

## AAN 67<sup>th</sup> ANNUAL MEETING ABSTRACT

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**Abstract Title:** Orally-administered TRPV1 and TRPA1 Activators Inhibit Electrically-induced Muscle Cramps in Normal Healthy Volunteers

**Press Release Title:** Help for People with Muscle Cramps?

**Objective:** To identify if orally-administered TRPV1 and TRPA1 ion channel activators inhibit electrically-induced muscle cramps

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**Background:** Recent evidence argues that repetitive firing of the  $\alpha$ -motor neuron and the resulting hyperexcitability of the motor circuit may underlie muscle cramping. Based on a general property of neuronal circuits whereby strong excitatory input increases overall inhibitory tone and reduces responsiveness to additional excitation, sensory input via activation of TRPV1 and TRPA1 in primary sensory neurons of the alimentary tract might increase inhibitory tone in the spinal cord and dampen motor neuron hyperexcitability.

**Design/Methods:** TRP channel activators were assessed in ex vivo human dorsal root ganglia (hDRGs) for the ability to promote ion channel activation and calcium influx. Orally-administered TRP channel activators were studied in healthy volunteers across three independent, randomized, blinded, placebo-controlled crossover studies for efficacy in inhibiting electrically-induced cramps.

**Results:** Testing of three naturally-occurring activators of TRPV1 and TRPA1 in hDRGs demonstrated, as single agents or in combination, an increase in intracellular calcium as evidence of TRP ion channel activation. A proprietary product containing TRP activators was found efficacious in preventing electrically-induced muscle cramps in the foot across three studies combined (37 completed subjects) significantly reducing cramp intensity by 3-fold ( $p < 0.001$ ) and demonstrating an effect within minutes lasting up to 6-8 hours when compared to untreated subjects.

**Conclusions:** These results demonstrate for the first time that TRP activation in humans alleviates muscle cramps. The mechanism is consistent with the hypothesis that a strong sensory stimulus can suppress  $\alpha$ -motor neuron hyperexcitability. Since  $\alpha$ -motor neuron hyperexcitability is most likely the general underlying cause of cramps and spasticity, TRP activation may provide efficacy for the 84% of MS patients who commonly experience spasticity and the estimated 4 million Americans over age 65 who suffer from daily nocturnal leg cramps for which no therapy currently exists.

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