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Research report

Hunger, ghrelin and the gut

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ABSTRACT

Hunger is defined as a craving or urgent need for food. Abundant evidence now indicates that homeostatic and cognitive mechanisms promote the sensation of hunger. Communication between the gastrointestinal (GI) tract and the central nervous system (CNS) regulate both homeostatic and cognitive mechanisms to control feeding behavior. In this context the GI derived feeding peptide ghrelin, targets the CNS to promote food anticipation, learning, hedonic feeding and motivation for food. Importantly meal expectation following nutrient deprivation or satiation is associated with elevation of plasma ghrelin, highlighting the propensity of each mechanism to stimulate GI ghrelin secretion. It is well established that multiple physiological processes control ghrelin secretion from the GI tract. For example activation of descending sympathetic and parasympathetic pathways, GI feeding peptides, metabolic factors and endocannabinoid signaling mechanisms all regulate ghrelin secretion. In parallel, activation of the CNS ghrelin receptor (GHSR-1a) controls food anticipation, food-based learning, spatial learning and the rewarding properties of food. Notably GHSR-1a is expressed within a network of CNS regions that regulate diverse aspects of feeding behavior. These examples suggest a redundancy regarding mechanisms that control GI ghrelin secretion and complexity for GHSR-1a-mediated regulation of food intake. Based on this collective data, we suggest that learned information linked to the receipt of food is transmitted from the CNS to the GI tract to stimulate ghrelin release. We further postulate that GI ghrelin release and ghrelin-GHSR-1a interactions adapt over time, metabolic status and environment to direct feeding behavior.

1. Cognitive control of feeding

Feeding behavior is controlled by direct and indirect mechanisms. Direct control is achieved through release of gastrointestinal (GI) peptides as nutrients accumulate during a meal. The net result of this meal-induced feedback is stimulation of satiety mechanisms that reduce food intake. It is important to point out here that the hindbrain is a critical region that integrates ascending signals from the GI tract and descending input from the central nervous system (CNS) to limit feeding behavior (Begg and Woods, 2013; Bray, 2000; Coll et al., 2007; Cummings and Overduin, 2007; Moran, 2004; Schwartz et al., 2000). In contrast indirect control of feeding behavior occurs through activation of forebrain and hypothalamic regions that stimulate meal anticipation and meal initiation. Importantly, indirect controls can override hindbrain satiety mechanisms to allow feeding to continue once energy reserves have been met. Moreover, indirect controls of feeding can be initiated by cues in the environment (Balleine, 2005; Holland and Petrovich, 2005; Johnson, 2013; Petrovich, 2011; Petrovich et al., 2005; Sobik et al., 2005; Yu et al., 2015) or those that inform an individual about metabolic state (Davidson et al., 2009; Davidson and Jarrard, 1993). The ability to anticipate a meal occurs secondary to mnemonic processes that enable environmental cues linked to receipt of food to acquire salience. In turn, these environmental cues stimulate anticipation of scheduled meals; thereby enabling increases in meal size, and increased body weight gain (Woods, 1991). When persistent, these indirect controls produce maladaptive changes in the CNS that diminish the homoeostatic control of food intake and produce excess body weight gain (Gearhardt et al., 2012; Gormally et al., 1982). Understanding the sequence of events that allow indirect controls to stimulate feeding in the absence of caloric need will provide better strategies to combat obesity. Presently, we know that cognitive control of feeding behavior involves communication between forebrain and hypothalamic brain regions to stimulate food anticipation and food intake.

2. Neural circuits that control hunger

Both preclinical and clinical studies have identified a distributed set of CNS nuclei that participate in cognitive control of feeding behavior. Preclinical studies that utilize restricted access

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feeding schedules (RFS) indicate that rodents learn to anticipate delivery of scheduled meals as indicated by increased locomotor activity prior to meal delivery (Poulin and Timofeeva, 2008). RFS models typically utilize a 20hr deprivation, 4hr feeding access paradigm. In this model rats are calorically restricted (CR) from food for 20 h and allowed to feed for 4 h per day. Rats initially loose weight on RFS schedules but gradually learn to anticipate meal delivery to allow ingestion of a large caloric load in a short period of time and increase body weight. RFS based feeding models critical aspects of dieting as it stimulates acquisition of cues that signal food availability in the context of restriction. This ability to anticipate scheduled meals is referred to as food entrainable oscillation (FEO). FEO is associated with activation of the hippocampus (Hp), medial prefrontal cortex (mPFC), nucleus accumbens (NAc), ventral tegmental area (VTA), arcuate (Arc), and dorsomedial (DMH) nucleus of the hypothalamus (Poulin and Timofeeva, 2008). Numerous lesions studies have failed to determine one single brain region in this network that reduces FEO suggesting that this behavior is controlled by distributed activity within this network. In contrast to RFS, restricted access to palatable meals (RPM) in non-restricted (NR) rats leads to activation of the mPFC, VTA, NAc, and the Arc (Blancas et al., 2014). Notably, neural activation persists even when rodents are no longer maintained RPM schedules indicating that activation of brain reward circuits may serve a time keeping function for hedonic food intake. In this context, clinical imaging experiments indicate that the visual presentation of palatable food cues in non-restricted patients activates a forebrain network of CNS regions including the frontal cortex, amygdala (AMG), striatum and midbrain (Grill et al., 2007; Ng et al., 2011; O'Doherty et al., 2002; Siep et al., 2009; Stice et al., 2008). Importantly, beyond FEO, presentation of food cues stimulates feeding in behaviorally sated rodents and also activates this forebrain network (Petrovich, 2011; Petrovich et al., 2005). Inactivation of the frontal cortex, amygdala, or functional disconnection of the amygdala from the lateral hypothalamus (LH) attenuates the ability of cues to stimulate feeding in sated rodents (Petrovich et al., 2005). Moreover, pharmacological activation of the frontal cortex leads to binge type intake of palatable food, an effect that correlates with increased neuronal activation of the LH (Mena et al., 2013; Blasio et al., 2014). This collection of preclinical and clinical studies indicates that cognitive-emotional (mPFC, AMG), and reward regions (NAc) communicate with homoeostatic centers (Arc, LH) to control feeding in the absence of caloric need. Although we have increased our understanding regarding the neural substrates involved in cognitive feeding, we still do not understand 1) how this network is activated, or 2) once activated, how this network overrides homeostatic controls to induce feeding in the absence of caloric need. Specifically, we do not know which hormones or transmitter systems participate in these processes, how learning alters activity of these factors, when or where such factors are released, or how they interact with the CNS to control feeding behavior. The first step is to identify processes that promote anticipation for palatable food, because without that, sustained increases in meal size are unlikely to persist. Emerging evidence indicates that the GI peptide ghrelin is a key regulator of food anticipation and hedonic food intake, making it a likely candidate to link learning, anticipation and hunger with overconsumption of palatable food.

3. Ghrelin & cognitive control of feeding

Ghrelin is a 28 amino acid *orexigenic* peptide that stimulates food intake in rodents and patients (Andrews, 2011; Cummings, 2006; Horvath et al., 2001; Müller et al., 2015; Nakazato et al., 2001; Tschöp et al., 2000; Wren et al., 2001a,b). Ghrelin is produced and released by X/A-like oxytinic cells of the stomach, the predominant source of circulating ghrelin (Müller et al., 2015; Toshinai et al., 2001) and is passively transported into the CNS (Banks et al., 2002). Exogenous application of ghrelin increases food intake, body weight, and appetite in both humans and rodents (Nakazato et al., 2001; Tschöp et al., 2000; Wren et al., 2001a,b). Once released, ghrelin targets the ghrelin-receptor (GHSR-1a) at peripheral and multiple CNS locations to stimulate feeding behavior (Müller et al., 2015). Ghrelin targets the ventral tegmental area (VTA) to stimulate food-seeking behavior and palatable food intake (Dickson et al., 2011; Skibicka et al., 2011, 2012, 2013). Once released, ghrelin requires acylation on the third serine residue to become maximally active at GHSR-1a (Kirchner et al., 2009). Data from our lab indicate that acylation of ghrelin is required to promote operant responding for sucrose following caloric restriction and hedonic intake of palatable food in sated mice (Davis et al., 2012). These examples suggest that peripheral ghrelin signaling participates in both homeostatic re-feeding and hedonic feeding behaviors.

Functional imaging studies indicate that exogenous application of ghrelin in sated patients leads to increases in the subjective ratings for appetite and enhances activation of the mPFC, AMG and striatum (Malik et al., 2008). Notably, circulating levels of ghrelin peak prior to scheduled meals in patients and in rodents (Drazen et al., 2006; Frecka and Mattes, 2008), indicating that peripherally released ghrelin may serve as an "anticipation signal" thereby regulating the ability to predict meals. GI secreted ghrelin reaches the hippocampus (Hp) (Diano et al., 2006), a cognitive CNS region that regulates memory consolidation, and in particular consolidation of food-related memories (Davidson et al., 2009; Davidson and Jarrard, 1993). When applied directly to the Hp, ghrelin initiates cue-based feeding behavior (Kanoski et al., 2013). Moreover, ghrelin-induced feeding via the Hp requires communication with and activation of LH neurons (Hsu et al., 2015). In combination these observations indicate that peripheral ghrelin targets cognitive regions to stimulate cue-based feeding and that this phenomenon requires communication with homeostatic control points to ultimately stimulate food intake.

In this context, conditioned exposure to chocolate in NR rats or expectation of rodent chow following RFS leads to increased neuronal activation of the mPFC and LH prior to meal delivery (Choi et al., 2010). Notably this conditioned neuronal activation correlates temporally with conditioned ghrelin release (Drazen et al., 2006). More recently we discovered that conditioned expectation of a nutritionally complete high fat diet (HFD) leads to behavioral anticipation, conditioned ghrelin release, and binge-like intake of HFD. Importantly, blockade of peripheral ghrelin release attenuates binge intake of HFD, suggesting that pre-meal conditioned ghrelin release promotes binge-eating behavior (Sirohi et al., 2016). Notably, conditioned ghrelin release is present in obese patients prior to meal expectation (Frecka and Mattes, 2008), indicating that anticipatory surges in plasma ghrelin may act to maintain excess food intake in the context of obesity. These observations indicate that conditioned release of ghrelin is a powerful process capable of stimulating food intake in the absence of caloric need. Germane to this topic, central blockade of GHSR signaling attenuates behavioral anticipation of chocolate in NR rats (Merkestein et al., 2012). Additional work on this topic indicates that functional deletion of GHSR attenuates food anticipatory behavior in CR mice and spatial learning in the Morris water maze, suggesting that deficiencies in learning may attenuate food anticipatory responses (Davis et al., 2011). This collection of data highlight conditioned ghrelin release as a key event that initiates cognitive processes capable of stimulating feeding in the absence of caloric need.

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