Therapeutic Potential of Glepaglutide, a Long-Acting Glucagon-Like Peptide-2 Analog, in a Rat Model of Recurrent Indomethacin-Induced Small Intestinal Inflammation

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INTRODUCTION

Glepaglutide (ZP1848) is a novel, long-acting GLP-2 receptor analog that is currently in clinical development for the treatment of short-bowel syndrome. We have previously shown that treatment with glepaglutide in a rat model of indomethacin-induced small intestinal (SI) inflammation enhanced intestinal repair, as measured by increases in intestinal mass and plasma citrulline levels and decreases in inflammatory markers.

AIM

Here we investigated whether pre-treatment followed by an 8-day washout period or continuous treatment with glepaglutide would attenuate the SI inflammation response exposed to a second inflammatory episode in rats.

METHODS

Two cycles of SI inflammation were induced in male Wistar rats by indomethacin administration (7 mg/kg, s.c.) on day 0 and day 1 (primary challenge) and then again on day 18 and day 19 (secondary challenge). Rats were treated with glepaglutide (80 low dose) or 400 (high dose) nmol/kg, s.c. from day 0 to day 14 (pretreatment), or from day 0 to day 21 (continuous treatment). Groups of rats (n = 7-25/group) were sacrificed on days 15 and 22. Study endpoints were body weight, jejunal and ileal mass/BW, SI length, and SI levels of alpha 1 acid glycoprotein (α1-AGP; ELISA kit, Life Diagnostics) and myeloperoxidase (MPO; ELISA kit, Hyctul Biotechnology).

RESULTS

Glepaglutide reduces body weight loss during a primary and secondary SI inflammatory episode induced by indomethacin

Glepaglutide attenuates SI shortening and reduces inflammatory markers after the second phase of indomethacin-induced SI inflammation

RESULTS

Glepaglutide increases SI length and mass prior to the second phase of indomethacin-induced SI inflammation

CONCLUSION

Pre-treatment followed by an 8-day washout period, as well as continuous treatment with glepaglutide, protected the SI against the recurrent inflammatory episode. Pre-treatment with glepaglutide increased SI length and mass assessed prior to the induction of the second phase of inflammation, suggesting that these effects had rendered SI more resistant to the second inflammatory insult. In conclusion, glepaglutide may provide an attractive option for the treatment and/or prevention of the unpredictable course of inflammatory bowel disease.