Various mediators released during pathological pain states contribute to the sensitization and hyperexcitability of nociceptive neurons.

Simulation of somatosensory receptor 4 (SSTR) inhibits nociception in animals, and SSTR knock-out mice have heightened responses to painful stimuli compared with wild-type mice.

SSTR agonists can induce normalization of neuronal excitability, reducing inflammatory and neuropathic pain, and are a novel target for pain therapy.

CNTX-0290 is a human SSTR4 (hSSTR4) agonist under development as an oral analgesic for nociceptive and neuropathic pain.

**Mechanism of Action**

- **Somatostatin:** An inhibitory peptide that acts via 5 receptor subtypes (SSTR1-5).
- **While most SSTR subtypes are involved in homeostatic hormone regulation, SSTR4 appears to have a functional role in modulating sensory nerve transmission.**
- **SSTR4 has been shown to be localized to axons and cell bodies of dorsal root ganglia neurons in rats; calcium mobilization, and monocytes.**
- **SSTR4 controls nociceptive transmission by modulating multiple pathways in dorsal root ganglia neurons (Figure 1A).**
  - Enhances potassium currents by opening G protein–coupled inward rectifying potassium channels.
  - Decreases calcium currents by inhibition of voltage-gated calcium channels.
  - Blocks transient receptor potential vanilloid-1 and ankyrin-1 channels.

**In Vivo Potency and Selectivity**

- **CNTX-0290** demonstrated dose-dependent antinociceptive effects in modulating sensory nerve transmission.
  - Moderate species selectivity was identified for human vs macaque monkeys, and humans.
  - Cynomolgus monkey is the proposed nonrodent species for toxicology studies as SSTR4 is not expressed in dogs, pigs, and guinea pigs.

**In Vitro Potency and Selectivity**

- The affinity of CNTX-0290 to hSSTR1, 2, 3, and 5 is [nM] (Table 1), indicating a favorable selectivity profile.

**Preclinical Studies**

- CNTX-0290 activates the SSTR4 receptor, leading to normalization of excitability and reduction of synaptic transmission (Figure 1B).

**In Vivo Efficacy**

- CNTX-0290 (1 to 30 mg/kg) significantly reversed weight loss in the rat model of MIA (Figure 2).
- Efficacy was observed up to 24 hours after administration.

**In Vivo Efficacy in the Rat MIA Model of Diabetic Neuropathy**

- CNTX-0290 (10 mg/kg PO) showed dose-dependent antinociceptive effects in models of diabetic neuropathy.
- Maximal efficacy was achieved at 24 hours after administration.

**In Vivo Efficacy in the Rat CFA Model of Inflammatory Pain**

- CNTX-0290 (1 to 30 mg/kg) significantly reversed weight loss in the rat model of CFA (Figure 3).
- Efficacy was observed up to 24 hours after administration.

**In Vivo Efficacy in the Rat CFA Model of Osteoarthritis Pain**

- CNTX-0290 (10 mg/kg PO) significantly reversed weight loss in the rat model of osteoarthritis.
- Efficacy was observed up to 24 hours after administration.

**Partially Mediated by G Protein-Coupled Receptors**

- CNTX-0290 activates the SSTR4 receptor, leading to) normalization of excitability and reduction of synaptic transmission.

**Effect of Repeated Exposure**

- Repeated administration and lack of toxicity after repeated exposures were investigated in the same model.
- CNTX-0290 was shown to be safe and efficacious after repeated exposures.
- No evidence of tolerance was identified.

**Safety**

- Safety pharmacology studies were conducted in rats and cynomolgus monkeys.
- CNTX-0290 showed a selectivity profile similar to somatostatin, and is a potent inhibitor of growth hormone and insulin.
- CNTX-0290 may be administered as a single agent, or in combination with other analgesics.

**Central Nervous System Activity**

- CNTX-0290 did not affect glucose tolerance (Figure 7), while octreotide significantly increased glucose levels.

**Conclusion**

- CNTX-0290 was not associated with central nervous system side-effects observed with standard of care therapies (Table 2).

**References**


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