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Dark-Cycle Feeding and Meal Pattern Analysis in Rats Following Peripheral Administration of the Novel Amylin-Mimetic Peptide Davalintide

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Abstract

The current experiments examined dark-cycle feeding and meal patterns in rats treated with davalintide (DAV), a novel, second-generation peptide analog of rat amylin possessing a prolonged duration of action over the native hormone to reduce food intake. Male Sprague-Dawley rats (414-541 g, 32-45% kcal fat diet) received an IP injection of peptide (n = 5-8/group) at lights off and food consumption was measured for 20-24 h via an automated food intake recording system. Results showed amylin (100 µg/kg) to suppress food intake at hours 1, 2 and 4-6, compared to vehicle (p≤0.05). A second experiment showed a two-fold lower dose of DAV (50 µg/kg) to decrease food intake for up to 23 h post injection; this resulted in decreased body weight gain following 4 nights of treatment (DAV = -8.2 ± 1.5 g, vehicle = +1.6 ± 1.2 g, vehicle-corrected change = 2.1%, p<0.05). In experiment three, meal pattern analysis showed DAV (5, 10 and 20 µg/kg) to decrease meal size compared to vehicle (first meal) at all doses (vehicle = 4.5 ± 0.7 g; 5 µg/kg = 1.9 ± 0.5 g; 10 µg/kg = 2.4 ± 0.5 g; 20 µg/kg = 2.2 ± 0.3 g, p<0.05 for each). DAV at 20 µg/kg also increased latency to eat (vehicle = 8.5 ± 5.4 min; DAV = 173.7 ± 51.6 min, p<0.05). There were non-significant trends for DAV to increase intermeal interval (IMI), decrease meal duration and increase the satiety ratio (IMI/meal size). 24-h food intake was dose-dependently decreased, with significant reductions at all doses (vehicle = 18 ± 0.9 g; 5 µg/kg = 15 ± 1.5 g; 10 µg/kg = 14 ± 0.7 g; 20 µg/kg = 13 ± 0.9 g, p<0.05 for each). These data show DAV to reduce food intake in part through mechanisms involved in meal termination.

Introduction

- The pancreatic peptide neurohormone amylin is an anorexigenic agent which acts specifically to reduce meal size.[1,2]
- Preclinical studies have shown the second-generation amylin-mimetic peptide davalintide to possess enhanced pharmacological properties over the native hormone, including an extended duration of action, and greater efficacy to reduce dark-cycle feeding and body weight in rats.[3]
- The current studies examine the dose-related effects of davalintide on dark-cycle food intake and test whether this analog displays a similar feeding microstructure (selective reduction in meal size) to amylin.

Methods

- Adult male Sprague-Dawley rats (415-510 g) maintained on pelleted chow (32% fat kcal) received a single IP injection of vehicle or peptide 15 min prior to lights off and placed into the testing chamber. Food intake was monitored continuously for 24 h.
- The testing apparatus consists of a cage (10.5 x 19 x 8 in) equipped with a tunnel containing a food hopper at the end. As the animal eats, the food hopper is weighed every 5 seconds throughout the experiment (BioDAQ, Research Diets).
- For experiment 3, meal size, latency to eat, meal duration, the intermeal interval, and the satiety ratio (intermeal interval /meal size) for the first meal was obtained. The total number of meals during the dark and light cycle was also measured.

Experiment 1:

- Rats received rat amylin (100 µg/kg) for one night and 24-h food intake was measured (n = 4-8/group).

Experiment 2:

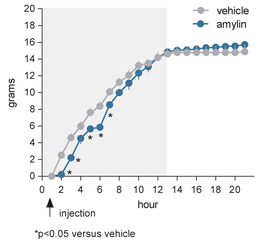
- Rats received davalintide (5 and 50 µg/kg) once nightly for 4 nights and 24-h food intake was measured (n = 4-6/group).

Experiment 3:

- Rats received davalintide (5, 10 and 20 µg/kg) for one night; 24-h food intake was measured and meal patterns were analyzed (n = 7-8/group).
- Cumulative food intake was analyzed using one-way ANOVA at each time point (experiments 1 and 2) or repeated measures mixed effects model with an autoregressive covariance model (experiment 3). Meal pattern measures were analyzed using one-way ANOVA. A Jonckherre-Terpstra trend test was used to look at dose-response trends.

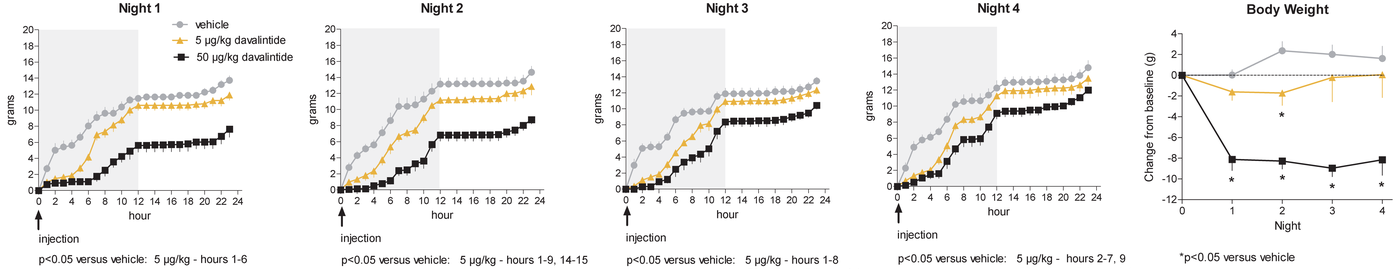
Results

Figure 1. Amylin Decreases Dark-Cycle Feeding up to 6 Hours Post-Treatment



*p<0.05 versus vehicle

Figure 2. Davalintide Displays an Extended Duration of Action to Decrease Dark-Cycle Feeding and Reduces Body Weight Across 4 Nights of Treatment



p<0.05 versus vehicle: 5 µg/kg - hours 1-6; 50 µg/kg - all time points

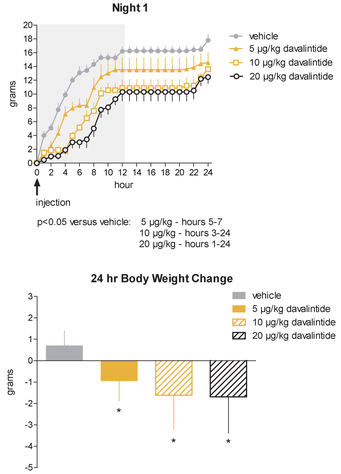
p<0.05 versus vehicle: 5 µg/kg - hours 1-9, 14-15; 50 µg/kg - all time points

p<0.05 versus vehicle: 5 µg/kg - hours 1-8; 50 µg/kg - all time points

p<0.05 versus vehicle: 5 µg/kg - hours 2-7, 9; 50 µg/kg - all time points

*p<0.05 versus vehicle

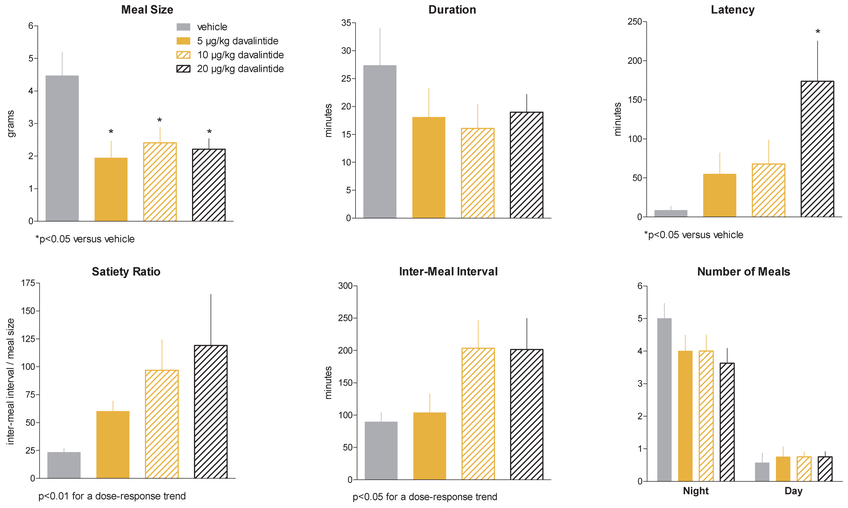
Figure 3. Davalintide Dose-Dependently Decreases Dark-Cycle Feeding



p<0.05 versus vehicle: 5 µg/kg - hours 5-7; 10 µg/kg - hours 3-24; 20 µg/kg - hours 1-24

*p<0.05 versus vehicle

Figure 4. Davalintide: Meal Pattern Analysis



*p<0.05 versus vehicle

*p<0.05 versus vehicle

p<0.01 for a dose-response trend

p<0.05 for a dose-response trend

Summary

- Davalintide shows greater potency, efficacy, and duration of action to reduce dark-cycle feeding compared to amylin.
- Similar to the parent peptide, davalintide (5 and 10 µg/kg) selectively reduced meal size; a dose dependent trend was also demonstrated showing an increase in the inter-meal interval and the satiety ratio.
- These data are consistent with the previously reported enhanced pharmacological actions of davalintide in preclinical models[3], and demonstrates that davalintide regulates food intake in part through mechanisms involving meal termination, similar to amylin.

References

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3. Mack CM, Soares CJ, Wilson JK, Athanacio JR, Turek V, Trevaskis J, Roth J, Smith PA, Gedulin B, Jodka CM, Roland BL, Adams SH, Lwin A, Herich J, Laugero KD, Vu C, Pittner R, Paterniti, Jr. JR, Hanley M, Ghosh S, Parkes DG. Davalintide (AC2307), a Novel Amylin Mimetic Peptide: Enhanced Pharmacological Properties Over Native Amylin to Reduce Food Intake and Body Weight. Int J Obes (Lond), 2010; 34(2):385-95.

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