Sustained Glucose-Lowering and Gastric-Emptying Effects of Amylin Agonism in Rats

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Abstract

Amylin is a β-cell hormone secreted in coordination with insulin in response to a meal and regulates postprandial glucose through suppressing nutrient-stimulated glucagon secretion, delaying gastric emptying, and decreasing food intake. A novel, second-generation amylinomimetic peptide, AC2307, which also reduces food intake in rats, has recently been described. This study examined the long-term glucoregulatory effects of amylin agonism in rodents by testing the ability of sustained treatment with amylin or AC2307 to lower glucose and delay gastric emptying. Male DIO Levin rats (body weight = 472 ± 4 g) were treated with amylin (69 nmol/kg/d, n = 10), AC2307 (69 nmol/kg/d, n = 10) or vehicle (50% DMSO, n = 9) for 4 wks via subcutaneous osmotic pumps. At 2 wks, overnight-fasted rats received a single oral dose of glucose (1.03 g/kg), and plasma glucose levels were measured at 30, 60, and 120 min. At 3 wks, overnight-fasted rats received a single oral dose of acetaminophen (33 mg/ml), and plasma acetaminophen levels were measured at 30 min. Compared to controls, plasma glucose (at 2 wks) following the glucose challenge was reduced at 30 and 60 min by amylin (20.5% and 21.2%) and AC2307 (26.8% and 30.9%)(P's <0.05). Glucose levels in the amylin- and AC2307-treated groups were not statistically different. The appearance of acetaminophen in plasma (at 3 weeks) was slowed by both amylin (46.9 ± 9.5%) and AC2307 (28.7 ± 11.1%) (P's <0.05). Acetominophen levels in amylin- and AC2307-treated groups were not statistically different. At 4 wks, amylin- and AC2307-treated rats showed significantly decreased food intake (P <0.05) and body weight gain (P <0.05) compared to controls, with greater vehicle-corrected weight loss observed with AC2307 vs amylin (17.0% vs 10.5%, P <0.05). These data show that the acute actions of amylin to slow gastric emptying and improve postprandial glucose are sustained in rats after prolonged treatment with amylin and the novel amylinomimetic peptide AC2307. Furthermore, AC2307 maintained the glucoregulatory actions of amylin, while producing greater weight loss.

Introduction

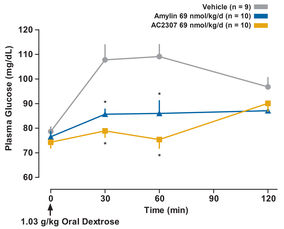
- Amylin is a pancreatic beta-cell hormone secreted in coordination with insulin in response to a meal
- Amylin regulates postprandial glucose through suppression of nutrient-stimulated glucagon secretion, delayed gastric emptying, and decreased food intake[1]
- A novel, second-generation amylinomimetic peptide, AC2307, which possesses greater efficacy and potency than amylin to reduce food intake and body weight in rats, has recently been described[2,3]
- To examine the long-term glucoregulatory effects of amylin and AC2307 in rodents, the current study tested the ability of sustained treatment with amylin or AC2307 to lower glucose (following a glucose challenge) and delay gastric emptying

Methods

- Subjects were individually housed male Levin DIO prone rats maintained on high-fat chow (32% kcals from fat) for 4 weeks
  - On Day 0, animals (472 ± 4 g) were implanted with 4-week osmotic pumps delivering vehicle (50% DMSO), amylin (69 nmol/kg/d: 300 µg/kg/d) or AC2307 (69 nmol/kg/d: 275 nmol/kg/d)
  - Plasma samples (tail vein) were also acquired at baseline; food intake and body weight were measured weekly
- After 2 weeks of treatment, overnight-fasted rats received 1.03 g/kg glucose by oral gavage, and glucose levels were measured at 30, 60, and 120 minutes (LifeScan OneTouch™ Ultra™ glucometer, Johnson & Johnson)
- At 3 weeks, overnight-fasted rats received a 33 mg/mL dose of acetaminophen, and plasma acetaminophen levels were measured at 30 minutes (Olympus AU400e™chemistry analyzer) to assess the rate of gastric emptying
- At termination (4 weeks), blood was collected via cardiac puncture and plasma cholesterol, glucose, triglycerides, and HbA_{1c} levels determined (Olympus)
  - Group differences were analyzed using ANOVA (P <0.05) and post-hoc analysis was performed with Fisher's least significant difference (LSD); data are presented as mean ± SEM

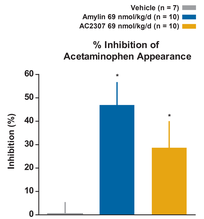
Results

Figure 1. Decreased plasma glucose levels post-oral glucose challenge following 2-week treatment with amylin or AC2307



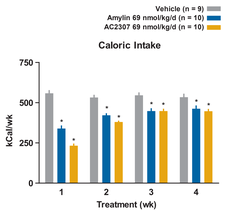
*P <0.05 compared to time-matched Vehicle group.

Figure 2. Slowing of gastric emptying following 3-week treatment with amylin or AC2307



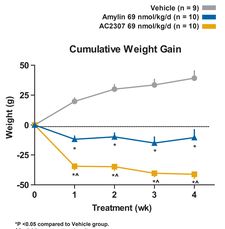
*P <0.05 compared to Vehicle group.

Figure 3. Reduction in food intake during 4-week treatment with amylin or AC2307



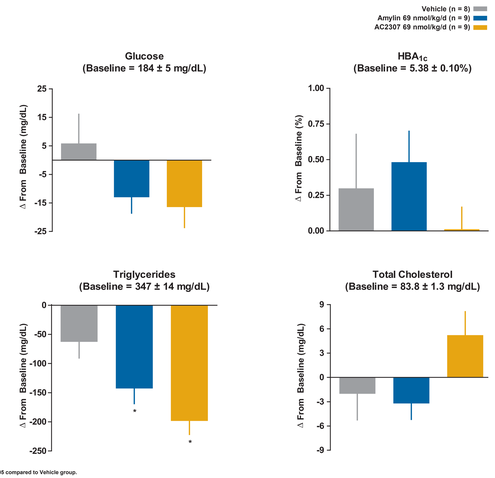
*P <0.05 compared to Vehicle group.

Figure 4. Reduction in body weight gain during 4-week treatment with amylin or AC2307



*P <0.05 compared to Vehicle group.
^P <0.05 compared to Amylin group.

Figure 5. Metabolic parameters following 4-week treatment with amylin or AC2307



*P <0.05 compared to Vehicle group.

Summary

- Decreased glucose excursion following an oral glucose challenge was observed with long-term treatment with amylin and the novel, second-generation amylinomimetic peptide AC2307
- Gastric emptying was also delayed by both amylin and AC2307 following prolonged treatment
- After 4 weeks of treatment, AC2307 produced greater vehicle-corrected body weight loss than amylin (17.0% vs. 10.5%)
- Plasma triglycerides were reduced in AC2307- and amylin-treated rats compared to controls

Conclusions

- The acute actions of amylin to slow gastric emptying and improve postprandial glucose are sustained in rats after prolonged treatment with both amylin and AC2307
- A similar pharmacodynamic profile on glucoregulatory parameters was observed with AC2307 compared with amylin
- AC2307 retained the glucoregulatory action (following a glucose challenge observed) of amylin, while producing greater weight loss

References

1. Young AA. Amylin's physiology and its role in diabetes. Curr Opin Endocrinol Diabetes 1997; 4:282-290.
2. Mack C, Soares C, Lewis D, Lin Q, Ghosh S, Lwin A, Herich J, Pittner R, Wilson J, Roan J, Alvarado L, Deconzo K, Jodka L, Guss S, Laugero K, Hanley M, Parkes D. Characterization of the anti-obesity actions of AC2307, a novel amylinomimetic peptide. Obesity 2006; 14(9 Suppl):178-P.
3. Gedulin B, Adams S, Smith P, Lei C, Ghosh S, Hanley M, Parkes D. Chronic administration of the amylinomimetic peptide AC2307 reduces body weight, food consumption and body fat mass in DIO Levin rats. Obesity 2006; 14(9 Suppl):179-P.