ACUTE GHRELIN CHANGES FOOD PREFERENCE FROM HIGH FAT DIET TO CHOW IN SCHEDULE-FED RATS

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INTRODUCTION

Ghrelin, an orexigenic hormone released from the empty stomach, provides a gut-brain signal that promotes many appetitive behaviours, including anticipatory and goal-directed behaviours for palatable treats high in sugar and/or fat. Here we sought to determine whether ghrelin is able to influence and/or may even have a role in binge-like behaviour in rodents. To this end, we used a palatable scheduled feeding (PSF) paradigm in which ad libitum chow-fed rodents are trained to "binge" on high fat diet (HFD) offered each day for a limited period of 2 hr.

STUDY DESIGN

Male Sprague-Dawley (SD) rats were schedule fed HFD for 2 hr each day in addition to chow to induce binge-like eating. After 2 weeks habituation to this PSF paradigm, on the test day and immediately prior to the 2 hr scheduled feed, rats were acutely administered ghrelin or vehicle by ICV (***study 1***) or by intra-VTA (***study 2***) route in a cross-over design (n=16 in each study). The effect of a 16 hr fast, to increase endogenous ghrelin, prior to the schedule feed was also investigated.

Animals with chronically altered ghrelin signalling were also investigated to determine whether they behave differently when exposed to a PSF paradigm. In ***study 3***, male SD rats were implanted with osmotic minipumps to deliver ICV ghrelin (n=8) or vehicle (n=8). After 10 days of chow feeding, rats were schedule fed with HFD for 18 days to investigate the chronic continuous ghrelin infusion on binge-like behaviour. In ***study 4***, ghrelin receptor (GHSR) knockout (KO) mice and their wildtype (WT) littermates were divided into 4 groups (n=6 per group) and half the mice were schedule fed (KO-SF and WT-SF) and the other half fed on chow only (KO-con and WT-con).

Data in study 1 and 2 were analysed by one-way ANOVA at each time point. Data in study 3 was analysed by independent samples t-tests on each day. In study 4, data was analysed by two-way ANOVA for the factors genotype (WT vs. KO) and feeding regime (scheduled feeding vs. control feeding). Significant results are shown as follows: * $P<0.05$ vs. vehicle and # $P<0.05$ vs. fasting. Data are presented as mean ± SEM.

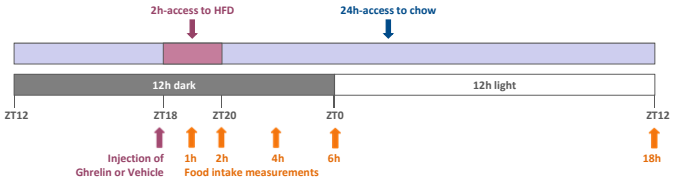

Figure 1. Overview of the study design. The palatable scheduled feeding paradigm was used in all studies. The injection and food intake measurement time points were used in study 1 and 2.

CONCLUSIONS

Our data provide evidence for a neurobiological action for the hunger hormone ghrelin, to steer dietary choice towards chow, even in rats highly motivated to consume large amounts of HFD in a PSF paradigm. Ghrelin may be able to enhance binge-like behaviour but we did not find evidence indicating that the ghrelin signalling system is required for mice to acquire this behaviour. Putting our data in the broadest possible context, in which dietary restriction may trigger or enhance bingeing behaviour, in certain, vulnerable obesity-prone individuals, we cannot rule out a role for ghrelin.

TAKE HOME MESSAGE

ACUTE GHRELIN IS A MODULATING FACTOR FOR BINGE-LIKE EATING BEHAVIOUR BY SHIFTING FOOD PREFERENCE TOWARDS A HEALTHIER CHOICE

RESULTS

Study 1: Impact of ICV ghrelin on PSF in rats

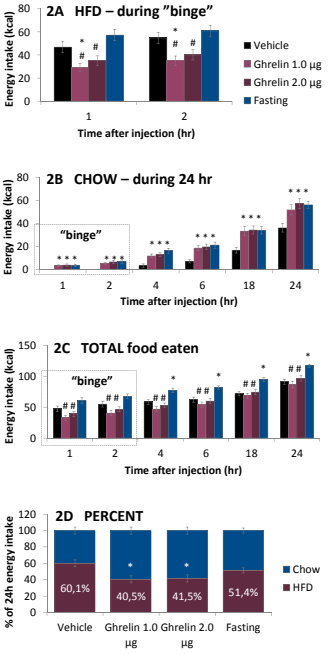

Figure 2. During the palatable scheduled feed, when rats normally only binge on HFD, those injected with ICV ghrelin started to eat more chow and less HFD. Chow intake remained above baseline for the rest of the 24 hr day. Fasting, which increases endogenous ghrelin, also increased chow intake but did not reduce HFD intake.

Study 2: Impact of intra-VTA ghrelin on PSF in rats

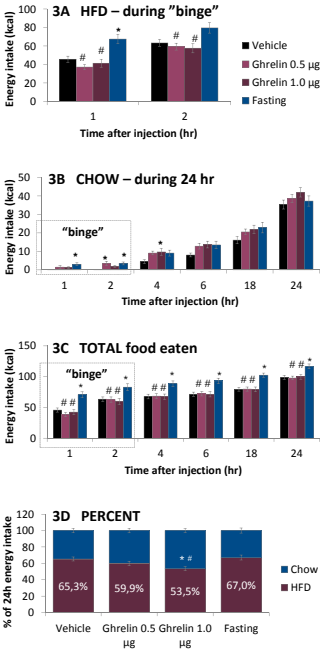

Figure 3. We identify the VTA (a key brain area involved in food reward) as a substrate involved as the effects seen in study 1 could be reproduced, in part, by intra-VTA delivery of ghrelin.

Study 3: Impact of chronic ICV ghrelin on PSF in rats

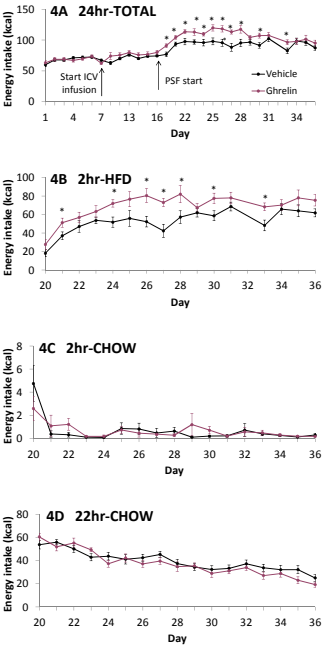

Figure 4. Chronic continuous central ghrelin infusion over several weeks enhanced binge-like behavior by increasing HFD intake in palatable schedule fed rats. Chow intake remained unchanged.

Study 4: PSF in GHSR-KO mice

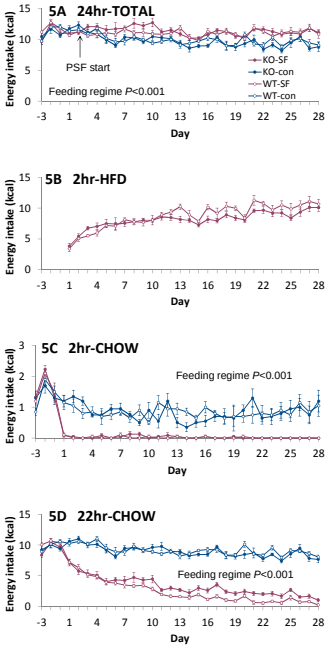

Figure 5. Over a 4 week period, GHS-R1A-KO mice were able to adapt and maintain large meals of HFD in a similar manner as WT mice.

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