Potency and selectivity of GSK1325831A, a small molecule ghrelin receptor agonist

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Ghrelin has role in modulating food intake and gastrointestinal motility in several species (Korbonits et.al., 2004). Since exogenous administration of ghrelin has been shown to accelerate gastric emptying in rats and humans (Carpino et. al., 2002), the ghrelin receptor has become a target for pharmaceutical intervention. The aim of these studies was to determine the efficacy of GSK1325831A (N-[6-[cis-3,5-Dimethyl-1-piperazinyl]-3-(methyloxy)-2-pyridinyl]-3fluoro-4-(5-methyl-2-furanyl)benzenesulfonamide hydrochloride (E3)), a small molecule ghrelin receptor agonist to increase gastric emptying.

The potency and selectivity of GSK1325831A at the ghrelin receptor was determined using a FLIPR (fluorescent imaging plate reader) and CEREP™ screen. In the FLIPR assay, GSK1325831A, at the human and rat recombinant ghrelin receptor gave pEC50 values of 8.4 and 8.2 respectively. GSK1325831A was selective for the ghrelin receptor since it had no affinity (≤ 25% inhibition) across a panel of 50 receptors, receptors and ion channels in a CEREP screen run at 1µM, with the exception of the 5HT1B and 5HT6 receptors (↓43 and ↓37% respectively). The methods used to determine the efficacy of GSK1325831A to increase gastric emptying were based on those described by Droppleman et al. (1980). Experiments were performed on male CD rats (Charles River; 180 – 300g), fasted overnight before the experiment. On the day of the experiment, each rat received either GSK1325831A (0.03 - 10 mg/kg orally) or vehicle (1% methylcellulose), prior to an orally administered semisolid nutrient test meal. 1h after the meal, the rats were sacrificed and their stomach excised. The difference between the weight of the full and emptied stomach was subtracted from the weight of the administered meal. The percentage changes in gastric emptying were tested for statistical significance compared to vehicle control using one-way ANOVA and Dunnett’s test.

GSK1325831A significantly increased gastric emptying at all doses. The maximally effective dose was 1 mg/kg: producing a 50% increase in the percentage of the nutrient meal emptied compared to vehicle control (p<0.001, n=5-6/group). Increasing the dose of GSK1325831A (3 or 10mg/kg) resulted in no further increase, with 10mg/kg failing to reach significance. The effect of GSK1325831A (1 mg/kg orally) over time was also investigated. Rats displayed significant increases in gastric emptying at 20, 60, 120 and 180 minutes following meal administration (47% (p<0.05), 82%, 39% and 21% (p<0.001) compared to vehicle control), respectively (n=4-9/group/timepoint).The data from this study indicate that GSK1325831A is a potent and selective ghrelin receptor agonist that increases gastric emptying in the rat. These data are supportive of the view that development of ghrelin receptor agonists may be useful for the treatment of gastrointestinal motility disorders.

Carpino et.al., (2002). Bioorganic and Medicinal Chemistry Letters. 12, 3279-3282