INAPPETENCE

Capromorelin, An Orally Active Ghrelin Agonist, Caused Sustained Increases in IGF-1, Increased Food Intake and Body Weight in Cats

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Abstract

Capromorelin is a ghrelin agonist that, when dosed orally in laboratory dogs, has been shown to stimulate food intake, weight gain, growth hormone (GH) and insulin-like growth factor-1 (IGF-1) (Zollers et al., 2014). This randomized, placebo-controlled study was performed to determine if capromorelin would also increase food consumption, promote weight gain and increase serum IGF-1 levels in laboratory cats.

Thirty-two cats (16 neutered males, 16 females) were divided into 4 treatment groups including 4 animals of each sex per group. The cats were acclimated to the study environment for 10 days prior to study start. All cats were orally dosed with placebo (Group 1) or capromorelin (30 mg/ml oral solution) at 1 mg/kg (Group 2), 2 mg/kg (Group 3) or 3 mg/kg (Group 4), for 21 days, with dosing starting on Day 1. Physical examinations were performed on Day -10 and general health observations made daily. Body weights were evaluated on Days -10, -8, -1, 1, 8, 15 and 22 days. Cats were fed approximately 1 hour after dosing; 300g of commercial dry cat food was provided for 5 hours and then removed and the amount of food consumed (g) calculated per cat. On Days 1, 14 and 21, blood samples were collected prior to daily dose administration and 8 hours post-dose and serum processed for measurement of IGF-1 levels. On Day 12, two study animals (one male each from Groups 1 and 4) were removed for reasons unrelated to the study and were not included in the data analysis.

All treatment groups were observed to have increased mean food consumption from baseline (average of Days -3, -2 and -1) to study period (average of Day 1 to Day 21). The placebo cats (Group 1) had a mean food intake increase of 10.83% over baseline, while the three capromorelin groups (Groups 2, 3 and 4) had mean food intake increases over baseline of 25.32%, 45.67% and 29.59%, respectively with only Group 3 showing a statistically significant ($p < 0.01$) increase in food consumption when compared to the placebo group.

Mean body weights for the capromorelin treatment groups increased during the 21-day exposure period. Groups 2, 3 and 4 had increases of 5.41%, 6.61% and 3.92% respectively whereas the placebo group lost a small amount of weight (minus 1.11%). Statistically significant differences from placebo ($p < 0.05$) in mean percent body weight change were observed for Group 3 at all 3 time points measured with increases of 3.23%, 5.97% and 6.61% on Days 8, 15 and 22, respectively. Additionally, Group 2 had mean percent body weight changes that were statistically significantly increased ($p < 0.05$) when compared to placebo at Day 15 (4.24%) and Day 22 (5.41%) but not at Day 8.

The interaction of treatment by sex was not statistically significant ($p > 0.05$) for either food consumption or weight gain, indicating that the effect of treatment was similar in male and female cats.

In Group 1, IGF-1 levels remained at baseline levels throughout the study. On Day 1, group mean serum IGF-1 levels increased from 0 to 8 hours post-dose by 46.69%, 29.38% and 36.77% for Groups 2, 3 and 4, respectively. On Day 14, IGF-1 levels were sustained at a higher level at hour 0. Therefore, the group mean increase in serum IGF-1 levels was lessened from 0 to 8 hours post-dose (17.27%, 9.00% and 18.56% for Groups 2, 3 and 4, respectively).

On Day 21, the trend of a smaller IGF-1 response continued as group mean IGF-1 levels increased from 0 to 8 hours post-dose by 9.81%, 2.68% and 5.17% for Groups 2, 3 and 4, respectively. The smaller increases of IGF-1 levels following capromorelin treatment on Day 14 and Day 21 were due to the fact that by Day 14 there was a sustained elevation in IGF-1 resulting from repeated daily capromorelin treatment.

In conclusion, capromorelin increased food intake, promoted weight gain and caused sustained increases in IGF-1 in laboratory cats.

Introduction

Capromorelin is a small molecule drug that mimics the action of ghrelin, the gastric hormone known as the "hunger hormone", which stimulates appetite by its action in the hypothalamus.[1] In addition, capromorelin acts as a growth hormone secretagogue, a class of small molecule compounds discovered in the mid-1990s, causing the release of growth hormone (GH) in a variety of species, including humans and dogs.[2] Our objective was to study the effects of capromorelin, a ghrelin receptor agonist (GH secretagogue), on food consumption and body weight in cats and its ability to cause GH secretion as evidenced by the downstream endocrine effects of increased insulin-like growth factor-1 (IGF-1).

Mechanism of Action of Capromorelin

Ghrelin Physiology

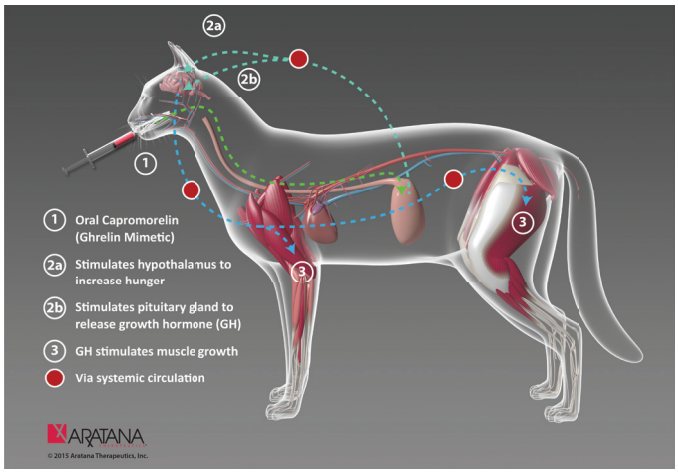
Ghrelin is a 28-amino acid peptide produced predominantly in the stomach and is an endogenous ligand of the ghrelin receptor, also known as GH secretagogue receptor (GHS-R). Ghrelin has a short half-life (~10 minutes), and accumulates in the bloodstream gradually between meals, reaching higher concentrations as the time since the previous meal extends. Ghrelin binds to receptors and affects signaling in the hypothalamus, causing the feeling of hunger, and enhancing food intake.

In addition to its effects on appetite, ghrelin stimulates GH secretion by activation of GHS-Rs in the hypothalamus and pituitary gland, which subsequently increases IGF-1 production. This effect acts to build lean body mass, which has been shown to modestly increase strength and prevent further loss of strength in frail elderly people.[1]

Capromorelin Physiology

Capromorelin is a potent and selective GHS-R agonist, which causes GH secretion and appetite stimulation. Capromorelin is orally active and therefore, unlike ghrelin, which is very short-acting when injected into animals, capromorelin has more sustained effects.

The pharmacologic mechanism of action involves binding to GHS-R, a G-protein-coupled receptor that activates protein kinase C and stimulates GH releasing hormone (GHRH) release from the hypothalamic neurons and GH release from the pituitary gland, resulting in the elevation of circulating GH levels. The GH-releasing activity of capromorelin has also been demonstrated in cats (Zollers et al., unpublished data).



Study Design

Our hypotheses were that in cats treated orally with capromorelin for 21 days, we would see an increase in food consumption and body weight and in addition, capromorelin treatment would result in a sustained increase in serum IGF-1 levels.

Thirty-two (32) laboratory adult cats (Domestic Short Hair) were randomized into four groups (n = 4 neutered males, 4 intact females/group) based on Day -1 body weight. Physical examinations were performed on Day -10 and general health observations made daily. Cats were dosed orally once daily with a flavored solution of either placebo (Group 1) or capromorelin at doses of 1 mg/kg (Group 2), 2 mg/kg (Group 3) or 3 mg/kg (Group 4) for 21 days. Food consumption was measured daily from Day -10 to Day 21. Cats were weighed on Days -10, -8, -1, and then on Days 1, 8, 15 and

22 prior to dosing and feeding. Blood samples were collected from each cat on Days 1, 14 and 21 at pre-dose (0 hours) and 8 hours post-dose and serum separated and frozen for measurement of IGF-1. Serum samples were sent to Cornell Veterinary Diagnostic Laboratory and IGF-1 measured via radioimmunoassay. Cats were observed daily for adverse events. Two cats (1 male from Group 1 and 1 male from Group 4) were removed from the study due to handling issues.

Statistical Analysis

Food Consumption and Body Weight

For each cat, baseline food consumption was calculated as the average of Days -3, -2 and -1. Food consumption was also calculated using the following treatment period intervals: average of Days 1 through 21, average of Days 1 through 7, average of Days 8 through 14 and average of Days 15 through 21. For body weight, the baseline was the weight measured on Day 1. For each cat, the percent change from baseline to each day (Days 8, 15 and 22) was derived as 100 x (treatment period minus baseline)/baseline.

Descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum values) were presented for baseline, each treatment period interval and for the difference/percent change from baseline to treatment period interval for each treatment group. Possible differences between treatment groups were evaluated using analysis of variance modeling with treatment group as effect. Pairwise comparison for each active group to placebo was adjusted using Dunnett's procedure.

IGF-1

Descriptive statistics (number of subjects, mean and standard deviation) were calculated for each time point.

Results

Food Consumption

Capromorelin-treated cats increased food consumption when compared to controls.

Comparing food consumption during the baseline period (mean of Days -3, -2 and -1) to the total treatment period (mean of Days 1-21), the placebo group showed an increase of 10.8%. Groups 2, 3 and 4 had increases of 25.3%, 45.7% and 29.6% respectively ($p = 0.0066$ for all treatment groups when compared to the placebo group; see Figure 1).

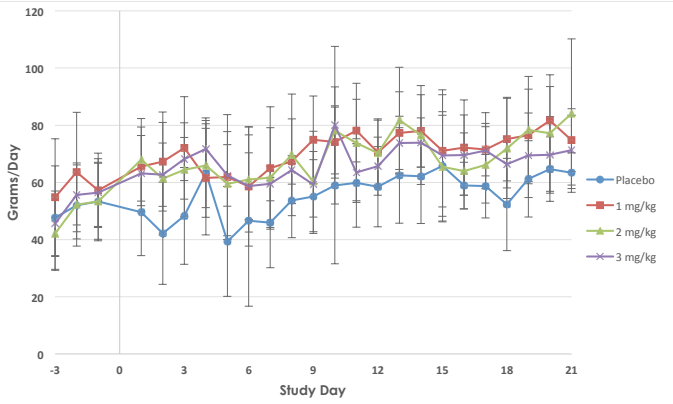


Figure 1. Mean (± SD) food consumption in cats treated with placebo or capromorelin for 21 days. Baseline food consumption was measured for the 3 days prior to dosing.

Food consumption was compared weekly during the treatment period (mean of Days 1-7; Days 8-14; Days 15-21) to the baseline period (mean of Days -3, -2 and -1). In the Days 1-7 comparison, the placebo group showed a decrease of 6.4%. Groups 2, 3, and 4 had increases of 13.1%, 30.1% and 23.3% respectively ($p = 0.0004$ for all treatment groups when compared to the placebo group). In the Days 8-14 comparison, the placebo group showed an increase of 15.7%. Groups 2, 3, and 4 had increases of 31.4%, 54.4% and 31.6% respectively ($p = 0.0164$ for all treatment groups when compared to the placebo group). In the Days 15-21 comparison, the placebo group showed an increase of 23.2%. Groups 2, 3, and 4 had increases of 31.5%, 52.5% and 34.0% respectively ($p = 0.0989$ for all treatment groups when compared to the placebo group).

Body Weight

Capromorelin-treated cats increased body weight from Day 1 to Day 22 when compared to the placebo group. The placebo group showed a decrease of

1.11%. Groups 2, 3, and 4 had increases of 5.41%, 6.61% and 3.92% respectively (p = 0.0103 for all treatment groups when compared to the placebo group; see Figure 2).

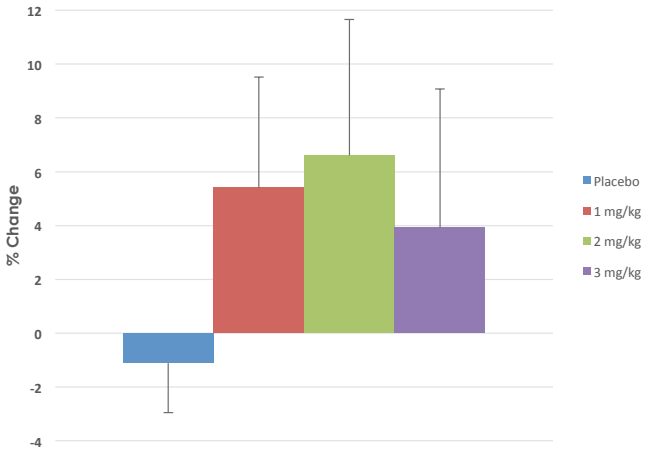


Figure 2. Mean (± SD) percentage change in body weight from Day 1 (baseline) to Day 22 in cats treated with placebo or capromorelin.

Group 2 (1 mg/kg dose) had mean percent body weight increases ($p < 0.05$) when compared to Group 1 (placebo) at Day 15 (4.24%) and Day 22 (5.41%), but not at Day 8. Additionally, mean percent body weight change ($p < 0.05$) was observed for Group 3 (2 mg/kg dose) compared to Group 1 at all 3 time points measured with increases of 3.23%, 5.97% and 6.61% on Days 8, 15 and 22, respectively. There was no statistically significant difference observed in mean percent body weight changes on Days 8, 15 or 22 between Group 4 (3 mg/kg dose) and Group 1.

IGF-1

IGF-1 remained at baseline levels in the placebo group throughout the 21-day study. On Day 1, mean serum IGF-1 levels gradually increased from 0 to 8 hours post-dose by 46.69%, 29.38% and 36.77% for Groups 2, 3 and 4, respectively (see Figure 3). On Day 14, IGF-1 levels were sustained at a higher level at hour 0 (pre-dose) when compared to baseline levels at hour 0 on Day 1. Therefore, the mean increase in serum IGF-1 levels on Day 14 (see Figure 4) was lower from 0 to 8-hours post-dose (17.27%, 9.00% and 18.56% for Groups 2, 3 and 4, respectively). On Day 21, the trend of a smaller IGF-1 response continued as mean IGF-1 levels increased from 0 to 8 hours post-dose by 9.81%, 2.68% and 5.17% for Groups 2, 3 and 4, respectively (see Figure 5). The smaller increases of IGF-1 levels following capromorelin treatment on Day 14 and Day 21 indicate that by Day 14 there was a sustained elevation in IGF-1 resulting from repeated daily capromorelin treatment.

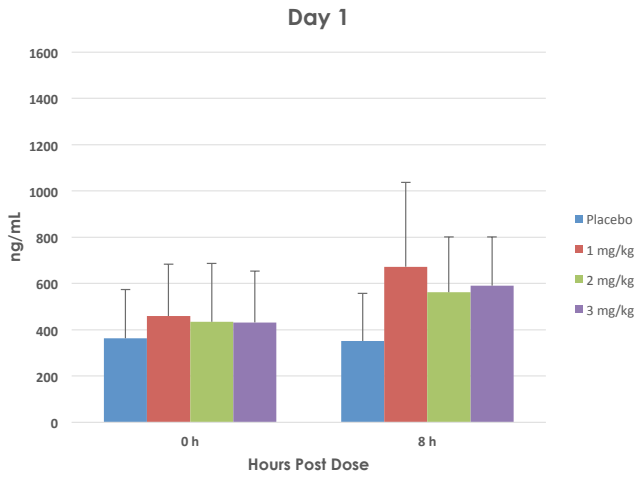


Figure 3. Mean (± SD) IGF-1 levels on Day 1 of treatment with capromorelin or placebo.

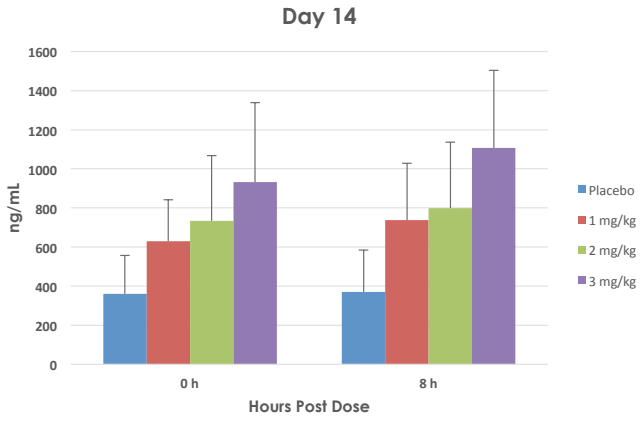


Figure 4. Mean (± SD) IGF-1 levels on Day 14 of treatment with capromorelin or placebo.

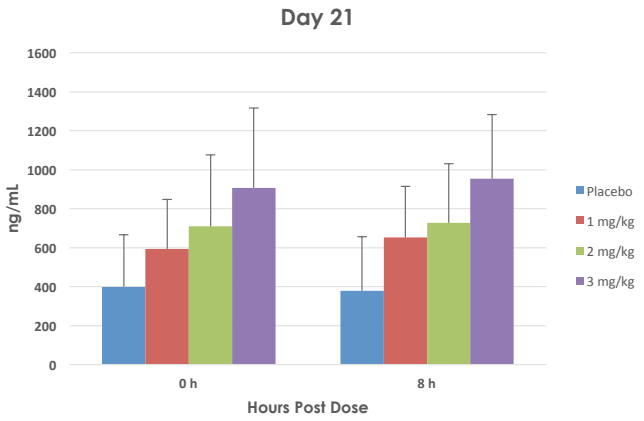


Figure 5. Mean (± SD) IGF-1 levels on Day 21 of treatment with capromorelin or placebo.

Discussion

Treatment of cats with capromorelin, a ghrelin agonist, caused a clear statistically significant increase in food consumption and body weight. The placebo-treated cats showed a substantially smaller increase in food consumption and lost weight.

In addition, we note a similar biological effect in cats on the GH/IGF-1 axis as previously noted in dogs.[2] In this study, capromorelin caused IGF-1 levels to gradually increase from 0 to 8 hours after the first dose. By Day 14 of capromorelin treatment, IGF-1 levels were sustained at a higher level at hour 0 when compared to baseline levels at hour 0 on Day 1. We hypothesize that capromorelin caused a pattern of GH and IGF-1 as was seen in dogs; that is, a spike of GH after the first dose with GH levels returned to baseline levels by 8 hours post-dose. This initial spike in GH would result in gradually increasing levels of IGF-1, which we saw in this study. These IGF-1 levels increase to a sustained level following repeated daily treatment with capromorelin. This IGF-1 elevation, as seen in cats in this study, likely serves as a negative feedback signal, damping down the subsequent post-dose GH secretion and preventing hyper-stimulation of the GH/IGF-1 axis, although we did not directly measure serum GH in this study.

The goal of treating cats with capromorelin is to increase body weight. This drug may be useful in a variety of chronic clinical conditions in which appetite is suppressed and body weight has decreased such as chronic kidney disease, heart failure, cachexia and muscle wasting.

This drug class was originally developed to treat cachexia and muscle wasting and is currently being investigated in humans with cancer anorexia cachexia syndrome.[3] We hypothesize that the accompanying increase in IGF-1 demonstrated in this study may also result in positive effects on lean muscle mass, as has been shown in dogs treated with GH.[4] These results are consistent with the action of this class of drugs, which has been demonstrated in humans to be beneficial in various human clinical conditions, such as elderly people recovering from hip fracture.[5]

Conclusions

Capromorelin is a new therapeutic under development for cats that works through a well-defined endocrine mechanism. When treated with capromorelin for 21 days, cats in this study consumed more food and gained body weight. The increase in IGF-1 levels seen post-treatment is an expected consequence of the therapeutic as a ghrelin agonist. Further studies are warranted in cats with chronic clinical conditions that could benefit from the increased food consumption and gain in body weight.

References

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Disclosure Statement

The following disclosures* are related to this poster: B. Zollers, J. Allen, C. Kennedy and L. Rhodes are employees of Aratana Therapeutics, Inc. and participate in the employee equity program.

*Disclosures include spouse and immediate family.

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