ATH-1020, a Small Molecule Positive Modulator of Hepatocyte Growth Factor (HGF)/MET, Has Robust and Persistent Therapeutic Effects in a Rat Model of Diabetic Neuropathic Pain

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CONCLUSIONS

1. In a rat model of DNP, treatment with ATH-1020 significantly reduced pain-related behaviors, as evaluated through mechanical allodynia and thermal hyperalgesia
2. The therapeutic effects on pain persisted following a 7-day treatment washout
3. Q12h oral treatment with ATH-1020 may be more effective than QD treatment for pain reduction

KEY TAKEAWAY

These data indicate the therapeutic potential of ATH-1020 in managing pain resulting from diabetes

Acknowledgments

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Disclosures

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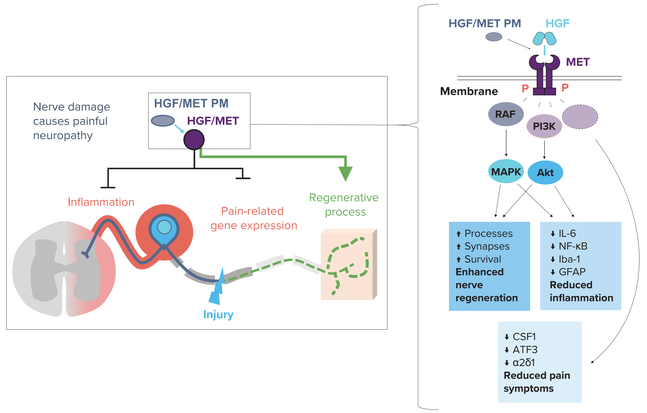
INTRODUCTION

- Approximately 60% of people with diabetes experience neuropathic pain[1]
- Symptoms of DNP include spontaneous pain, pain in response to stimuli, paresthesia, and hypersensitivity, all of which arise from underlying inflammation and damage to sensory neurons[2]
- The HGF/MET pathway plays a key role in neurogenesis and nervous system repair. Stimulation of this system provides neuroprotective effects[3-6] and promotes analgesia, both preclinically[7] and clinically[8]
- Here, we assess the therapeutic effects of QD and Q12h treatment with ATH-1020, a small-molecule positive modulator of HGF/MET, in a rat model of DNP

Figure 1. Positive modulators of the HGF/MET pathway may promote neuroprotective, neurotrophic, and anti-inflammatory cascades



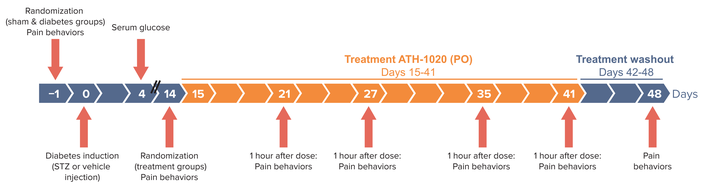
Positive modulation of the HGF/MET pathway stimulates systems that decrease inflammation and increase nerve regeneration, possibly reducing symptoms of pain.

OBJECTIVE

To evaluate the efficacy of QD or Q12h oral treatment with ATH-1020 in treating symptoms of pain in a rat model of DNP

METHODS

Figure 2. Experimental timeline



After diabetes induction (or sham injection) on day 0, rats were stratified by BGL and pain behaviors and then randomly assigned to treatment groups on day 14. Treatment administration and behavioral tests progressed as indicated, with pain severity assessed through evaluation of mechanical allodynia and thermal hyperalgesia.

Diabetic neuropathic pain induction and evaluation

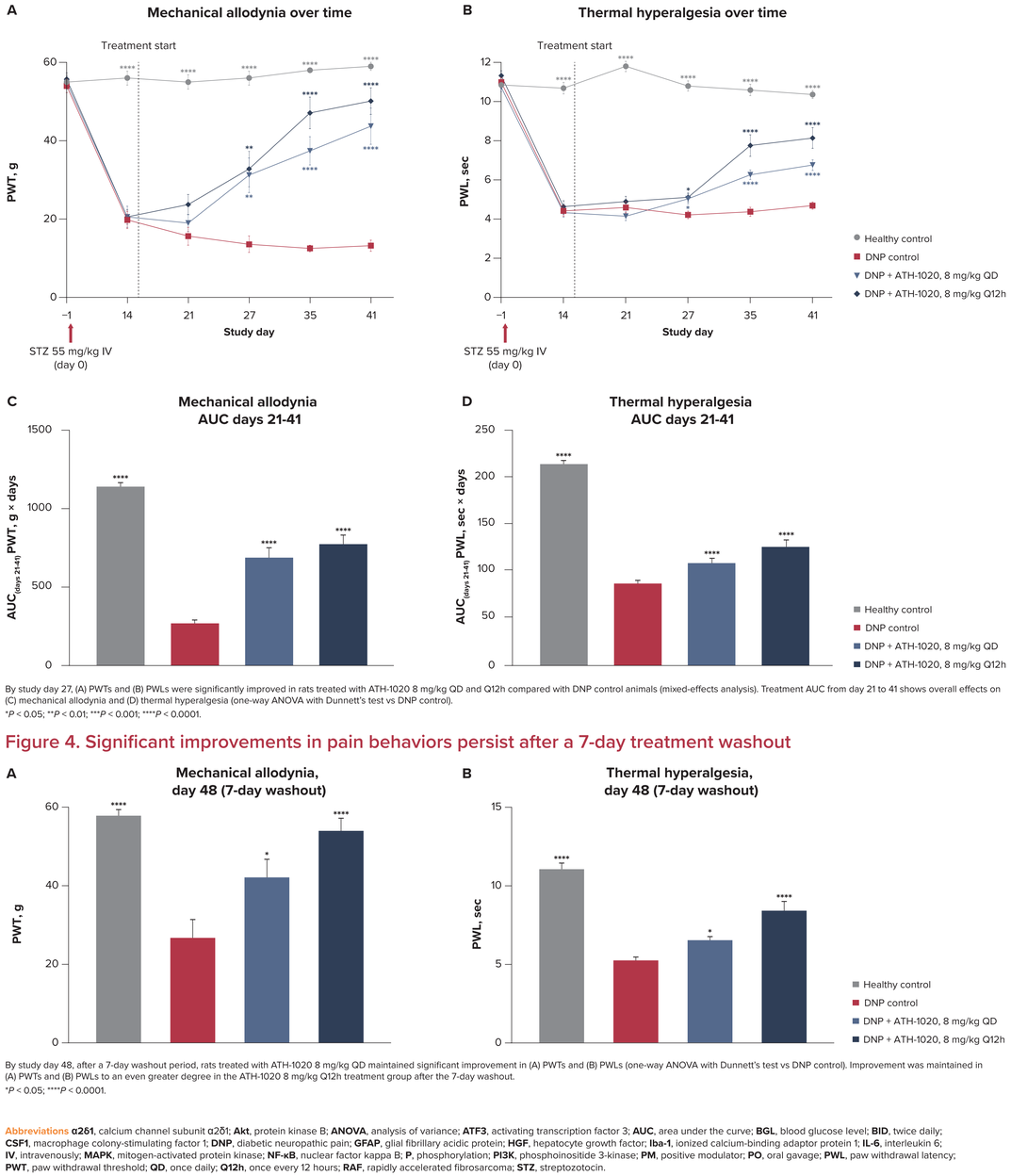
- An injection of STZ (55 mg/kg IV) was used to induce diabetes in male Sprague Dawley rats at 7-8 weeks of age (n = 14); citrate buffer was injected as a sham control (n = 12)
- Diabetic status was confirmed by BGL
- Painful phenotypes were confirmed with tests of mechanical allodynia and thermal hyperalgesia at day 14
  - PWT (in grams) was assessed using Aesthesio manual Von Frey filaments (1.4, 4, 10, 15, 26, 48, and 60 g) as a measure of mechanical allodynia
  - PWL (in seconds) was assessed using the hot plate test (52.5 °C) as a measure of thermal hyperalgesia

Treatment groups

- Animals were randomly assigned to one of the following groups and were treated PO BID:
  - Healthy control (citrate buffer injection, vehicle)
  - DNP control (STZ injection, vehicle)
  - DNP + ATH-1020 (STZ injection, ATH-1020 8 mg/kg QD)
  - DNP + ATH-1020 (STZ injection, ATH-1020 8 mg/kg Q12h)

RESULTS

Figure 3. ATH-1020 significantly ameliorates mechanical allodynia and thermal hyperalgesia in a rat model of DNP



By study day 27, (A) PWTs and (B) PWLs were significantly improved in rats treated with ATH-1020 8 mg/kg QD and Q12h compared with DNP control animals (mixed-effects analysis). Treatment AUC from day 21 to 41 shows overall effects on (C) mechanical allodynia and (D) thermal hyperalgesia (one-way ANOVA with Dunnett's test vs DNP control).

*P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

Figure 4. Significant improvements in pain behaviors persist after a 7-day treatment washout

By study day 48, after a 7-day washout period, rats treated with ATH-1020 8 mg/kg QD maintained significant improvement in (A) PWTs and (B) PWLs (one-way ANOVA with Dunnett's test vs DNP control). Improvement was maintained in (A) PWTs and (B) PWLs to an even greater degree in the ATH-1020 8 mg/kg Q12h treatment group after the 7-day washout.

*P < 0.05; ****P < 0.0001.

Abbreviations **α2δ1**, calcium channel subunit α2δ1; **Akt**, protein kinase B; **ANOVA**, analysis of variance; **ATF3**, activating transcription factor 3; **AUC**, area under the curve; **BGL**, blood glucose level; **BID**, twice daily; **CSF1**, macrophage colony-stimulating factor 1; **DNP**, diabetic neuropathic pain; **GFAP**, glial fibrillary acidic protein; **HGF**, hepatocyte growth factor; **Iba-1**, ionized calcium-binding adaptor protein 1; **IL-6**, interleukin 6; **IV**, intravenously; **MAPK**, mitogen-activated protein kinase; **NF-κB**, nuclear factor kappa B; **P**, phosphorylation; **PI3K**, phosphoinositide 3-kinase; **PM**, positive modulator; **PO**, oral gavage; **PWL**, paw withdrawal latency; **PWT**, paw withdrawal threshold; **QD**, once daily; **Q12h**, once every 12 hours; **RAF**, rapidly accelerated fibrosarcoma; **STZ**, streptozotocin.

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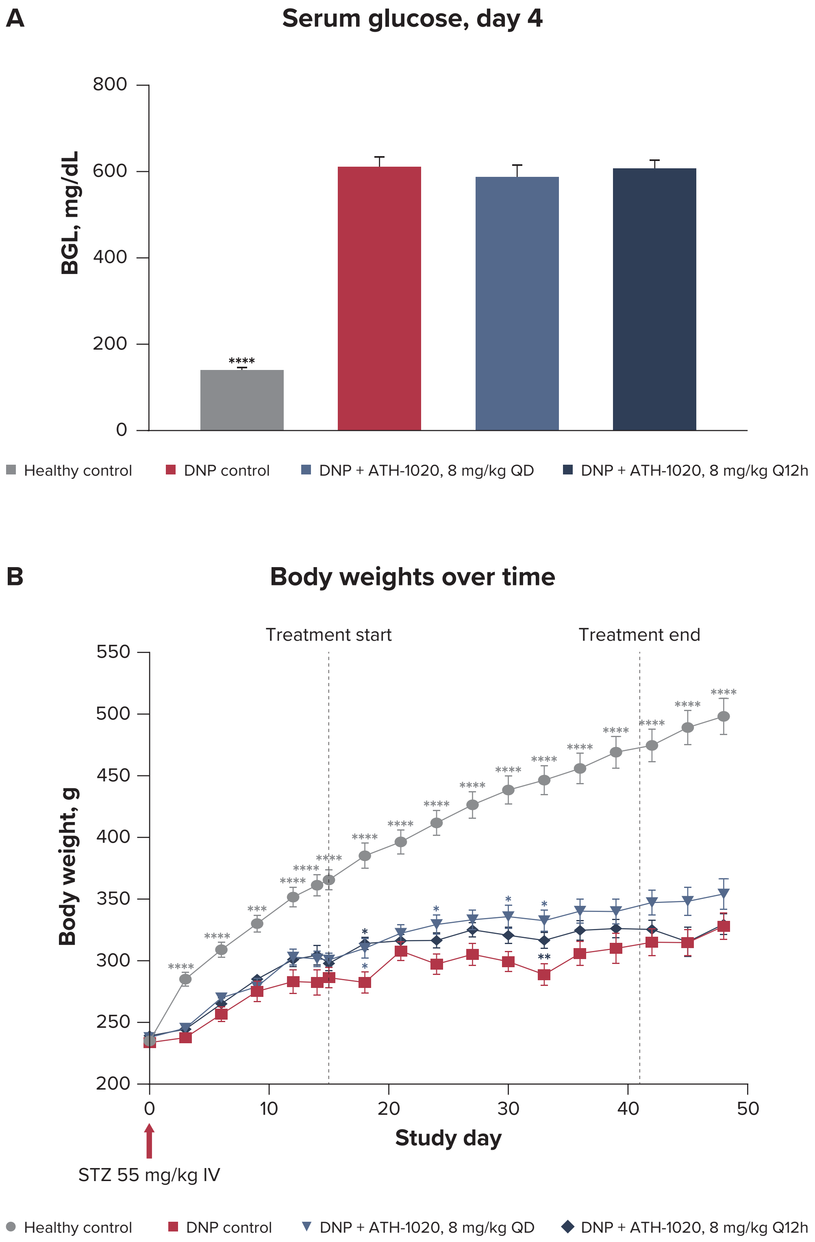
SUPPLEMENTAL INFORMATION

Figure S1. Blood glucose levels and body weight reductions confirm diabetic state in rats administered STZ



(A) Diabetes induction was confirmed at day 4, with rats in all DNP groups showing elevations in BGL after STZ administration (one-way ANOVA with Dunnett's test vs DNP control).
(B) Rats in the DNP control group had lower body weights compared with healthy controls, and groups treated with ATH-1020 had modestly improved body weights compared with DNP controls at some timepoints (mixed-effects analysis).
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

Abbreviations **BGL**, blood glucose level; **DNP**, diabetic neuropathic pain; **IV**, intravenously; **QD**, once daily; **Q12h**, once every 12 hours; **STZ**, streptozotocin.

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