The effects of the FABP5 inhibitor ART26.12 in a rat model of painful diabetic neuropathy

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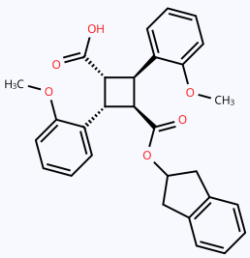
Introduction

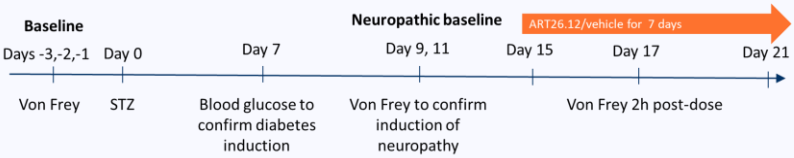
Fatty acid binding proteins (FABPs) are cytosolic proteins that chaperone lipophilic molecules intracellularly. FABP5 is extensively distributed in the dorsal root ganglion, spinal cord and TRPV1+ nociceptors, and genetic deletion of FABP5 reduces pain via CB_1 and PPARα activation, blunting TRPV1 sensitization. Inhibitors of FABP5 are effective in multiple models of pain, and cannabinoid target activation has been shown to reduce pain in preclinical diabetic neuropathy.

The aim of the present study was to examine the potential of ART26.12 in another peripheral neuropathy; the streptozotocin (STZ)-induced model of painful diabetic neuropathy.

Methods

On Day 0, 78 adult male Wistar rats were treated with STZ (55 mg/kg IP), which selectively ablates insulin-producing β cells in the pancreas. By Day 9, 11, animals developed neuropathy as assessed by measurement of paw withdrawal threshold (PWT) using calibrated Von Frey monofilaments applied to the plantar surface of the hindpaw, and diabetes (measured via blood glucose levels, ~30 mmol/L). Animals were treated orally with ART26.12 (25 or 100 mg/kg BID) from Day 15 for seven days, with Von Frey measurements on Day 15, 17 and 21, approximately 2 h after dosing. Duloxetine (60 mg/kg PO) was given on test days as an example of standard care.





Results

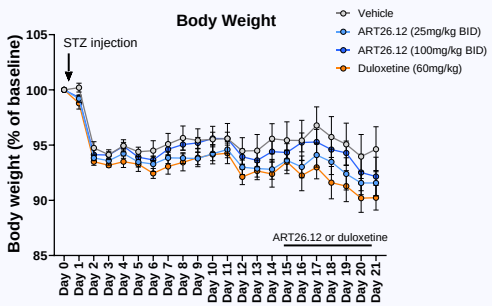


Figure 1. There were no significant differences in body weight between the treatment groups.

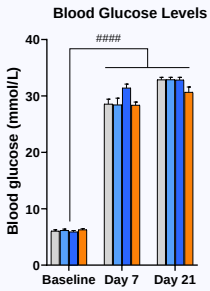


Figure 2. Blood glucose levels were elevated on Day 7 and Day 21 in all treatment groups ($p < 0.0001$).

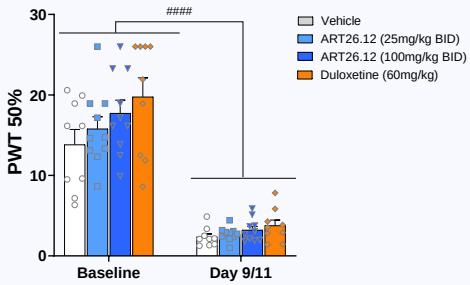


Figure 3. PWT scores in all treatment groups were significantly lower at Day 9,11 when compared to baseline ($p < 0.0001$), demonstrating the induction of neuropathy.

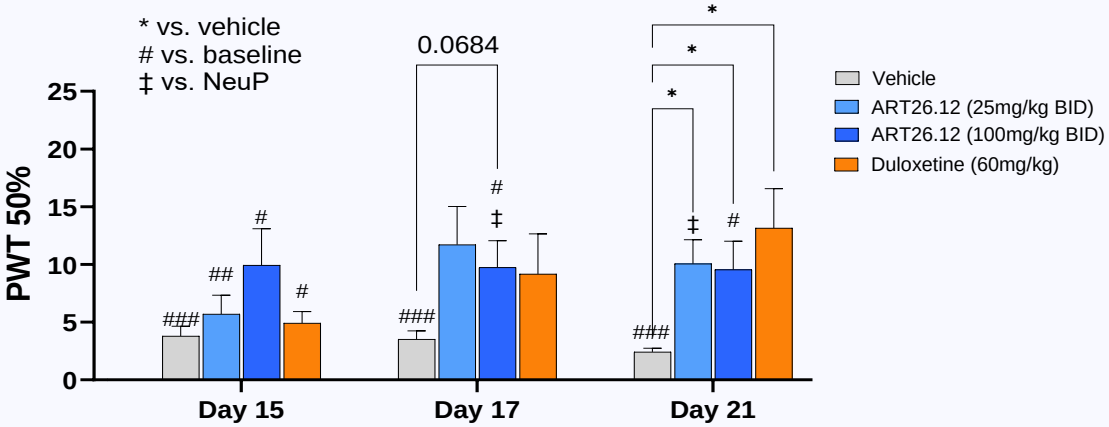


Figure 4. Animals treated with ART26.12 (25 mg/kg BID) and duloxetine did not show reduced PWTs on Day 17 and 21 (day 3 and 7 of drug treatment) when compared with HBL, indicating attenuation of allodynia. When compared with the neuropathic baseline (Day 9,11; NeuP), ART26.12 (25 and 100 mg/kg BID) increased PWT scores on Day 21 and 17, respectively. On Day 21, all treatment groups significantly increased PWT scores when compared with vehicle to a similar extent ($p < 0.05$). Mean plasma concentrations for ART26.12 (25 and 100 mg/kg BID) were 5.1 ± 1.2 µM and 39.3 ± 5.7 µM, respectively.

Conclusions

- ART26.12 (25 mg/kg and 100 mg/kg BID) reversed the pain behaviour induced by STZ in male rats to levels similar to duloxetine
- ART26.12 also treats pain behaviours in chemotherapy-induced neuropathy and cancer-induced neuropathy preclinical models
- FABP5 inhibition is a novel non-opioid, non-steroidal analgesic strategy effective in multiple models of peripheral neuropathy