THE GHRELIN AGONISTS, ANAMORELIN AND IPAMORELIN, ANTAGONIZE CISPLATIN-INDUCED ANOREXIA AND EMESIS IN THE FERRET

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Introduction

Ghrelin has well-known appetite stimulating properties, gastric prokinetic activity, and short acting anti-emetic effects against cisplatin-induced emesis in ferrets. However, clear anti-emetic effects are only seen following i.c.v. administration. Our previous studies in shrews showed that the brain penetrating ghrelin mimetic HM01 was more effective than the less brain penetrating mimetic, HM02.

Objectives

To explore the potential of two potent synthetic ghrelin agonists, anamorelin and ipamorelin, to reduce cisplatin-induced acute and delayed emesis and associated anorexia in ferrets.

Methods

Ferrets were administered anamorelin (1-3 mg/kg, i.p.), ipamorelin (1-3 mg/kg, i.p.), or saline 30 s before cisplatin (5 mg/kg, i.p.); treatment with saline or ghrelin agonists were repeated every 24 h. In a separate experiment, anamorelin (10 µg), or saline, were administered i.c.v. 30 s before cisplatin (5 mg/kg, i.p.) and repeated every 24 h. Behaviour was recorded for up to 72 h and food and water consumption was measured every 24 h.

Results

Peripheral Administration

Both compounds administered i.p. had no effect on cisplatin-induced emesis, but ipamorelin (Ipa) at 3 mg/kg, i.p. antagonized the associated anorexia by 28 and 22 % at 48 and 72 h, respectively ($P<0.05$); 1 mg/kg, i.p., also reduced anorexia by 20 % at 72 h ($P<0.01$). Anamorelin (Ana) at 1 mg/kg, i.p., reduced cisplatin-induced anorexia by 18 % at 72 h ($P<0.05$); There were also benefits on bodyweight changes (see below).

Results

Intraventricular Administration

Anamorelin, 10 µg, i.c.v., antagonized cisplatin-induced acute emesis by 60 % ($P<0.05$) and improved food and water intake by 22 ($P<0.001$) and 40 % ($P<0.001$), respectively; weight loss was also reduced by 27 % ($P<0.05$) at 48 h. There were also benefits on bodyweight changes (see below).

Conclusions

Brain penetrating ghrelin mimetics have the potential to reduce weight loss and emesis induced by chemotherapeutic drugs. The effect on appetite may relate to an ability to reduce nausea, but this requires further investigation.

n = 7-8 (* $P<0.05$; ** $P<0.01$; ANOVA, post hoc tests)

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