Effects of Gabapentin and the $\alpha_2\delta_1$ Voltage Sensitive Calcium Channel Subunit in Skeletal Muscle

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Introduction: Gabapentin (GBP) is a neuropathic pain drug prescribed to millions of Americans which binds the auxiliary $\alpha_2\delta_1$ subunit of voltage sensitive calcium channels (VSCCs) to modulate calcium (Ca^{2+}) influx. GBP functions by decreasing Ca^{2+} signaling in neurons; however, muscle dysfunction is commonly reported with GBP use. We hypothesized that GBP treatment, and deletion of the $\alpha_2\delta_1$ subunit, impairs skeletal muscle function by disrupting neuromuscular junction (NMJ) transmission.

Methods: Heterozygous breeder pairs for *Cacna2d1*, the gene encoding $\alpha_2\delta_1$, were used to generate knockout (KO) mice (male: 9 WT, 9 KO; female: 6 WT, 5 KO). The Aurora muscle contractility system determined maximum torque, rate of contraction, rate of relaxation, and fatigue of the plantarflexors. Compound muscle action potentials (CMAPs) and single motor unit potentials (SMUPs) provided motor unit number estimates (MUNEs). qPCR analyses on skeletal muscle assessed NMJ homeostasis. Male C57BL/6 mice received GBP (150 mg/kg) or vehicle (saline) twice daily via oral gavage (n=8 mice/drug group). Muscle testing was conducted at 0, 2, and 4 weeks. Gene expression in muscle was analyzed by qPCR.

Results: Males deplete of $\alpha_2\delta_1$ had decreased plantarflexion torque ($p<0.001$), max rate of contraction ($p<0.001$), max rate of relaxation ($p<0.01$), SMUP ($p<0.001$), and MUNE ($p<0.01$). Plantarflexion torque ($p<0.01$), and max rate of contraction ($p<0.05$) were decreased in female KO mice. *Hspg2* ($p<0.01$) and *Musk* ($p<0.05$) expression was decreased in Male $\alpha_2\delta_1$ KO mice. However, expression of these genes was not altered in female mice. GBP treatment resulted in decreased max-torque ($p<0.01$), rate of contraction ($p<0.001$), rate of relaxation ($p<0.01$), and SMUP ($p<0.001$). *Hspg2* ($p<0.05$), *Lrp4* ($p<0.05$), *Agrin* ($p<0.01$), and *Chrne* ($p<0.01$) expression was decreased in muscle from GBP treated mice.

Conclusion & Significance: As GBP is a widely used neuropathic pain drug, understanding the consequences of chronic use on musculoskeletal tissues is of utmost importance. My data demonstrates that GBP treatment and $\alpha_2\delta_1$ KO decreased muscle performance. These data will help clinicians consider potential side-effects when prescribing GBP.