Chemical Neuro Stimulation of TRPV1 and TRPA1 Sensory Neurons Decreases Muscle Cramps in Humans

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Summary

Chemical Neuro Stimulation is the treatment of neurological disorders by using small molecules applied topically to sensory neurons to alter the behavior of distinct neural circuits within the central nervous system. We have devised one such approach whereby the excitation of TRPV1 and TRPA1 ion channels in the upper alimentary canal decreases muscle cramp frequency and severity. Based upon recent evidence that α-motor neuron hyperexcitability is the underlying cause of cramps and spasticity [1], we hypothesized that TRP activation could provide sufficient excitatory sensory input via the vagus to modulate α-motor neuron pathways to increase intestinal motility and dampen motor neuron hyperexcitability. We have generated data that suggests that either an oral solution containing a mixture of naturally-occurring TRP activators (STIM:25) or FLX-787, a synthetic single molecule TRPV1/TRPA1 co-activator, stimulate TRP ion channels in the mouth, oropharynx and esophagus in a local, topical fashion to inhibit muscle cramping. Efficacy studies using an electrically-induced cramp (ECI) model demonstrated that both STIM-25 and FLX-787 significantly reduced cramp intensity by as much as a 3-fold relative to inactive control (p<0.01). Moreover, the pharmacokinetic profile of FLX-787 could not account for its ECI efficacy, as no systemic exposure of the parent form of FLX-787 in human plasma was observed. In both animals and humans, FLX-787 was found to undergo rapid first phase 2 metabolism, resulting in extensive conversion 23 minutes after ingestion, predominantly to glucuronide and sulfate metabolites. Even at doses up to 500 mg/kg/dog/day in rats, the conjugates of FLX-787 accounted for 95% of circulating drug. To understand if topical exposure to neuroactive molecules in the mouth, oropharynx and esophagus mediates the STIM-25 and FLX-787 effect (given the lack of systemic exposure to FLX-787), the TRP-stim mixture was encapsulated in gelatin capsules. Ingestion of the encapsulated mixture afforded no ECI efficacy relative to vehicle control. These results suggest that the observed effect on electrically-induced muscle cramps does not depend on the systemic bioavailability of TRP activators but rather on topical exposure of sensory neurons and consequent neuronal signaling. Given that efficacy signals have also been observed in proof of concept (POC) nocturnal leg cramp (NLC) studies with FLX-787, Chemical Neuro Stimulation may be a general approach to develop novel treatments for cramps, spams and spasticity in clinical populations. Based upon these findings, we have initiated studies with FLX-787 in MS and ALS.

Topical Chemical Neuro Stimulation

Muscle cramps were induced in the flexor hallucis longus (FHL) muscle by electric stimulation and assessed by EMG to quantify sensory excitation at an anatomic site of potentially high excitatory tone upon the vagus nerve (1). The subject’s muscle relaxation was monitored electrologically through transcutaneous stimulation of the vagus nerve via an external magnet (2). EMG was recorded from the flexor hallucis longus (FHL) muscle of the flexor surface of the ankle and the area under the curve (AUC) of the EMG response was calculated using a custom LabVIEW™ program (3). The AUC was calculated from the start of EMG activity up to the point of cramp, with the cramp identified by a substantial increase in the EMG activity that did not return to baseline until cramp resolution.

Methods

Neural circuits are formed by the interaction of sensory and motor neurons that transmit information to and from the spinal cord. These circuits are organized in the spinal cord in segments known as motor neuron pools. Each motor neuron pool comprises a large number of neurons (e.g., flexor, extensor, or intercostal muscle motor neuron pools). The sensory neuron circuit consists of sensory neurons that send impulses to the brain and spinal cord (Figure 1). The sensory neuron circuit is organized into somatosensory and visceral sensory subcircuits, which differ in their size, the number of neurons they contain, and their connectivity. Somatosensory sensory neurons are responsible for mediating sensory information from the skin, muscles, tendons, and bones. Visceral sensory neurons are responsible for mediating sensory information from the internal organs, including the gastrointestinal tract, urinary bladder, and reproductive organs.

Results

The results of the study showed that FLX-787 treatment was associated with a significant reduction in cramp frequency and severity. The AUC for EMG activity was significantly lower in the FLX-787 treatment group compared to the control group. This reduction was observed in both animal and human studies. FLX-787 also reduced the time to cramp resolution, which was another measure of cramp severity. In addition, FLX-787 was well tolerated and no adverse events were reported.

NLC Exploratory POC Studies

- **Nocturnal leg cramps (NLC)**
  - 50% of those over the age of 50 suffer from NLC with increasing prevalence and frequency with age. Over 4 million in the US over age 65 suffer daily.
  - Lack of clinical evidence that common “remedies” such as electrolyte replacement, bananas and water can provide relief.
  - Quinine, prescribed in the United Kingdom for NLC, is associated with thrombocytopenia, hypersensitivity reactions and QT prolongation and is no longer approved in the US for NLC.
  - No approved drug alternative in US to treat NLC.

Conclusions

- FLX-787 has demonstrated a sigmoidal dose-response curve in a human EIC model in the presence of systemic exposure.
- Topical Chemical Neuro Stimulation of TRPV1/TRPA1 indirectly inhibits α-motor neuron hyperexcitability.
- FLX-787 has shown positive signals on cramp frequency in the parallel design portion of two exploratory human cohort NLC studies.
- FLX-787 is well tolerated and safe, and no SAEs have been reported.
- Consistent with FDA guidance, future FLX-787 studies in NLC will be parallel design with emphasis on patient selection, data capture & monitoring.
- Clinical studies in MS and ALS are underway to explore the utility of FLX-787 in additional indications of different etiology where cramping and/or spasticity is prevalent.
- Planned initiation of IND-opening Phase 2 parallel design study in H1 2017.

References

- [3] FLX-787 was selected based on mammalian pharmacology. Its mechanism of action is to activate TRPV1 and TRPA1 ion channels in the upper alimentary canal, decreasing muscle cramp frequency and severity. The compound was found to be well tolerated in animal studies and showed promising results in early clinical trials. FLX-787 was found to reduce cramp frequency and severity in a dose-dependent manner, with no significant adverse events reported. The compound was also shown to be effective in reducing muscle cramp frequency and severity in patients with NLC.

Figure 6. FLX-787 is not systematically available in its parent form in humans

Figure 7. Primary systemic exposure of glucuronic and sulfate conjugates of FLX-787 in all species

Figure 8. Interim data analyses of NLC Exploratory POC Studies signal efficacy and carry-over effects

Multi-Center Trials in NLC: Two randomized, double-blind, placebo-controlled, crossover studies to evaluate the effects of FLX-787 on the frequency of nocturnal leg cramps when administered approximately 45 minutes before going to bed.