Sex Differences of AMPK Activators on Neuropathic Pain

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Introduction and Process

Abstract

Neuropathic pain is a condition that affects millions of people, but the most commonly prescribed treatments have dangerous side effects. Previous studies have shown the efficacy of relatively safe Adenosine Monophosphate Kinase (AMPK) activators on resolving neuropathic pain, especially that of the FDA-approved diabetes drug, Metformin.[1] This drug has been shown to decrease mechanical hypersensitivity following peripheral nerve injury in male mice and rats.[2] Given these recent findings, additional experiments were completed to test its efficacy in females. Our hypothesis was that females and males would respond in a similar (if not identical) manner to Metformin treatment following nerve injury. Using the spared nerve injury (SNI) model of neuropathic pain[3], male and female mice were tested for mechanical hypersensitivity and cold allodynia both before and after treatment with Metformin.

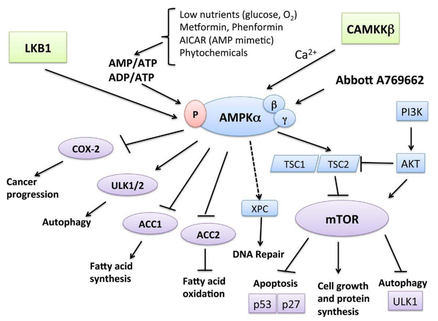

Figure 1. Function and regulation of AMPK leading to tumor suppression.[4]

Inducing and Treating Neuropathic Pain

Male and Female CD-1 mice were given SNI surgery, cutting the tibial and common peroneal branches of the sciatic nerve to sensitize the lateral aspect of the posterior left paw. (Figure 2) Mice were tested at days 7, 10, and 14 post surgery to assess the development of neuropathic pain. Increased paw withdrawal frequency (Von Frey method) indicated the presence of neuropathic pain at 14 days post surgery. Males and Females were given a 200mg/kg dose of Metformin in 0.9% saline (Metformin group) or 0.9% saline (Vehicle group) daily for 7 days starting at 14 day post surgery. Injections were given intraperitoneally.

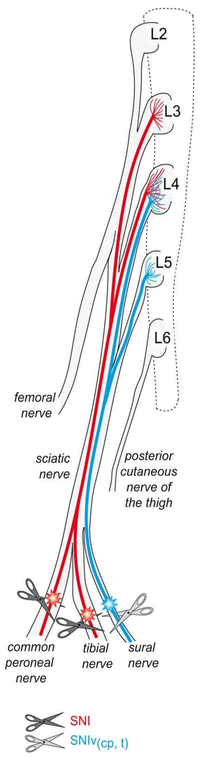

Figure 2. Schematic View of Sciatic Nerve Branches with Projections of Injured Fibers into DRG.[5]

Results

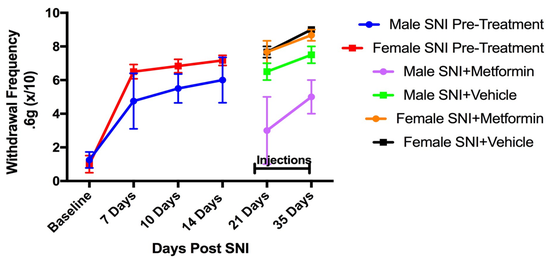

Figure 3. Von Frey withdrawal frequency using 0.6 gram filament.
Animals were subjected to 10 touches with a 0.6 gram filament, number of paw withdrawals, shakes or licks recorded.

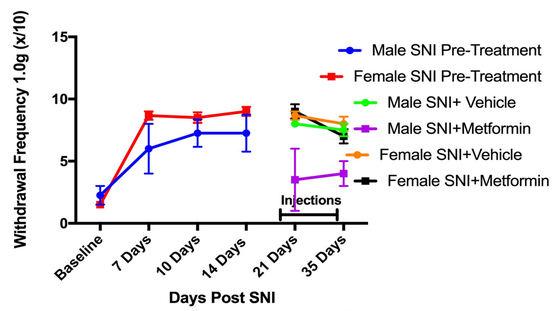

Figure 4. Von Frey withdrawal frequency using 1.0 gram filament.
Animals were subjected to 10 touches with a 1.0 gram filament, number of paw withdrawals, shakes or licks recorded.

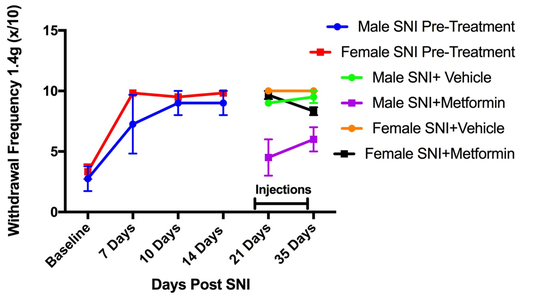

Figure 5. Von Frey withdrawal frequency using 1.4 gram filament.
Animals were subjected to 10 touches with a 1.4 gram filament, number of paw withdrawals, shakes or licks recorded.

It is clear Metformin was effective at alleviating mechanical hypersensitivity in males, but was not able to do the same in females. Cold allodynia was also tested (data not shown) using the acetone test in males and females, but the results were not conclusive. Male and female spinal cord and dorsal root ganglia (DRGs) were compared and Metformin decreased microglial activation (Fig. 6) while alleviating a break in nonpeptidergic IB4 neurons along the dorsal horn of the spinal cord in males, but not females (not pictured). DRGs in males and females have not yet had conclusive results from staining.

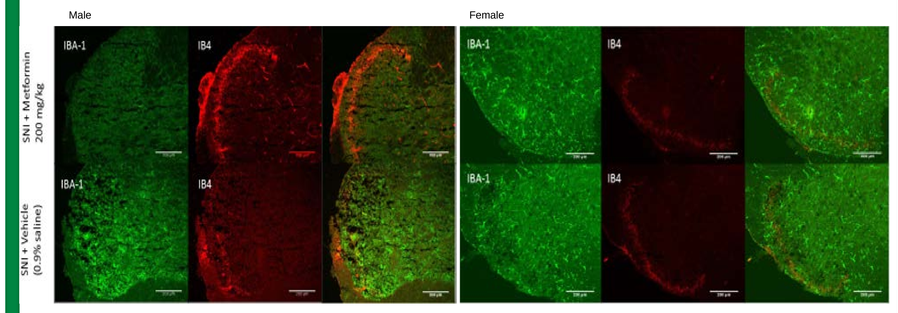

Figure 6a. Metformin treatment decreased the amount of microglia activation as well as restored IB4 signaling in the dorsal horn of male spinal cords. [6]

Figure 6b. Metformin treatment had no effect on the amount of activated microglia, IB4 signaling, or nonpeptidergic neurons in female mice.[6]

Conclusion and References

Conclusion

The sex differences of the efficacy of the AMPK activator Metformin on neuropathic pain incites questions of the drug's efficacy for other purposes. There have been no reports of Metformin having varied efficacy on males versus females for diabetes treatment- however, the dosage for diabetes is 20x less (typically 10 mg/kg) than that used here. In diabetes, the targeted pathway is also different (Figure 1), which could explain the sex differences in one application and not the other. Whatever the reason, it is certainly clear that there is a difference between sexes when it comes to the treatment of neuropathic pain with AMPK activators; however, the mechanisms behind the sex differences in this application are still largely unknown. There are many steps to follow to discover these unfound reasons. Following imaging of the current tissues, it should be determined if there are sex differences in the developmental stages of the neuropathic pain itself. It would also be fruitful to investigate sex differences in pain development and treatment in other models of pain, such as chemotherapy induced pain or diabetic neuropathy, and to test sex differences in different organisms, such as rats, to determine if the results obtained are uniform for AMPK activators treating neuropathic pain in all species.

References

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