Small-Molecule Hepatocyte Growth Factor/MET Positive Modulators Effectively Reduce Pain-Related Behaviors in a Rat Model of Diabetic Neuropathy

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CONCLUSIONS

1. In a model of diabetic neuropathic pain (DNP), ATH-1018 and ATH-1020 significantly improved both mechanical allodynia and thermal hyperalgesia
2. Reductions in pain behaviors were sustained after washout periods of 23 hours for both compounds and 7 days for ATH-1020
3. Therapeutic effects were more persistent than the standard of care for analgesia, pregabalin

KEY TAKEAWAY

These results support the continued clinical development of ATH-1018 and ATH-1020 as potential therapies for painful diabetic neuropathy in the clinic

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Acknowledgments

This study was sponsored by Athira Pharma, Inc. Medical writing support was provided by Katie Henderson, PhD, of ApotheCom, and funded by Athira Pharma, Inc.

Disclosures

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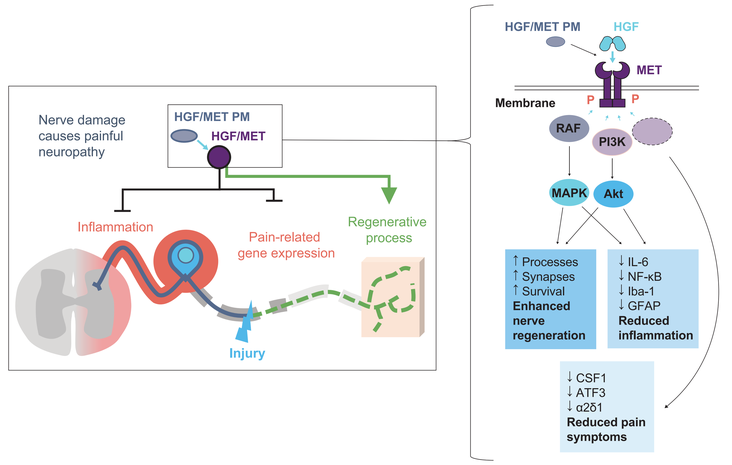
Presented at Neuroscience 2022; November 12-16, 2022; San Diego, California

INTRODUCTION

- Neuropathic pain impacts roughly 60% of people with diabetes[1]
  - Underlying damage to sensory neurons causes overt symptoms, which can include spontaneous pain, pain in response to stimuli, paresthesia, and hypersensitivity[2]
- The hepatocyte growth factor (HGF)/MET pathway plays a critical role in neurogenesis and nervous system repair, and stimulation of this endogenous system provides neuroprotective effects[3-6] and reduced severity of pain symptoms in clinical trials[7]
- We present the effects of two small-molecule positive modulators (PMs) of HGF/MET, ATH-1018 and ATH-1020, in a rat model of diabetic neuropathic pain (DNP)

Figure 1. Positive modulators of the HGF/MET pathway may promote regenerative processes and reduce inflammation



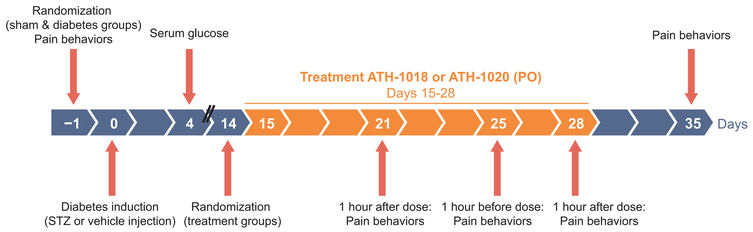
Positive modulation of the HGF/MET pathway stimulates several downstream processes that enhance nerve regeneration, decrease inflammation, and reduce severity of pain symptoms.

OBJECTIVE

To evaluate the effects of ATH-1018 and ATH-1020 on symptoms of pain in a rat model of DNP

METHODS

Figure 2. Experimental timeline



Animals were randomly assigned by serum glucose and pain behaviors to one of four treatment groups (day 14). Treatment and behavioral assessments progressed as indicated; painful sensation was determined through behavioral assessments of mechanical allodynia and thermal hyperalgesia.

Diabetic neuropathic pain induction and evaluation

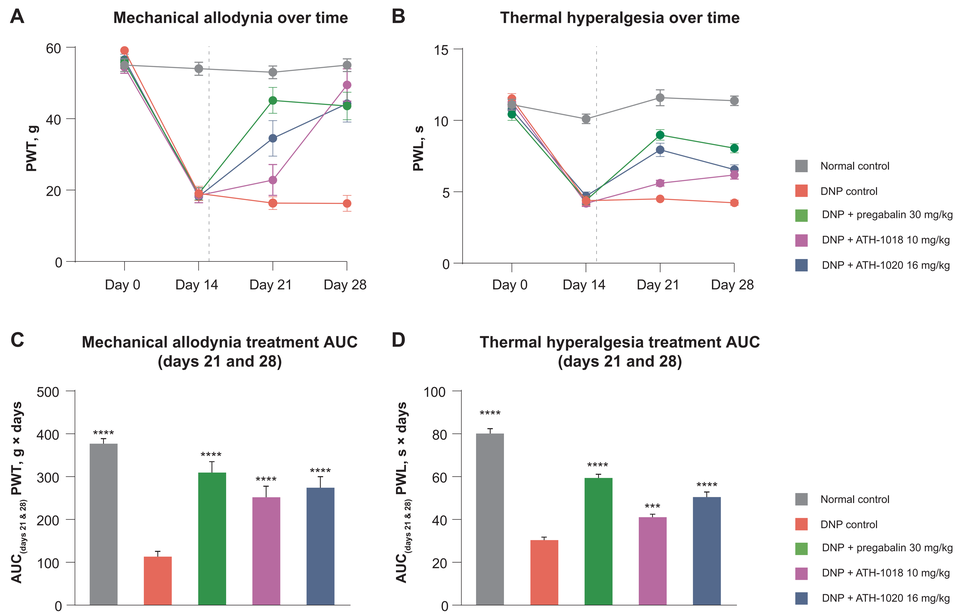
- An injection of streptozotocin (STZ) (55 mg/kg intravenously [IV]) was used to induce diabetes in male Sprague Dawley rats 6-8 weeks of age (14 per treatment group); citrate buffer was injected as a sham control in 12 rats
- Diabetes was confirmed by body weight change and serum glucose level (**Figures S1, S2; QR Code**)
- Pain response to mechanical allodynia and thermal hyperalgesia was confirmed at day 14
- Paw withdrawal threshold (PWT) was assessed using Aesthesio manual Von Frey filaments (1.4, 4, 10, 15, 26, 48, and 60 g) as a measure of mechanical allodynia
- Paw withdrawal latency (PWL) was assessed using the hot plate test (52.5 °C) as a measure of thermal hyperalgesia

Treatment groups

- Animals were assigned to one of the following groups:
  - Sham control (citrate buffer, vehicle oral gavage [PO] once daily [QD])
  - DNP control (STZ, vehicle PO QD)
  - DNP + pregabalin (STZ, pregabalin 30 mg/kg PO QD; positive control)
  - DNP + ATH-1018 (STZ, ATH-1018 10 mg/kg PO QD)
  - DNP + ATH-1020 (STZ, ATH-1020 16 mg/kg PO QD)

RESULTS

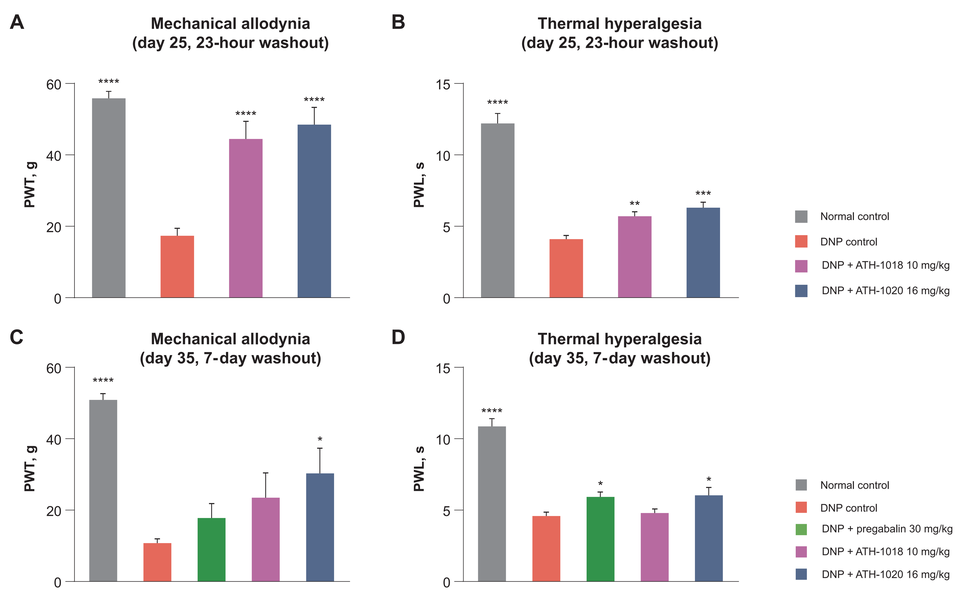
Figure 3. ATH-1018 and ATH-1020 significantly reduce pain behaviors over a period of 14 days of treatment



(A) Reductions in PWTs were observed in all DNP groups by day 14, indicating increased mechanical allodynia; this persisted through day 28 in DNP control animals. (B) Reductions in PWLs were also noted in all DNP groups by day 14, indicating increased thermal hyperalgesia; this persisted through day 28 in DNP control animals. (C) ATH-1018 and ATH-1020 both significantly increased PWTs (one-way analysis of variance [ANOVA] with Dunnett test vs DNP control). (D) ATH-1018 and ATH-1020 both significantly increased PWLs (one-way ANOVA with Dunnett test vs DNP control). (A, B) Approximate treatment start (day 15) is indicated by a gray dashed line. Pain assessments were performed 1 hour after dosing on study days 21 and 28.

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

Figure 4. Reduction in pain persists after washout of ATH-1018 and ATH-1020



After a 23-hour washout period (complete clearance of ATH-1018 and ATH-1020 [>7× the half-life]; pregabalin is not shown because of incomplete clearance at this time point), (A) PWTs and (B) PWLs were highly significantly increased in animals previously treated with ATH-1018 or ATH-1020 (one-way ANOVA with Dunnett test vs DNP control). (C) Animals treated with ATH-1020 16 mg/kg maintained significant improvement in PWT by day 35 after a 7-day washout period, in contrast with standard-of-care pregabalin (one-way ANOVA with Dunnett test vs DNP control). (D) PWLs in thermal hyperalgesia also remained increased in the ATH-1020–treated group after a 7-day washout period, with significance comparable with the current standard of care, pregabalin (one-way ANOVA with Dunnett test vs DNP control).

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

Abbreviations **α2δ1**, calcium channel subunit α2δ1; **Akt**, protein kinase B; **ANOVA**, analysis of variance; **ATF3**, activating transcription factor 3; **AUC**, area under the curve; **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; **RAF**, rapidly accelerated fibrosarcoma; **STZ**, streptozotocin.

References **1.** Callaghan BC et al. *Curr Opin Neurol*. 2012;25:536-541. **2.** Baron R et al. *Lancet Neurol*. 2010;9:807-819. **3.** Nicoleau C et al. *Stem Cells*. 2009;27:408-419. **4.** Desole C et al. *Front Cell Dev Biol*. 2021;9:683609. **5.** Maina F, Klein R. *Nat Neurosci*. 1999;2:213-217. **6.** Ko KR et al. *Sci Rep*. 2018;8:8316. **7.** Kessler JA et al. *Ann Clin Transl Neurol*. 2015;2(5):465-478.

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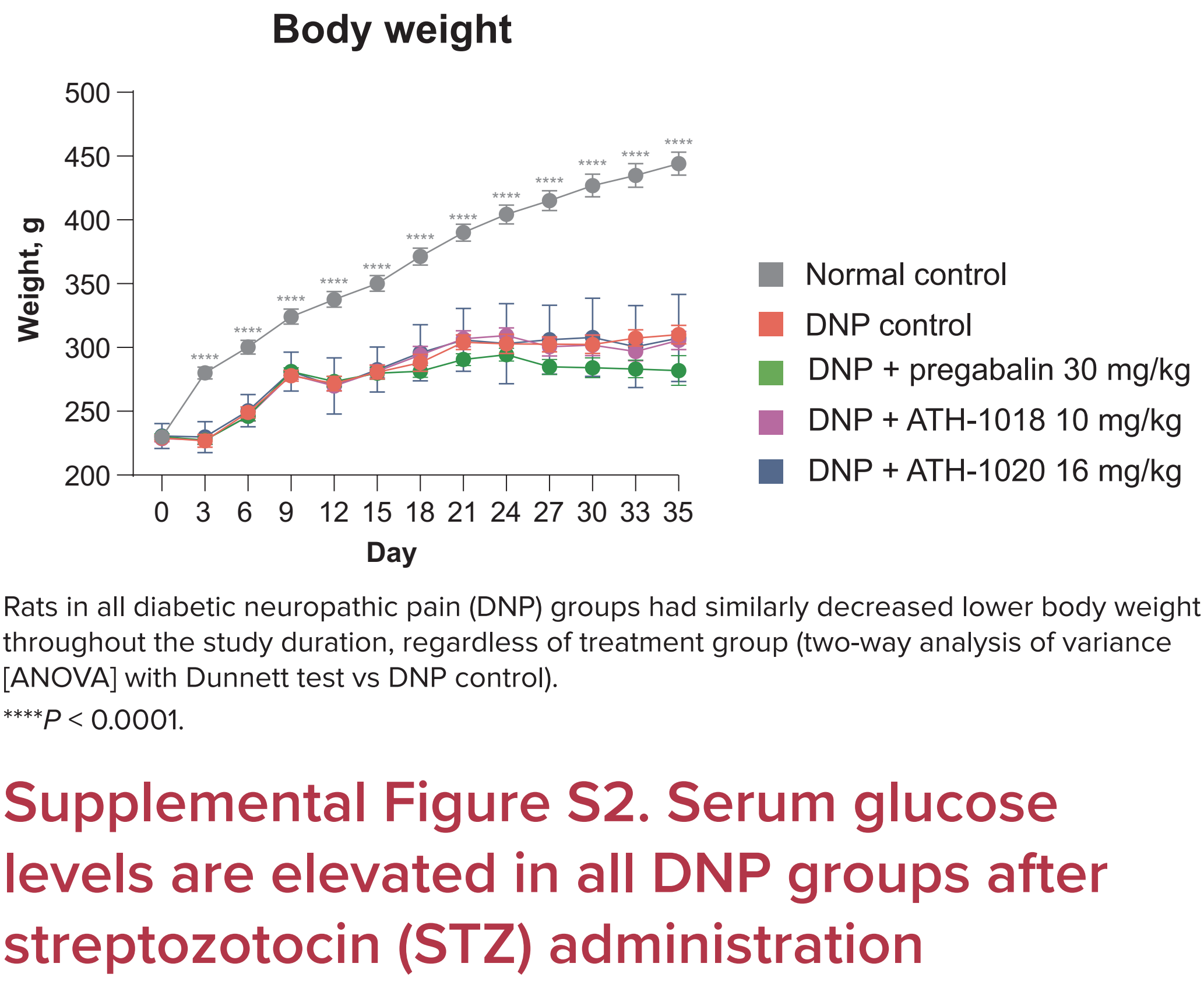
SUPPLEMENTAL INFORMATION

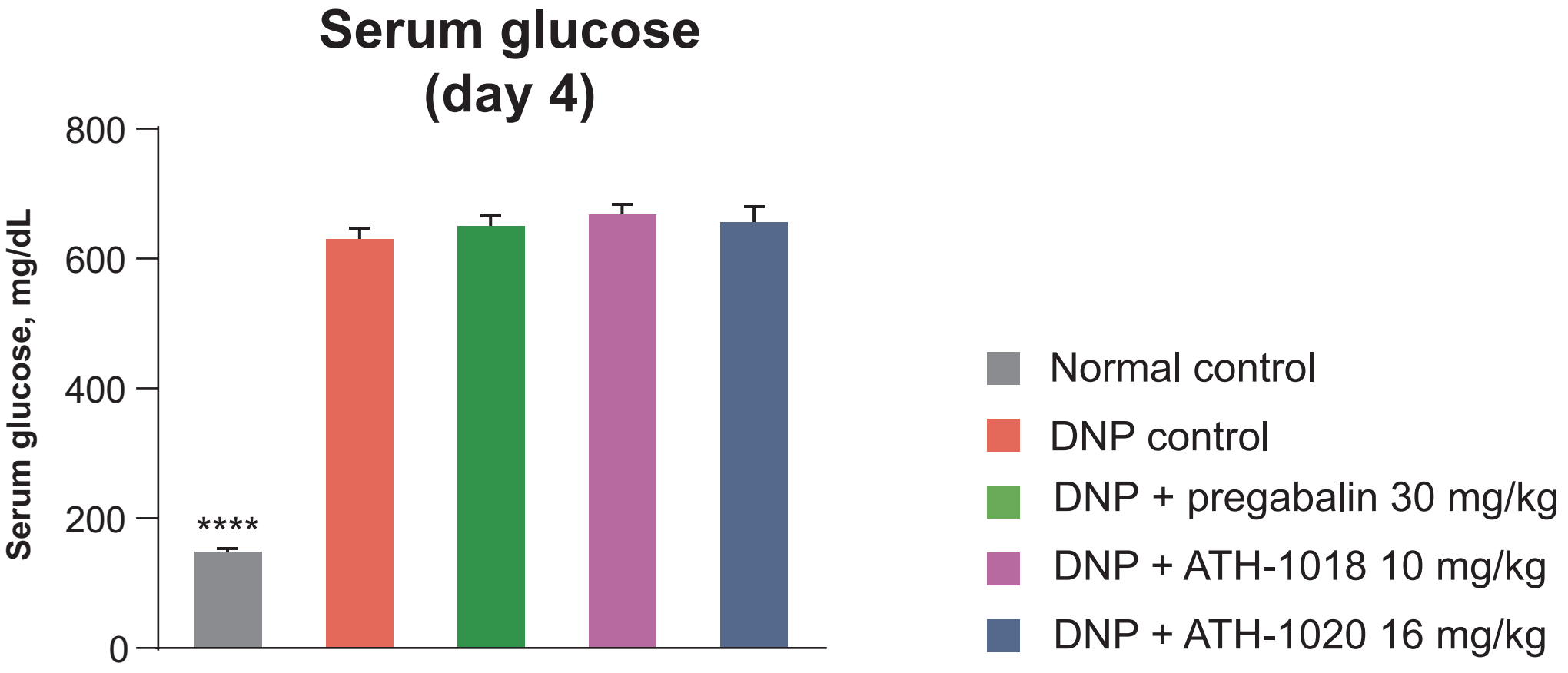
Supplemental Figure S1. Body weight is consistent across all DNP experimental groups



Rats in all diabetic neuropathic pain (DNP) groups had similarly decreased lower body weight throughout the study duration, regardless of treatment group (two-way analysis of variance [ANOVA] with Dunnett test vs DNP control).

****$P < 0.0001$.

Supplemental Figure S2. Serum glucose levels are elevated in all DNP groups after streptozotocin (STZ) administration



Rats across all DNP groups had similarly increased serum glucose levels four days after STZ administration, indicating successful induction of the diabetic phenotype (one-way ANOVA with Dunnett test vs DNP control).

****$P < 0.0001$.

Abbreviations **ANOVA**, analysis of variance; **DNP**, diabetic neuropathic pain; **STZ**, streptozotocin.

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