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Analgesic and Anti-inflammatory Effects of Small Molecule Negative Allosteric Modulators of TrkA

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Aim

The aim was to study analgesic and anti-inflammatory effects of TrkA-Negative Allosteric Modulators (TrkA-NAM) on NGF-induced heat sensitivity and inflammation.

Background

The NGF/TrkA pathway is a well validated pathway in pain sensation. Targeting the TrkA receptor with a negative allosteric modulator (NAM) with low blood-brain permeability might offer a selective way of disrupting the NGF signaling, thus possibly avoiding the observed side effects with the anti-NGF antibodies.
Intraplantar injection of NGF in the hind paw is described to induce acute thermal hyperalgesia and local edema, partially mediated by CGRP, histamine and TRPV1.
AC-0027838 is a potent, selective, and orally bioavailable TrkA-NAM with an IC50 of 0,64 nM on TrkA and >40,000, respectively 23,000 fold selectivity over TrkB and TrkC.

Methods

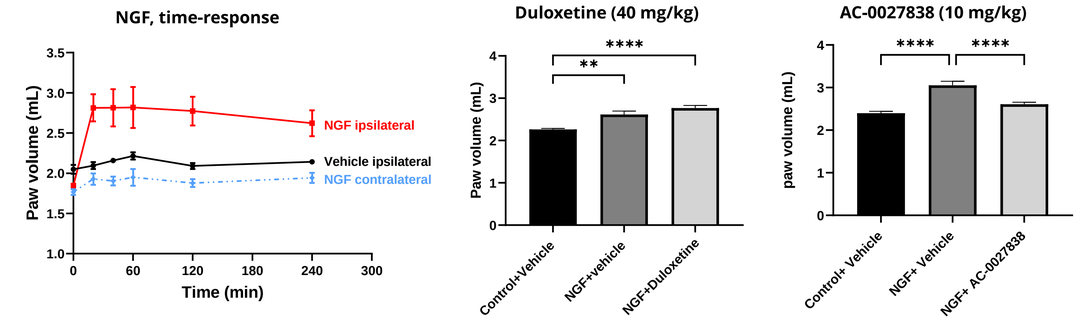
NGF (5 μg) or vehicle was given as a single intraplantar injection into the left hind paw. Thermal sensitivity was determined on both the contralateral and the ipsilateral paw 4 hours after injection of NGF or PBS using the Plantar test (Hargreaves test). Local edema was determined by the use of a plethysmometer. Levels of interleukin (IL)-18 and calcitonin gene-related peptide (CGRP) were evaluated from skin biopsies.

Results

Intraplantar injection of 5 ug NGF in the left hindpaw led to increased thermal sensitivity and inflammation in the paw as measured by increased edema. Clinical symptoms of inflammation were clearly evident as early as 20 minutes after injection of NGF. Oral administration of Duloxetine or AC-0027838 one hour after NGF-injection led to a significant reduction in thermal sensitivity. Interestingly, while AC-0027838 demonstrated a highly significant and efficacious anti-inflammatory effect as indicated by decreased local edema, Duloxetine demonstrated no such effect. Moreover, skin biopsies from the ipsilateral paw demonstrated a significant NGF-dependent increase of CGRP, which essentially could be reversed by AC-0027838. Interleukin-18 demonstrated a trend towards NGF-dependent increase.

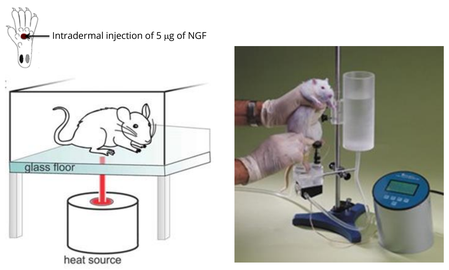
Anti-inflammatory effects

Figure 2. Effects of Duloxetine or AC-0027838 (TrkA-NAM) on NGF-induced edema in rat hind paw



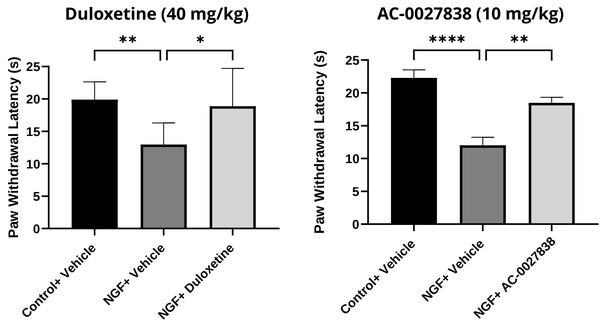
Analgesic effects

Figure 1. Effects of Duloxetine and AC-0027838 (TrkA-NAM) on NGF-induced heat sensitivity using the Plantar test



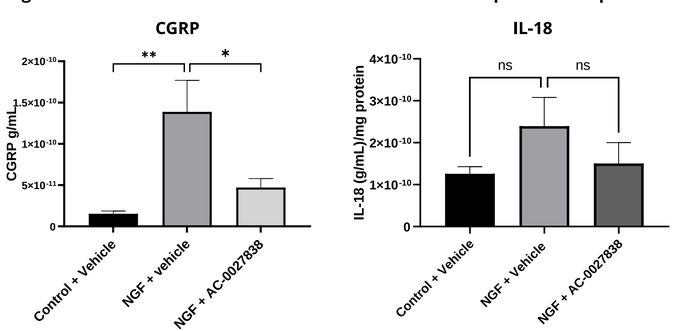
Pain, heat sensitivity

Edema, plethysmometer



CGRP and IL-18 levels in paw skin biopsies

Figure 3. Effects of AC-0027838 on CGRP and IL-18 levels in paw skin biopsies



Conclusion

The NGF/TrkA pathway is a well validated and a promising alternative for new analgesics without the side effects and dependency issues observed with opioids. Identification of selective and potent TrkA-NAM's could potentially avoid some of the side effects observed for anti-NGF antibodies or for non-selective Trk-inhibitors, while retaining the analgesic efficacy. We have in our lead optimization program identified potent and selective TrkA-NAM's demonstrating analgesic and anti-inflammatory effects in vivo.

TrkA-NAM compounds can be useful for the treatment of inflammatory arthritis or other severe pain conditions.

Contact

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