THE ACTION OF THE ORALLY BIOAVAILABLE GHRELIN AGONIST, HM01, TO ANTAGONISE CHEMOTHERAPY-INDUCED EMESIS MAY INVOLVE A SUPPRESSION OF FREE RADICAL PRODUCTION

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Introduction

Ghrelin has well-known appetite stimulating properties, gastric prokinetic activity, and short acting anti-emetic affects against cisplatin-induced emesis in ferrets. The emetic action of cisplatin may involve free radical damage that contributes to a release of 5-HT and an activation of 5-HT₃ receptors to drive the emetic response. HM01 alone, or in combination with palonosetron and netupitant, is useful to reduce cisplatin-induced emesis. However, it is not known if HM01 can prevent emesis induced by other chemotherapeutic drugs, free radicals, or mechanisms associated with elevated 5-HT levels.

Objectives

To explore the potential of HM01 to prevent cyclophosphamide-induced emesis and the emesis induced by the free radical generator, pyrogallol, and the selective serotonin reuptake inhibitor, fluoxetine.

Methods

Male *Suncus murinus* (40-80 g) were used. HM01 (3-30 mg/kg, p.o.) or vehicle (water, 2 ml/kg, p.o.) was administered 1 h prior to the injection of cyclophosphamide (200 mg/kg, i.p., 24 h observation), pyrogallol (128 mg/kg, i.p., 8 h observation), or fluoxetine (100 mg/kg, p.o., 24 h observation). The number of retches and/or vomits were recorded.

Results

Cyclophosphamide

Cyclophosphamide induced 53.7±9.5 retches+vomits that were dose-dependently antagonised by HM01 (ID₅₀ ~2.7 mg/kg; maximum reduction ~92 %, P<0.01).

Results

Pyrogallol and Fluoxetine

Pyrogallol and fluoxetine induced 69.0±21.5 and 49.8±16.6 retches+vomits, respectively. HM01 antagonised the emetic response induced by pyrogallol (ID₅₀ ~2.9 mg/kg; maximum reduction ~99 %, P<0.01), but was less effective against fluoxetine (a non-significant 46 % reduction was seen at 10 mg/kg, P>0.05).

Conclusions

The profile of anti-emetic action of HM01 suggests that a suppression of free radical production may contribute to mechanisms of emesis induced by chemotherapy. HM01 also improved food consumption in cyclophosphamide treated animals. Ghrelin mimetics alone may be useful against the side effects of moderately emetogenic chemotherapeutic drugs.