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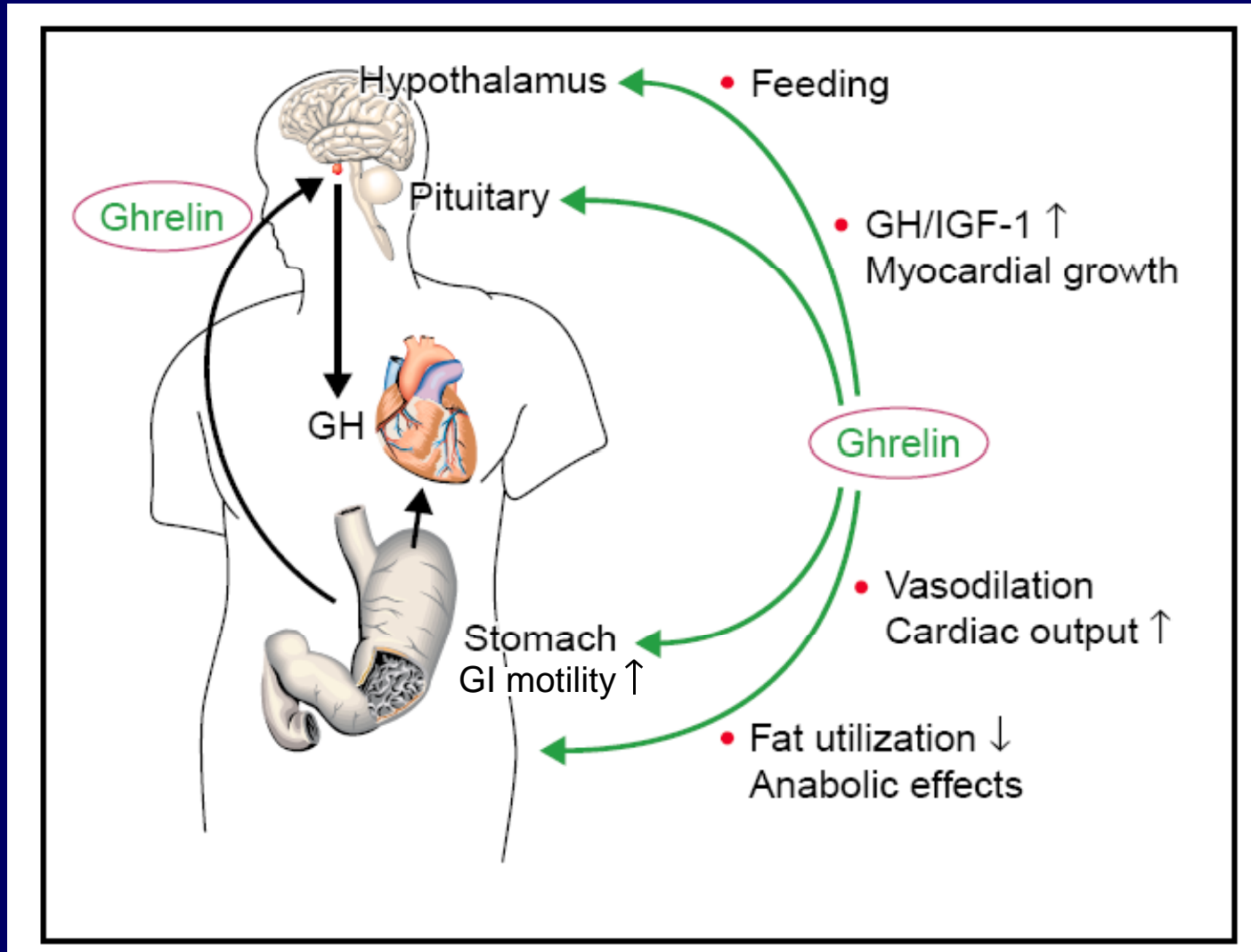
Pharmacological Demarcation of the Central Effects of Ghrelin on Growth Hormone Release and Food Intake with a Novel Ghrelin Receptor Agonist

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Ghrelin Pharmacology



TZP-101

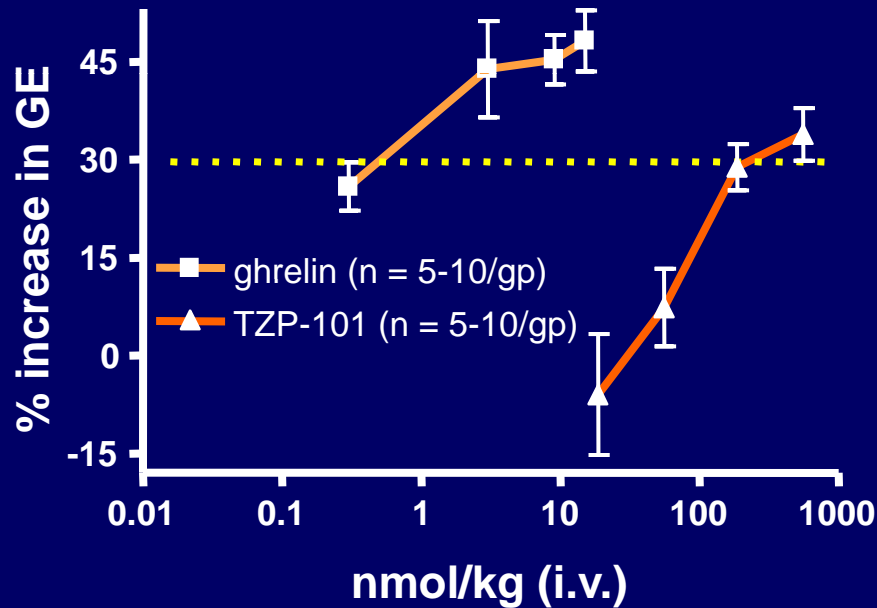
Small-Molecule Ghrelin Receptor Agonist

- Binding potency (K_i) = 22 nM (*h*)
 - ghrelin, K_i = 0.02 nM
- Agonist Activity
 - Cell-based models, EC_{50} = 25 nM (*h*)
 - ghrelin, EC_{50} = 2 nM
- Efficacy*
 - Gastric emptying (rat), MED = 80 nmol/kg (i.v.)
 - ghrelin, MED = 0.6 nmol/kg (i.v.)
 - GH release (rat), not detected up to 1900 nmol/kg (i.v.)
 - ghrelin, MED = 1 nmol/kg (i.v.)

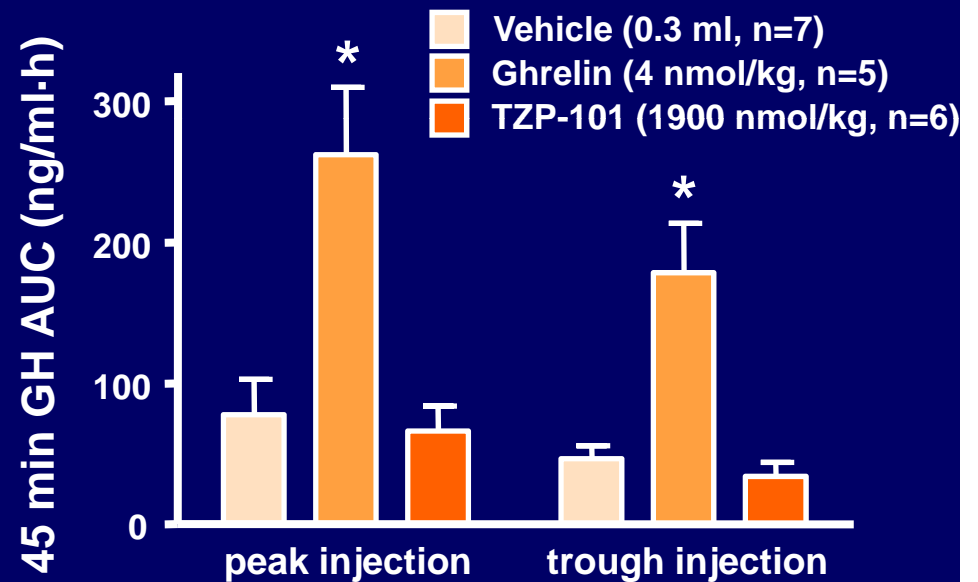
**G.L. Fraser et al., ENDO 2005 Abs# P3-2*

TZP-101 (i.v.) Accelerates Gastric Emptying but Fails to Stimulate Pulsatile GH Secretion

Gastric Emptying



Pulsatile GH Secretion (AUC)

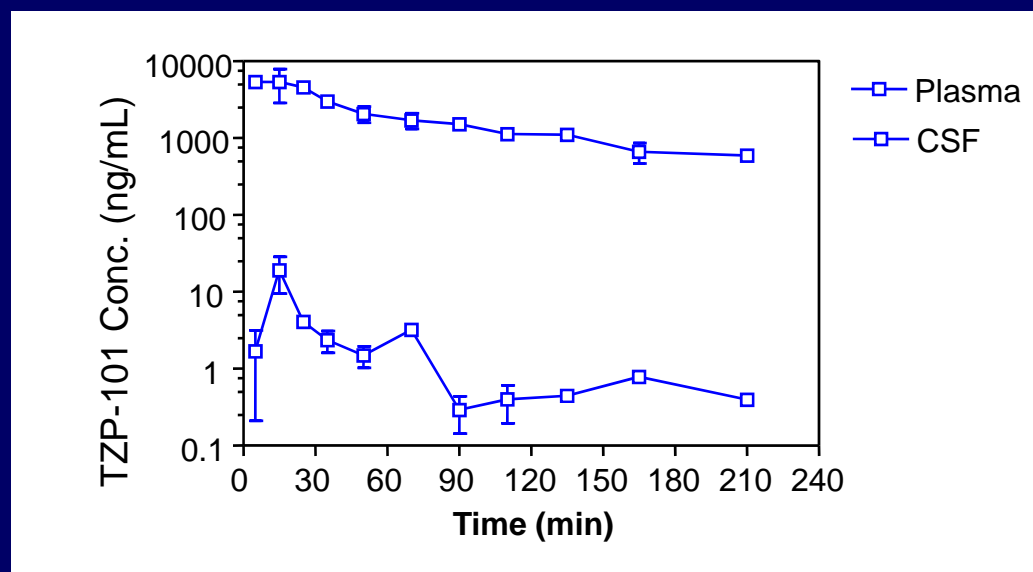


One-way ANOVA followed by t-test
* P < 0.004 vs. veh and TZP-101

TZP-101 Pharmacokinetic Profile

2 mg/kg (i.v.) in rat

- Terminal half-life: 99 min
- Clearance: 4.0 mL/min/kg
- $V_{ss} = 450$ mL/kg
- Blood-brain (AUC_{CSF}/AUC_{plasma}) : 0.09%



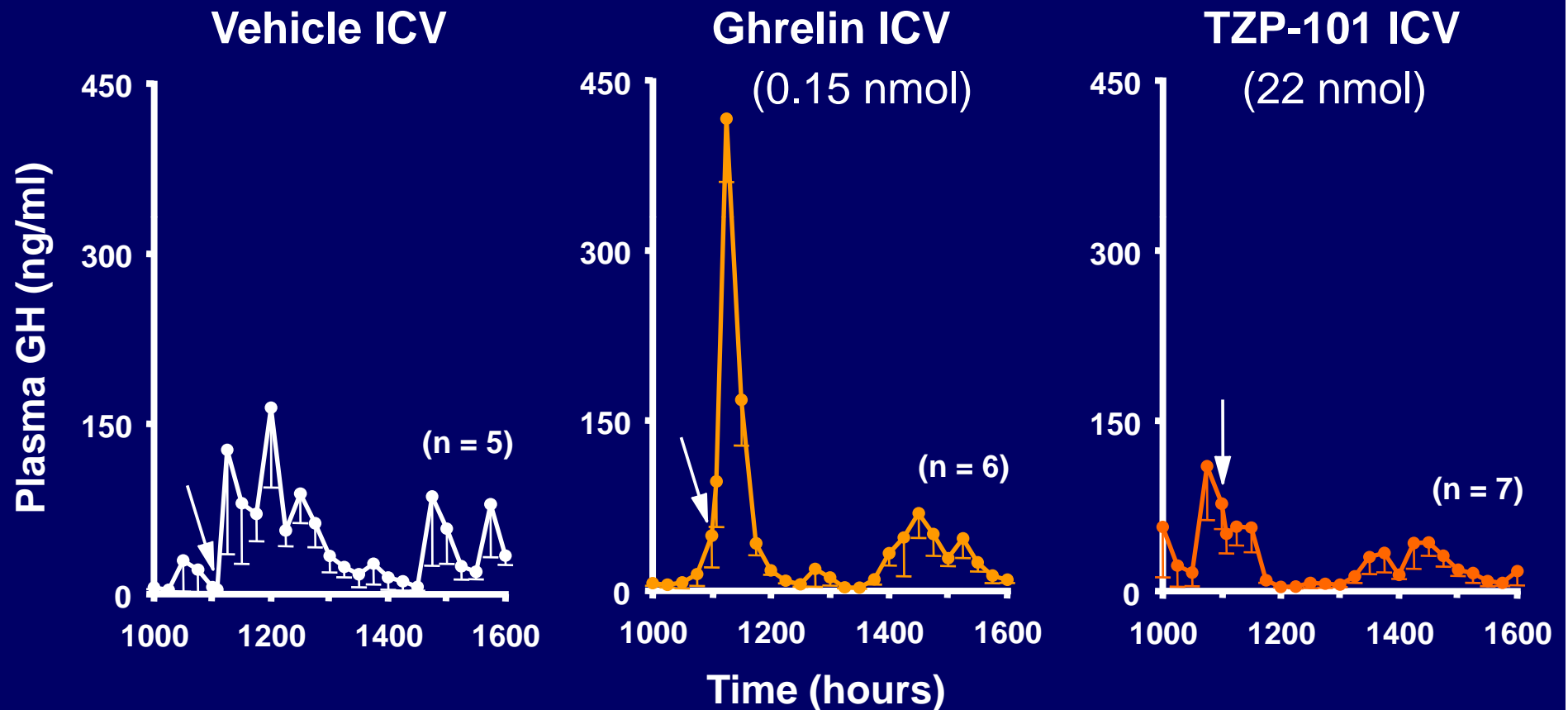
Aims of the Study

- To determine the effects of central administration of TZP-101 on GH release
- To test whether TZP-101 (i.c.v.) has any effect on spontaneous food intake
- To further examine whether TZP-101 and ghrelin have different pharmacology in rats

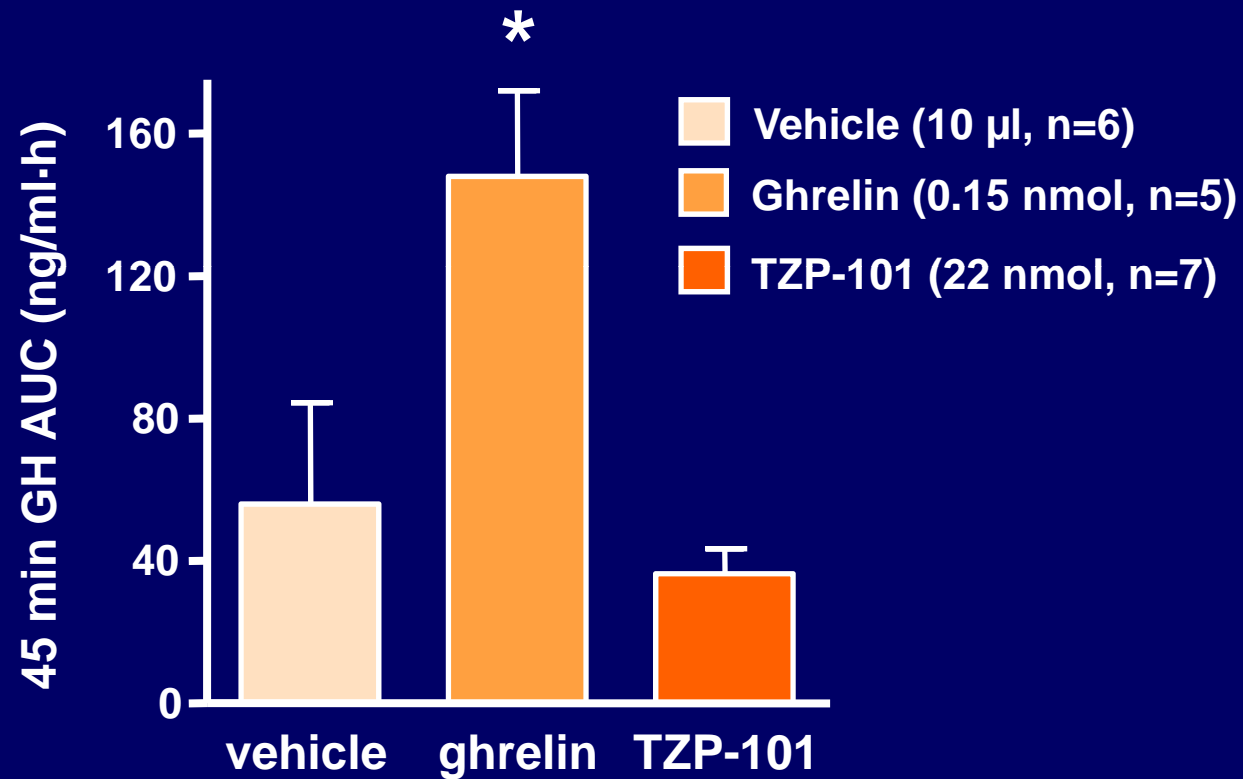
Methods: Measurement of GH Response

- Adult, male Sprague-Dawley rats (N=5-7/gp)
- Chronic, i.c.v. and jugular cannulae surgically implanted
 - i.c.v. cannulae placement confirmed by carbachol injection and methylene blue at sacrifice
 - rats allowed 5-7 days to recover from surgery
- Freely-moving animals injected with drug (or vehicle) i.c.v. at 1100h
 - typically a peak period of spontaneous GH secretion
- Blood samples drawn every 15 min. over 6-h sampling period
 - Plasma immediately collected for subsequent, double antibody GH radioimmunoassay

Plasma GH Response to Ghrelin and TZIP-101 Administered i.c.v. During Spontaneous Peak Periods of GH Secretion



Centrally-Administered TZP-101 Fails to Stimulate Pulsatile GH Secretion



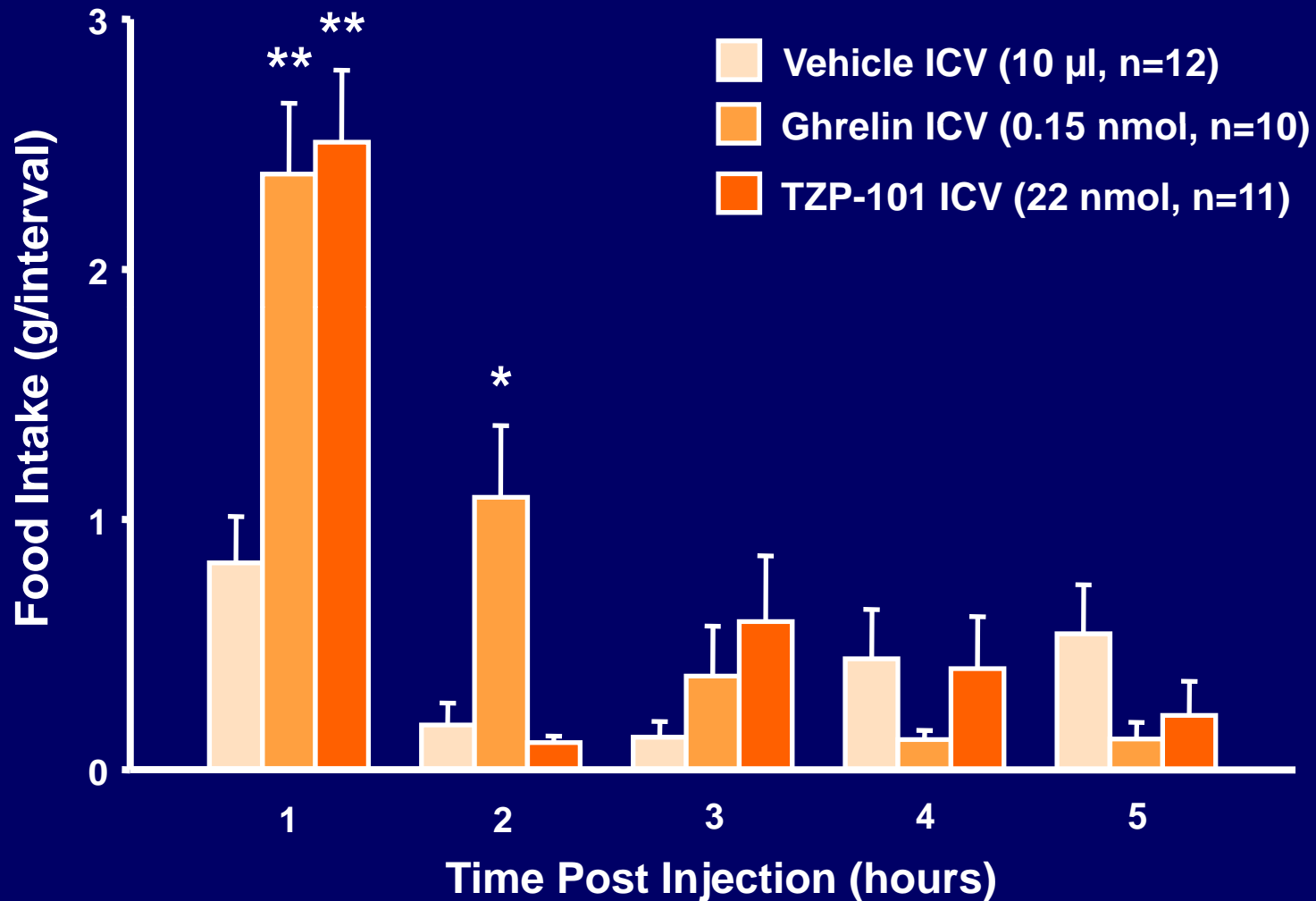
One-way ANOVA, $P=0.029$

* Bonferroni post-hoc, $P<0.05$ vs. veh, $P<0.01$ vs. TZP-101

Methods: Measurement of Food Intake

- Adult, male Sprague-Dawley rats (N=10-12/gp)
- Chronic, i.c.v. cannula surgically implanted as previously described
- Freely-moving animals injected with drug (or vehicle) i.c.v. at 1100h
- Food intake monitored on an hourly basis for five hours
- Latency of the onset of the first meal after injection and the duration of that meal were also measured for up to 60 minutes

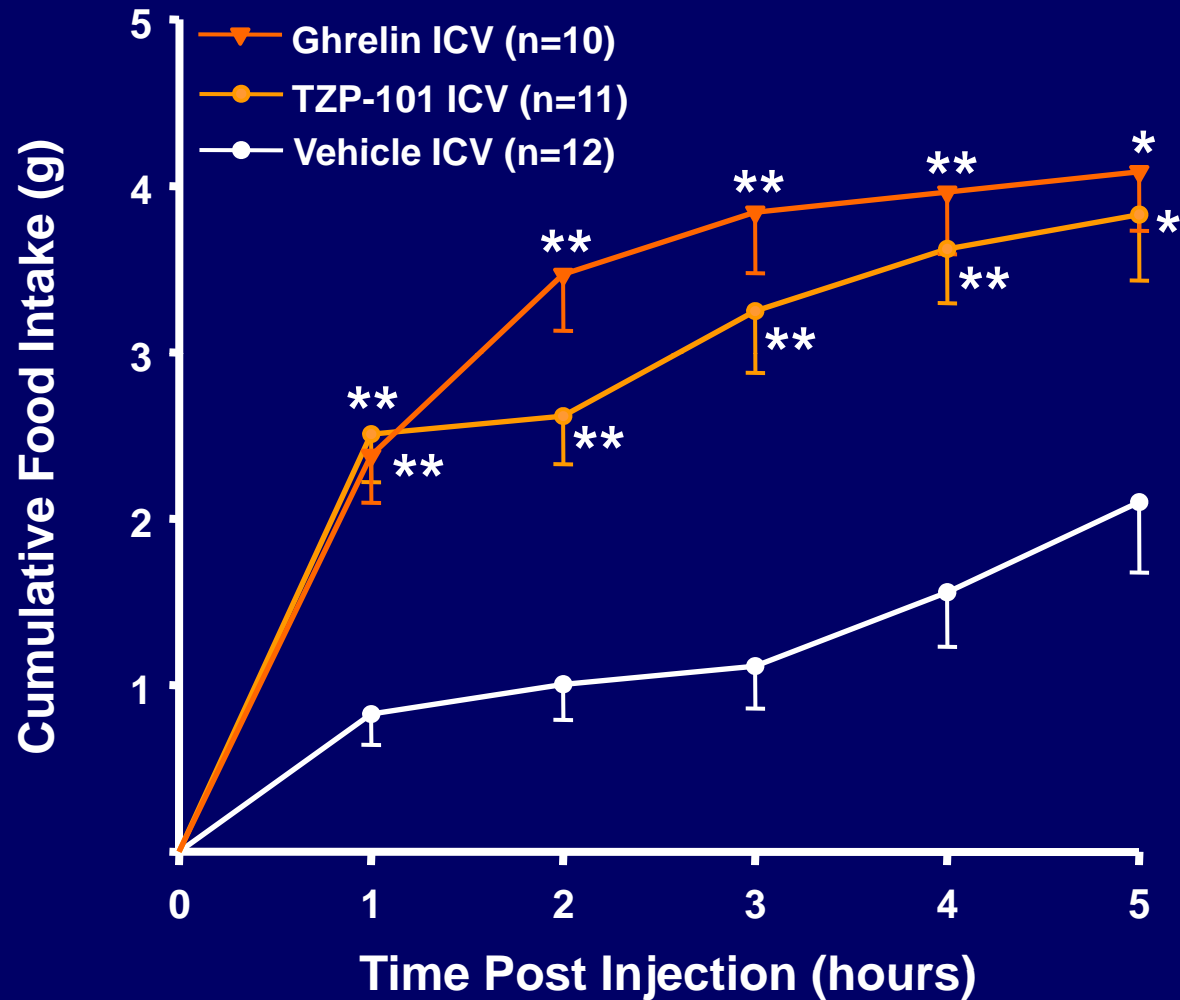
TZP-101 and Ghrelin Exert Similar Potent Orexigenic Actions at a CNS Level



Two-way ANOVA, $P < 0.0001$ (treatment, time)

Bonferroni post-hoc, ** $P < 0.001$ and * $P < 0.05$ vs. vehicle

Effects of TZP-101 and Ghrelin on Cumulative Food Intake

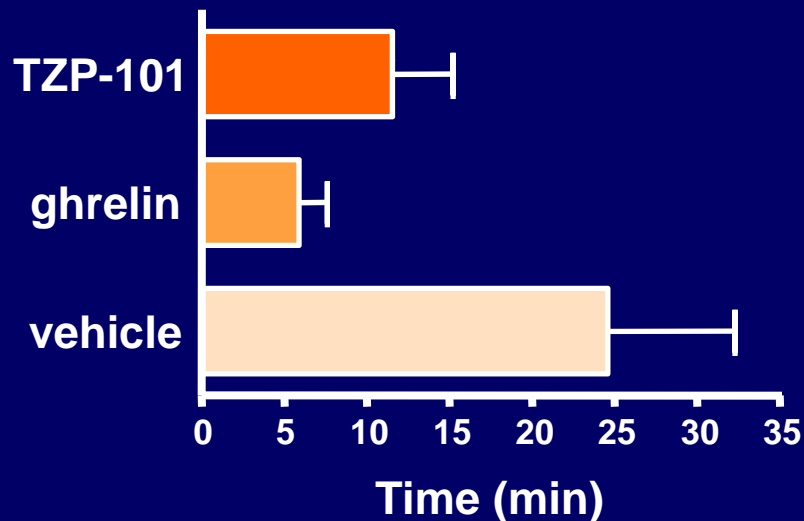


One-way ANOVA, $P < 0.005$ for all time-points

Bonferroni post-hoc, ** $P < 0.001$ and * $P < 0.005$ vs. vehicle

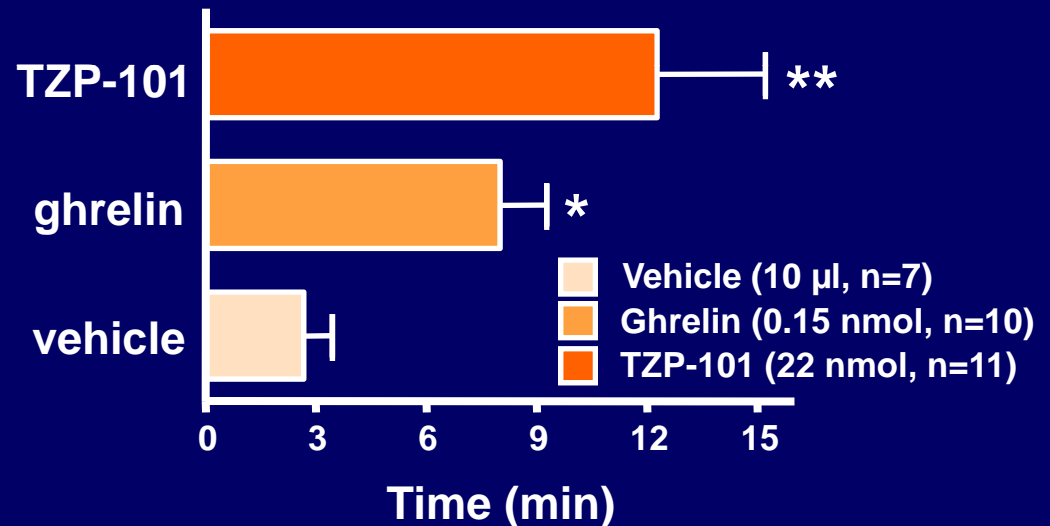
Latency to - and Duration of - First Meal in Response to Ghrelin and TZP-101 Administered i.c.v.

Latency to First Meal



One-way ANOVA, $P=0.054$;
no post-hoc tests

Duration of First Meal



One-way ANOVA, $P=0.006$
** $P<0.01$ and * $P<0.05$ vs. veh (Dunn's MCT)

Summary

- Ghrelin (i.c.v.) elicits GH release and spontaneous food intake in rat at a common dose
 - Historical data: ghrelin (i.v.) also elicits GH release and gastric emptying over a common dose range
- TZP-101 (i.c.v.) increases spontaneous food intake, but has no effect on GH release at the same dose (22 nmol, i.c.v.) in rat
 - Historical data: TZP-101 (i.v.) accelerates gastric emptying without effect on GH release even at >20-fold higher doses
- In contrast to ghrelin peptide, TZP-101 demonstrates comparative insensitivity to putative GRLN-mediated GH release in rat

Conclusions

- In total, these findings suggest that:
 - a common, TZP-101-sensitive signaling pathway mediates effects on food intake and GI activity;
 - whereas, GH release is modulated by a distinct pharmacological mechanism

Summary & Conclusions

- TZP-101 (i.c.v.) increases spontaneous food intake, but has no effect on GH release at the same dose (22 nmol, i.c.v.) in rat
 - Historical data: TZP-101 (i.v.) accelerates gastric emptying without effect on GH release even at 10-fold higher doses
- In contrast to ghrelin peptide, TZP-101 demonstrates comparative insensitivity to putative ghrelin-mediated GH release in rat
- In total, these findings suggest that:
 - a common, TZP-101-sensitive signaling pathway mediates effects on food intake and GI activity;
 - whereas, GH release is modulated by a distinct pharmacological mechanism