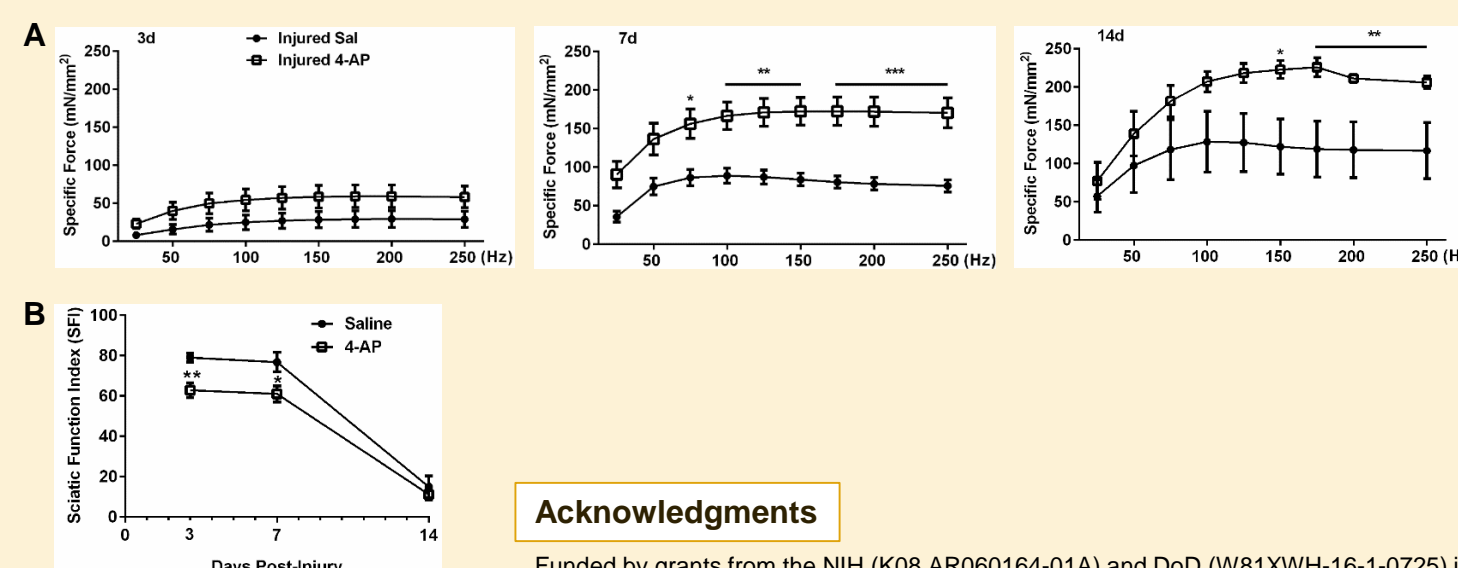


Figure 3. 4-AP Improves ex vivo Muscle Force and in vivo Motor Function (n = 3-6/group)



Acknowledgments

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RESULTS

Figure 4. 4-AP Treatment Decreases the Relative Expression of Atrophy Genes and Transcription Factors in Gastrocnemius Muscle (n = 3-7/group)

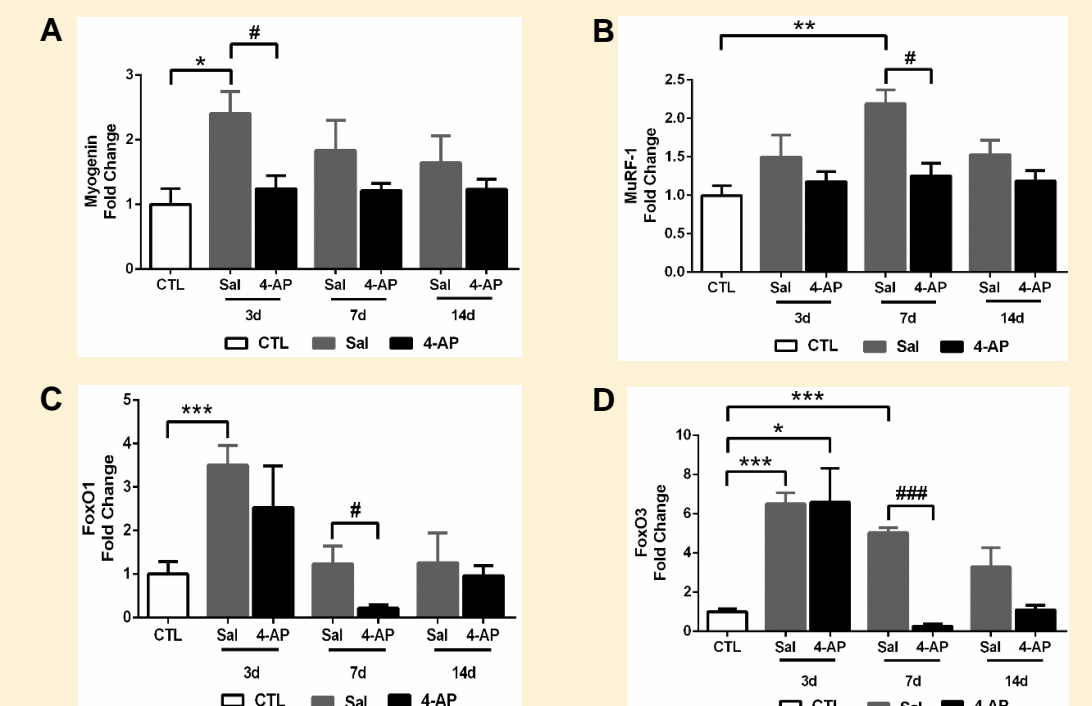


Figure 5. 4-AP Treatment Decreases the Expression of Myogenin in Gastrocnemius Muscle (n = 3-4/group)

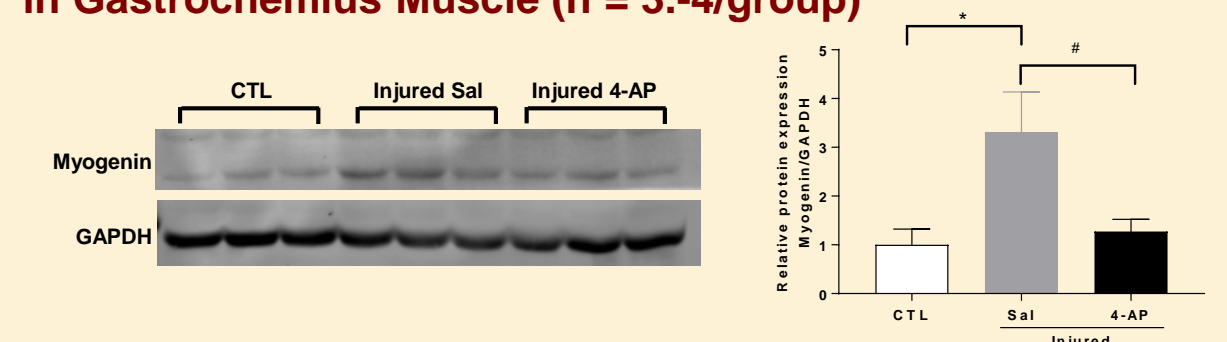
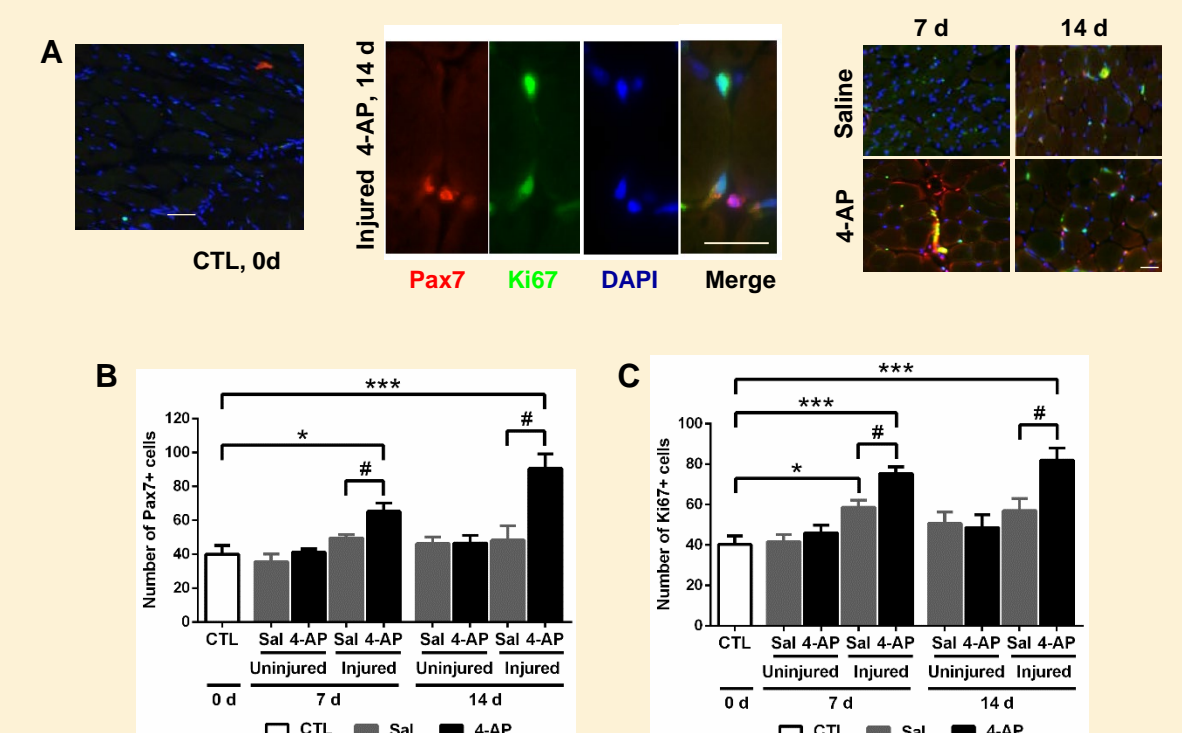


Figure 6. 4-AP Treatment Increases Pax7+ and Ki67+ Satellite Cells in TA and EDL Muscles of Injured Limb (n = 3/group)



CONCLUSIONS

These findings provide new insights into the beneficial effects of 4-AP in nerve injury-induced muscle atrophy and dysfunction, and open a new window for further investigation.