The effect of ghrelin on neural responses to high calorie foods

The effect of ghrelin on neural responses to high calorie foods in satiated healthy BMI individuals, obese BMI individuals with Binge Eating Disorder and underweight BMI individuals with Anorexia Nervosa – Restrictive type

Introduction

Appetite has been investigated through homeostatic and hedonic systems. Homeostatic mechanisms, focus on the role of processes used to identify nutrients by the hypothalamus (Waterson & Horvath, 2015). The hedonic system involves brain circuitry activity that processes nutritional state signals and food reward value (Berthoud, 2011). The reward value of food is increased during periods of hunger and this is often assessed by fMRI where enhanced responses to appetitive stimuli in reward-related brain areas can be seen (LaBar et al., 2001; Führer, Zysset & Stumvoll, 2008; Goldstone et al., 2009), whereas satiation is associated with decline in positive hedonic reactions to food (Berridge, 1991). Food that evokes a pleasurable hedonic response will elicit an association between characteristics of that food eg. sight or smell, with a positive consequence (liking response) and they will often become sought after (wanted) (Berridge, 2009). Knowledge of mechanisms underlying appetite control is crucial to understand healthy and disordered eating patterns found in Anorexia Nervosa (AN) (under-consumption) and Binge-Eating Disorder (BED) (overconsumption).

Neural circuitry

Dorsolateral prefrontal cortex (dlPFC) activation has been associated with higher levels of cognitive inhibitory control of food intake (Hare, Camerer & Rangel, 2009; Hollmann et al., 2011; MacDonald, 2000). Some evidence

exists for the activation of brain areas associated with food taste when viewing pictures of food (Chen, Papies & Barsalou, 2016). There is a significant difference in neural responses to rewarding food cues in satiated vs. fasted states. When satiated, there is reduced motivation to eat facilitated by enhanced activity in prefrontal regions involved in higher cognitive functions and decision making; the dlPFC and ventromedial prefrontal cortex (vmPFC). Activity in the dlPFC affects food motivation by modulating reward value signals encoded by the vmPFC (Hare, Camerer & Rangel, 2009; Hare, Malmaud & Rangel, 2011). Attenuation of vmPFC activity is consistent with satiety induced decreased reward (Fletcher et al., 2010; Kringelbach, 2003). When hungry, the desire to eat may be triggered by visual cues of food (Berry, Andrade & May, 2007), leading to increased activity in the vmPFC and reduced activity in the dlPFC. This indicates that interactions between the dlPFC and vmPFC are important in eating behaviour that is goal directed rather than simply food cue driven. Literature demonstrates that a there is an association between eating unhealthy foods and inhibition of reward-related brain activity (Hare et al., 2009, 2011), leading to negative long-term health outcomes.

The orbitofrontal cortex (OFC) is also associated with reward and pleasantness through responses to the sight, smell and taste of food (Kringelback, 2003). This emphasises the influence of sensory-specific alterations in pleasure and reward value of stimuli on eating behaviour (Rolls, 1999). Research has found that pleasantness of food declines in later stages of a meal (Hetherington, 1996). Sensory specific satiety may occur where this reduction in rewarding properties of food may be specific for that

food (Rolls et al., 1981) but there also may be a general decline in attractiveness of all foods (Cabanac, 1971, 1979).

The interactions between the dlPFC and vmPFC differ in healthy individuals and those with eating disorders. In individuals with a healthy BMI, Thomas et al (2015) found that satiation lead to increased dlPFC activity and reduced activity in the vmPFC. There was increased connectivity between these areas, possibly due to ‘ top down’ mechanisms contributing to reduced motivation to eat (Thomas et al., 2015). This activity is seen amongst normal eating patterns, so it reflects brain patterns associated with natural satiation. Failure to inhibit response to food stimuli when satiated often leads to overeating or eating in the absence of hunger, contributing to disordered eating patterns (Higgs, 2016; Martin and Davidson, 2014). In patients with BED, research has found that altered cognitive processes in OFC/vmPFC areas could exaggerate food reward value signals and diminish inhibitory control (Grabenhorst & Rolls, 2008). Reduced inhibitory control and greater vmPFC activity has commonly been found in studies where images of high calorie foods were presented to individuals with BED (Schienle, Schäfer, Hermann & Vaitl, 2009). Increased consumption amongst these individuals could be due to vmPFC activity altering the perceived attractiveness of foods and overriding satiety or inhibition signals (Balodis et al., 2013). Patients with AN are thought to exert excessive self-control. Research by Hare, Camerer and Rangel (2009) found that food choice is determined by the OFC which integrates competing goal values when choosing between healthy and unhealthy food and this process is modulated by the dlPFC.

Hormones

Hormonal responses can also modulate the activity of brain systems associated with eating behaviour. Ghrelin is a hormone that is associated with increased food intake (Nakazato et al., 2001). Research has shown circadian fluctuations in plasma ghrelin levels which increase during fasting and reduce following a meal in healthy individuals (Erlanson-Albertsson, 2005).

In a meta-analysis by …. several studies have shown that higher levels of fasting plasma ghrelin exist in individuals with AN-R (restrictive type) than normal weight, healthy controls (Monteleone et al., 2008; Otto et al., 2001; Janas-Kozik et al., 2007). It could be suggested that patients with AN are insensitive to the effects of ghrelin due to their overall reduced food intake and low BMI and body fat (Misra et al., 2005). Research by Tolle et al (2003) found that during fasting, plasma ghrelin concentrations in women with AN increased and remained high but normalised after re-nutrition, when compared to normal weight and constitutionally thin women with similar BMI as AN patients. This suggests that in patients with AN, ghrelin levels are affected by nutritional state. Changes in body adiposity has not been found to have an effect on upregulated circulating ghrelin levels during fasting (Tschop et al., 2001). However, ghrelin levels decrease in conditions of higher energy stores such as obesity (Soriano-Guillen et al., 2004). It could be suggested that in patients with AN, higher ghrelin levels are adaptive responses to stimulate eating and increase body weight. Studies have shown that following treatment of AN patients, after a BMI increase of 15%, circulating and fasting ghrelin levels decreased towards normal (Otto et al. 2001; Janas-Kozik et al., 2007). In patients with BED, greater food intake and

weight gain may be due to the high ghrelin levels. Although, Munsch et al (2009) showed that fasting and post meal ghrelin levels did not differ between obese individuals with BED and BMI-matched controls. Majority of research studies report that in obese individuals with BED, plasma ghrelin concentrations are decreased which is contrary to expectations (Geliebter et al., 2005; Troisi et al., 2005). Lower ghrelin levels may be due to down-regulation of ghrelin release in response to overeating. In obese BED patients, a small decline in ghrelin following a meal has been noted (Geliebter et al., 2005), and it can be suggested that the blunted post meal decline in ghrelin levels may act to maintain hunger.

There is still much to learn about the effects of ghrelin on cognitive neural circuitry. Neuroimaging studies suggest the ventral and dorsal neural circuit dysfunctions in patients with eating disorders are closely associated to ghrelin (Brooks et al., 2011). It is clear that the dlPFC and vmPFC play important roles in eating behaviour and therefore, represent targets areas for interventions that aim to improve dietary choices in at-risk populations. In past studies, administering ghrelin in a dose-dependent manner has been shown to promote food intake (Faulconbridge et al., 2003; Tschop et al., 2001). Furthermore, increased neural response to food pictures in reward circuitry in humans has occurred due to ghrelin (Malik, McGlone, Bedrossian & Dagher, 2008).

There is a lack of research assessing the effect of ghrelin on cognitive responses of pleasantness (OFC), reward (vmPFC) and inhibitory control (dlPFC) to rewarding food cues in satiated healthy participants and participants with eating disorders. After eating, plasma ghrelin levels are

reduced however, administration of ghrelin may enhance cognitive responses to consume more food which from a health perspective, is beneficial for underweight individuals with AN-R. There is a growing appreciation that obesity is associated with neurocognitive problems, particularly in the domains of decision-making (Horstmann, 2017). Giving rise to comorbidities between cognitive dysfunction and disordered eating allows for new interventions such as cognitive training programmes using ghrelin administration to strengthen the ability to inhibit or encourage intake of food. As high levels of plasma ghrelin exist when hungry, these interventions can improve general eating styles in healthy individuals and those with eating disorders.

Aims & Hypotheses

The aim is to investigate the effect of ghrelin administration on neural responses in the OFC, dlPFC and vmPFC to visual cues of high calorie foods in satiated individuals with a healthy BMI, obese BMI individuals with BED and underweight BMI individuals with AN-R.

Hypotheses:

In satiated, healthy BMI individuals and underweight BMI individuals with AN-R, ghrelin will have no effect, there will be reduced blood oxygen level dependent (BOLD) activity to rewarding stimuli in the vmPFC and OFC and increased BOLD activity in the dlPFC.

In satiated, obese BMI individuals with BED: ghrelin will have an effect causing increased BOLD activity to rewarding stimuli the vmPFC and OFC and decreased BOLD activity in the dlPFC.

Method

Design

- Between subjects design
- Laboratory-based study

Participants

- 10 individuals with a healthy BMI, 10 obese individuals with BED, 10 underweight individuals with AN-R will be recruited
- Participants must not have any psychiatric disorders
- Participants are not allowed to eat or drink 1 hour prior to the study

Procedure

- Researcher will discuss study information and right to withdraw with the participant
- Written informed consent from the participant will be received
- Participants will eat a meal of cheese sandwiches on oatmeal bread with a glass of water until satiated
- Participants will be administered a 1 µg/kg dose of ghrelin through an injection
- After 15 minutes, participant will undertake an fMRI scan
- Whilst in the scanner participants will view images of high calorie foods eg. chocolate cake, cookies, ice cream

- BOLD signals to the visual stimuli in the OFC, vmPFC, dlPFC will be recorded to assess the effect of ghrelin on activity responses in these areas

References

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