Muscle cramps can be painful and debilitating for healthy athletes as well as those suffering from nocturnal leg cramps, multiple sclerosis, amyotrophic lateral sclerosis, and other neurological diseases. Studies have demonstrated that hyperexcitability of α-motor neurons in the spinal cord is likely the underlying cause of cramp intensity and spasticity, and stimulants and stomach could yield sufficient excitatory input to dampen motor hyperexcitability. To test this hypothesis, we conducted human studies to assess the effectiveness of TRP activation to inhibit electrolytically induced cramps of the foot. An analgesic solution containing a mixture of TRPV1 and TRPA1 activators derived from natural extracts (TRP-stim extract mixture), was shown to prevent cramps within minutes of ingestion, lasting up to 6-8 hours. The aggregated results from these independent, randomized, blinded clinical studies showed a statistically significant reduction in cramp intensity by 3-fold (p<0.0001). To identify the likely active components, the extract mixture was analyzed by HPLC in relation to a series of molecules known to be present in the natural extracts. Compounds confirmed to be present in the extract mixture were analyzed for TRP agonist activity. The data showed that two compounds in particular, FLX-787 and FLX-788, were able to activate both TRPV1 and TRPA1 with similar potencies. When tested in an electrically-induced cramp model in normal healthy subjects, GMP-synthesized FLX-787 and FLX-788, as well as FLX-777 and FLX-779, each consisting of two GMP-synthesized TRPV1 and TRPA1 agonists, were statistically different to vehicle control (p<0.01). Moreover, FLX-787 and FLX-788 were observed to be significantly improved in comparison to the TRP-stim extract mixture (FLX-787: p<0.01, FLX-788; p<0.05). These results suggest that the single and double combinations are more effective than the mixture. Flex Pharma is now moving toward further clinical studies to evaluate the effectiveness of these compounds to treat nocturnal leg cramps and spasticity associated with multiple sclerosis and ALS. Taken together, these data demonstrate the utility of Flex Pharma’s proprietary products to treat cramps and the general strategy of chemical neuro stimulation to limit α-motor neuron hyperexcitability in other neurological diseases.

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REFERENCES

2. Nocturnal leg cramps affect millions of Americans, and there are no FDA-approved drug therapies.
3. We investigated the safety and efficacy of TRP activators in a randomized, controlled, blinded, cross-over study.
4. The study enrolled 50 healthy subjects (50-77 years) experiencing Nocturnal Leg Cramps at least four nights per week.
5. After an initial placebo run-in period, the subjects were randomized to either control or study product for two weeks then crossed over to the study treatment order as described in the original protocol (p<0.01). Both FLX-777 and FLX-778 were discovered to be significantly improved in comparison to the TRP-stim extract mixture.