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REVIEW

Appetite control: why we fail to stop eating even when we are full?

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Abstract **We often eat more than our body needs. We live in an environment where high calorie food is abundant and physical activities are limited. Living in this environment, maintaining healthy bodyweight becomes challenging and obesity becomes a social burden. Why do we continue to eat even after the metabolic needs are satisfied? Feeding is an ancient behavior essential to survive. Thus the mechanisms to regulate appetite, energy expenditure, and energy storage are well conserved throughout animals. Based on this conservation, we study why we fail to control appetite using a simple genetic model system *C. elegans*. We have discovered certain genetic components that when misregulated have animals eat more and store more fat. In this review we discuss how these genes work in the appetite control circuit to ultimately understand overall appetite control behavior. We will also briefly discuss how social influence affects feeding regardless of the metabolic status of an animal.**

Keywords cGMP, TGFβ, *C. elegans*, satiety, appetite, obesity

Introduction

In 2008, WHO announced that approximately a billion of us (35% of world population) are obese. Studies from obese patients who are deficient in leptin (Montague et al., 1997) or who carry mutations in melanocortin 4 receptors (MC4R) (Farooqi et al., 2000) demonstrate that failure of appetite control and resulting obesity can be an inheritable genetic disease. To date, despite tremendous effort, however, there are only 11 genes identified as genetic causes of obesity (Mutch and Clément, 2006). Moreover, aside from leptin and MC4R, we do not know the molecular mechanisms by which those mutations contribute to obesity.

To stop or start eating based on an animal's metabolic status, the appetite control center in the brain integrates signals from the gut that convey the animal's metabolic status. Under pathological conditions, however, this communication within the appetite control circuit is often broken and the animal eats more than it needs or does not eat even if it needs to. This misregulation happens when the brain overrides metabolic signals or when the metabolic signals misfire. All 11 genes associated with human obesity are involved in the regulation of appetite, suggesting that an intact circuit to control appetite is critical to maintain normal bodyweight. In this review, we will discuss the neuronal regulation of appetite focusing on two signaling pathways, TGFβ and cGMP.

Locomotive activity reflects animal's nutritional status

Food is important to any animal, and a large part of the behavioral repertoire is concerned with ensuring adequate nutrition. Two main nutritional sensations, hunger and satiety, produce opposite behaviors. Hungry animals seek food, increase exploratory behavior and continue feeding once they encounter food. Satiated animals decrease exploratory behavior, take a rest, and stop feeding. Therefore locomotive activity often reflects an animal's nutritional status. In a recent study, we used a newly developed tracking system combined with a Hidden Markov Model analysis to validate the notion in *C. elegans*. *C. elegans* has been a powerful genetic model system to discover many complex yet evolutionarily conserved molecular pathways (Han and Sternberg, 1990; Hengartner et al., 1992). Moreover, Ashrafi et al (2003) provided genetic evidence that fat metabolism and energy

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expenditure are conserved between worms and mammals. In addition, we discovered that the signaling and the behavior controlling food intake, which contributes directly to obesity, are also conserved between *C. elegans* and mammals; after a big meal, worms become quiescent, mimicking the behavioral sequence of satiety in mammals (You et al., 2008). The finding of this behavior has given us a chance to use *C. elegans* to study the genetics of food intake and therefore the potential genetic contribution to obesity. We monitored an individual worm's locomotive activity throughout the refeeding period and analyzed the speed to find the particular behavioral state of the worm at a given time point during refeeding. Our study shows that hungry worms move more than satiated worms and thus that locomotive activity faithfully reflects an animal's metabolic status (Fig. 1). In addition we found that the TGFβ pathway and the cGMP pathway in a pair of head sensory neurons ASI mediate satiety behavior in *C. elegans* (Gallagher et al., 2013a, 2013b).

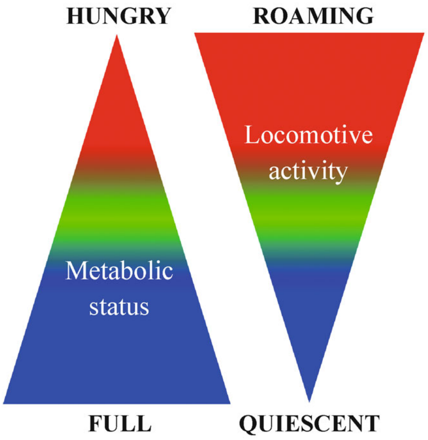

Figure 1 Locomotive activity reflects metabolic status: A schematic diagram to show how metabolic status can be reflected by locomotive activity.

TGFβ and food intake

Transforming growth factor β (TGFβ) signaling is well studied in cell proliferation, differentiation and tumor formation (Feng and Derynck, 2005). In addition, studies suggest a role of TGFβ in food intake and fat metabolism: (1) Overexpressing a TGFβ family member (MIC-1/GDF-15) in the brain inhibits food intake in wild type mice and causes weight loss by reducing food intake in leptin-deficient *ob/ob* mice (Johnen et al., 2007). Deficiency of MIC-1, on the other hand, causes an increase in food intake (in females) and induces obesity (in both genders) (Tsai et al., 2013). (2) Exercise activates TGFβ in the brain, and this increase of TGFβ correlates with increased fat mobilization (Shibakusa et al., 2006). (3) Orexin, a neuropeptide that increases appetite, upregulates expression of four sets of signaling genes including TGFβ/SMAD (Sikder and Kodadek, 2007). (4) In *C. elegans*, neuronal TGFβ signaling controls fat metabolism (Greer et al., 2008) as well as post-prandial quiescence (You et al., 2008). These results suggest that TGFβ signaling regulates food intake and fat metabolism both in mammals and worms, potentially through a conserved molecular mechanism. The molecular and cellular mechanisms, however, remain unknown. We have shown one way by which the TGFβ pathway regulates appetite in *C. elegans*. We found that ASI, which is known to regulate several nutrition-related behaviors such as calorie restriction-dependent longevity (Bishop and Guarente, 2007), is activated by nutrients. In addition, the expression of TGFβ in ASI neurons increases after the worms reach nutritional satisfaction. We also showed that the TGFβ from ASI inhibits two downstream neurons called RIM and RIC, thus suggesting a satiety circuit consisting of ASI → RIM + RIC. RIM and possibly RIC are thought to be activated during starvation (Alkema et al., 2005; Suo et al., 2006; Greer et al., 2008; Crocker et al., 2010). Also RIM and RIC neurons are the only known neurons that synthesize and secret octopamine, the invertebrate norepinephrine, to regulate alert responses. Based on these results, we propose that upon metabolic satisfaction, ASI gets activated and releases TGFβ, which in turn suppresses 'alert/ hunger responding neurons', RIM and RIC (Fig. 2) (Gallagher et al., 2013b). This inhibition of RIM + RIC by ASI suggests a potential antagonism between ASI and RIM + RIC neurons that could mimic the mammalian appetite control center in the hypothalamus where orexigenic NPY expressing neurons and anorexigenic AGRP expressing neurons antagonize each other.

Interestingly, worm neuro-anatomy shows a potential input from ASH to RIM + RIC neurons. ASH is another pair of head sensory neurons that sense most noxious stimuli. If these three neurons act as a small circuit by themselves, this circuitry would cause the worms to be alert and to flee so as to avoid noxious stimuli. The potential existence of this 'appetite suppress' circuit outside of nutrition sensing neurons ASI is quite reasonable because integrating the noxious signals into the appetite control center can provide a gate to integrate social influence into appetite control.

Our finding combined with previously known function of ASI shows that ASI inhibits the activity of RIM and RIC through the TGFβ pathway. However, interesting questions such as how suppressing RIM and RIC evokes satiety, what are the hunger signals released from RIM and RIC, and whether the signal released from RIM and RIC can antagonize ASI as negative feedback still remain to be answered.

cGMP a conserved cue for metabolism?

The cGMP signaling pathway is involved in many essential functions; it regulates phototransduction in the eyes,

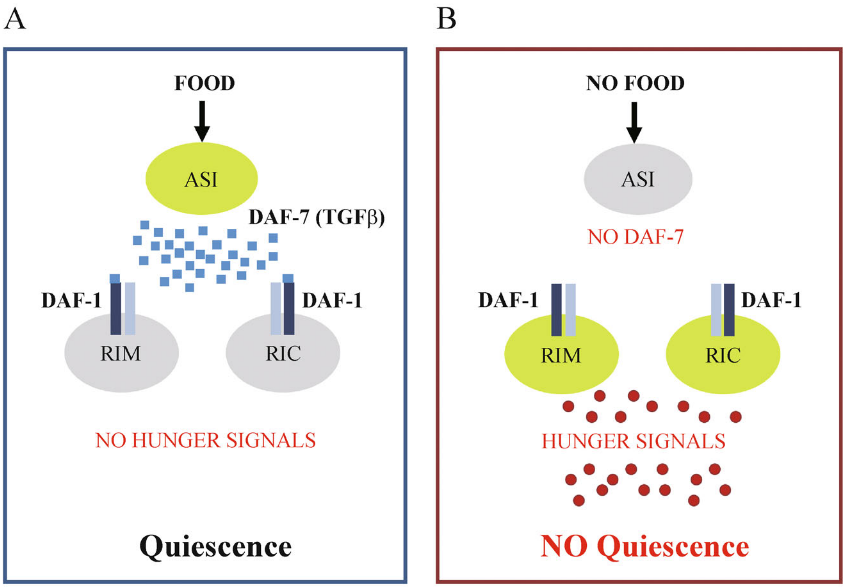

Figure 2 Neuronal circuitry to regulate appetite in *C. elegans*. (A) Upon activation by nutritional well-being, ASI releases DAF-7 TGFβ. Binding of TGFβ to its receptor DAF-1 in RIM and RIC neurons inhibits RIM and RIC's role in releasing hunger signals. In the absence of hunger signals worms become satiated and quiescent. (B) When food is not available, DAF-7 is not released therefore RIM and RIC are activated to release hunger signals.

hypertension, reproduction, attention and hyperactive behavior, vasodilation, circadian rhythms, intestinal homeostasis and cancer progression (Januszewicz, 1995, Oster et al., 2003, Yau and Hardie, 2009, Francis et al., 2010, Zhang et al., 2010, Gong et al., 2011, Arshad and Visweswariah, 2012, Kim et al., 2013). In addition, it regulates body size, exploratory behavior, stress-induced development, sleep and feeding in invertebrates (Fujiwara et al., 2002, Raizen et al., 2008, You et al., 2008). Its role in appetite control and obesity, however, was only recently discovered by us in worms and Valentino et al. in mammals. In mammals, a gut peptide, uroguanylin, is released upon feeding and binds to GUCY2C, its receptor in the hypothalamus, to suppress feeding (Valentino et al., 2011). GUCY2C is a membrane guanylyl cyclase that produces cGMP upon its activation. Interestingly, there are several previous studies that suggest cGMP functions in obesity. For instance, sildenafil, a medicine that inhibits degradation of cGMP to treat erectile dysfunction, has protective effects in weight gain on a high-fat diet (Ayala et al., 2007, Mitschke et al., 2013). Natriuretic peptides (NP) that bind to NP receptors (also guanylyl cyclases(GCYs)) to produce cGMP are not only important to control blood pressure and heart function (Takei, 2001) but also plays an important role in lipolysis in adipose tissue via phosphorylation of hormone sensitive lipase (HSL) by cGMP dependent protein kinase (PKG) (Sengenès et al., 2000). Furthermore, epidemiological studies show that a certain allele of the NP receptor type C gene is associated with a lean phenotype (Sarzani et al., 2004), suggesting a critical role of NP in fat metabolism.

In worms, the cGMP signal is used to perceive most sensations including temperature, smell and light (Komatsu et al., 1996, Ward et al., 2008). The cGMP signal is essential for worms to show satiety quiescence as well; lack of functional cGMP-dependent protein kinase (PKG) led to increased fat storage and defect in satiety quiescence (You et al., 2008). Together, these findings in mammals and worms highlight an essential role for cGMP signaling in appetite control and metabolism. Understanding molecular mechanisms by which cGMP regulates appetite will open up a potential use of well-established pharmacological inhibitors as an effective treatments for obesity.

Social influence in feeding

Walking into any restaurant, one can easily observe people eating in social groups. These people are not just consuming necessary calories but they are socializing, unaware of the influences they have on each other. Eating in a social setting with a group can result in social facilitation or social inhibition of meal size. There is a positive correlation between the number of people present in a group during the consumption of a meal and the portion size consumed by the group members; meal sizes increased as much as 44% (de Castro and de Castro, 1989, Pliner et al., 2006). In addition to increasing meal size, individuals were also found to experience 30% less satiation when their meal is eaten in a group when compared to meals eaten alone. Meals eaten with others also have a higher number of calories and proportionately contain more fat when compared to meals eaten alone (de Castro and de Castro, 1989). Longer meal duration (36 min compared to 12 min) in a group results in a larger meal size as well (Pliner et al., 2006). This increase in meal size and the fat content has been found to increase more when the meal was consumed with friends (Hetherington et al., 2006). It has also been found that an individual eating in the presence of another who consistently eats a large meal or a small meal will model their feeding behavior to match (Herman et al., 2003). Individuals who believe their meal companions are judging or evaluating them based on their meal size will adjust their consumption accordingly, in an attempt to control the impression of their meal companions (Herman et al., 2003).

Interestingly all wild strains of *C. elegans* are social feeders; they eat as a group (de Bono and Bargmann, 1998, de Bono et al., 2002, Félix and Braendle, 2010). Although it is unknown whether social feeding contributes to changes in fat storage or satiety behavior in worms, the gene that regulates social feeding, NPR-1, is a homolog of human NPY receptor which has a clear implication in appetite control (de Bono et al., 2002). This could suggest an interesting possibility that social feeding is an evolutionarily old behavior and that the integration of social cues in feeding behavior might have contributed to certain advantages during evolution.

Feeding is regulated not only by energy need but also by many other extrinsic cues such as stress and anxiety that also can come as a result of social influence (Booth, 1989, Woods, 2005, Fehm et al., 2006, Berthoud, 2007). These signals from multiple brain regions such as the amygdala and forebrain often override the signals of metabolic need that are integrated in the lateral hypothalamus (Weingarten, 1983, Stroebele and de Castro, 2004, Popkin et al., 2005, Petrovich and Gallagher, 2007). Therefore, misregulation of feeding which directly contributes to obesity can be caused by genetic predisposition as well as social influence.

Conclusions

We live in an environment foreign to our bodies; less than a century ago, food was scarce and physical labor was intense. In our new environment where calorie rich food is abundant and physical labor is required less (if not at all), our metabolism and desire to eat have not evolved to adjust to this new environment. It is necessary to understand that the current pandemic of obesity is a result of evolutionary conserved mechanisms to make us efficient in energy intake, storage and use. This understanding will be a basis to exploit simple genetic organisms such as *C. elegans* to discover novel yet conserved genetic mechanisms of appetite controls.

Food intake is controlled not only by metabolic need but also genetic predisposition and social influence. Despite intense studies, genetic causes of obesity and the mechanisms by which the known monogenic factors of obesity work are still largely unknown. Especially how the neuronal misregulation either by genetic defects or by social influence overrides metabolic need is still largely unknown. Again, considering the robust conservation in feeding behavior and metabolism in most animals, using a simple model system to dissect the feeding circuit will help to advance the understanding of how this complicated feeding behavior is regulated.

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Compliance with ethics guidelines

Kristen Davis and Young-Jai You declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Alkema M J, Hunter-Ensor M, Ringstad N, Horvitz H R (2005). Tyramine Functions independently of octopamine in the *Caenorhabditis elegans* nervous system. Neuron, 46(2): 247–260

Arshad N, Visweswariah S S (2012). The multiple and enigmatic roles of guanylyl cyclase C in intestinal homeostasis. FEBS Lett, 586(18): 2835–2840

Ashrafi K, Chang F Y, Watts J L, Fraser A G, Kamath R S, Ahringer J, Ruvkun G (2003). Genome-wide RNAi analysis of *Caenorhabditis elegans* fat regulatory genes. Nature, 421(6920): 268–272

Ayala J E, Bracy D P, Julien B M, Rottman J N, Fueger P T, Wasserman D H (2007). Chronic treatment with sildenafil improves energy balance and insulin action in high fat-fed conscious mice. Diabetes, 56(4): 1025–1033

Berthoud H R (2007). Interactions between the “cognitive” and “metabolic” brain in the control of food intake. Physiol Behav, 91 (5): 486–498

Bishop N A, Guarente L (2007). Two neurons mediate diet-restriction-induced longevity in *C. elegans*. Nature, 447(7144): 545–549

Booth D A (1989). Mood- and nutrient-conditioned appetites. Cultural and physiological bases for eating disorders. Ann N Y Acad Sci, 575 (1 The Psychobio): 122–135, discussion 157–162

Crocker A, Shahidullah M, Levitan I B, Sehgal A (2010). Identification of a neural circuit that underlies the effects of octopamine on sleep: wake behavior. Neuron, 65(5): 670–681

de Bono M, Bargmann C I (1998). Natural variation in a neuropeptide Y receptor homolog modifies social behavior and food response in *C. elegans*. Cell, 94(5): 679–689

de Bono M, Tobin D M, Davis M W, Avery L, Bargmann C I (2002). Social feeding in *Caenorhabditis elegans* is induced by neurons that detect aversive stimuli. Nature, 419(6910): 899–903

de Castro J M, de Castro E S (1989). Spontaneous meal patterns of humans: influence of the presence of other people. Am J Clin Nutr, 50 (2): 237–247

Farooqi I S, Yeo G S, Keogh J M, Aminian S, Jebb S A, Butler G, Cheetham T, O’Rahilly S (2000). Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. J Clin Invest, 106(2): 271–279

Fehm H L, Kern W, Peters A (2006). The selfish brain: competition for energy resources. Prog Brain Res, 153: 129–140

Félix M A, Braendle C (2010). The natural history of *Caenorhabditis elegans*. Curr Biol, 20(22): R965–R969

Feng X H, Derynck R (2005). Specificity and versatility in tgf-beta signaling through Smads. Annu Rev Cell Dev Biol, 21(1): 659–693

Francis S H, Busch J L, Corbin J D, Sibley D (2010). cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. Pharmacol Rev, 62(3): 525–563

Fujiwara M, Sengupta P, McIntire S L (2002). Regulation of body size and behavioral state of *C. elegans* by sensory perception and the EGL-4 cGMP-dependent protein kinase. Neuron, 36(6): 1091–1102

Gallagher T, Bjorness T, Greene R, You Y J, Avery L (2013a). The geometry of locomotive behavioral states in *C. elegans*. PLoS ONE, 8(3): e59865

Gallagher T, Kim J, Oldenbroek M, Kerr R, You Y J (2013b). ASI regulates satiety quiescence in *C. elegans*. J Neurosci, 33(23): 9716–9724

Gong R, Ding C, Hu J, Lu Y, Liu F, Mann E, Xu F, Cohen M B, Luo M (2011). Role for the membrane receptor guanylyl cyclase-C in attention deficiency and hyperactive behavior. Science, 333(6049): 1642–1646

Greer E R, Pérez C L, Van Gilst M R, Lee B H, Ashrafi K (2008). Neural and molecular dissection of a *C. elegans* sensory circuit that regulates fat and feeding. Cell Metab, 8(2): 118–131

Han M, Sternberg P W (1990). let-60, a gene that specifies cell fates during *C. elegans* vulval induction, encodes a ras protein. Cell, 63(5): 921–931

Hengartner M O, Ellis R E, Horvitz H R (1992). *Caenorhabditis elegans* gene ced-9 protects cells from programmed cell death. Nature, 356 (6369): 494–499

Herman C P, Roth D A, Polivy J (2003). Effects of the presence of others on food intake: a normative interpretation. Psychol Bull, 129(6): 873–886

Hetherington M M, Anderson A S, Norton G N, Newson L (2006). Situational effects on meal intake: A comparison of eating alone and eating with others. Physiol Behav, 88(4–5): 498–505

Januszewicz A (1995). The natriuretic peptides in hypertension. Curr Opin Cardiol, 10(5): 495–500

Johnen H, Lin S, Kuffner T, Brown D A, Tsai V W, Bauskin A R, Wu L, Pankhurst G, Jiang L, Junankar S, Hunter M, Fairlie W D, Lee N J, Enriquez R F, Baldock P A, Corey E, Apple F S, Murakami M M, Lin E J, Wang C, During M J, Sainsbury A, Herzog H, Breit S N (2007). Tumor-induced anorexia and weight loss are mediated by the TGF-beta superfamily cytokine MIC-1. Nat Med, 13(11): 1333–1340

Kim G W, Lin J E, Waldman S A (2013). GUCY2C: at the intersection of obesity and cancer. Trends Endocrinol Metab, 24(4): 165–173

Komatsu H, Mori I, Rhee J S, Akaike N, Ohshima Y (1996). Mutations in a cyclic nucleotide-gated channel lead to abnormal thermosensation and chemosensation in *C. elegans*. Neuron, 17(4): 707–718

Mitschke M M, Hoffmann L S, Gnad T, Scholz D, Kruithoff K, Mayer P, Haas B, Sassmann A, Pfeifer A, Kilic A (2013). Increased cGMP promotes healthy expansion and browning of white adipose tissue. FASEB J, 27(4): 1621–1630

Montague C T, Farooqi I S, Whitehead J P, Soos M A, Rau H, Wareham N J, Sewter C P, Digby J E, Mohammed S N, Hurst J A, Cheetham C H, Earley A R, Barnett A H, Prins J B, O'Rahilly S (1997). Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature, 387(6636): 903–908

Mutch D M, Clément K (2006). Unraveling the genetics of human obesity. PLoS Genet, 2(12): e188

Oster H, Werner C, Magnone M C, Mayser H, Feil R, Seeliger M W, Hofmann F, Albrecht U (2003). cGMP-dependent protein kinase II modulates *mPer1* and *mPer2* gene induction and influences phase shifts of the circadian clock. Curr Biol, 13(9): 725–733

Petrovich G D, Gallagher M (2007). Control of food consumption by learned cues: a forebrain-hypothalamic network. Physiol Behav, 91 (4): 397–403

Pliner P, Bell R, Hirsch E S, Kinchla M (2006). Meal duration mediates the effect of "social facilitation" on eating in humans. Appetite, 46 (2): 189–198

Popkin B M, Duffey K, Gordon-Larsen P (2005). Environmental influences on food choice, physical activity and energy balance. Physiol Behav, 86(5): 603–613

Raizen D M, Zimmerman J E, Maycock M H, Ta U D, You Y J, Sundaram M V, Pack A I (2008). Lethargus is a *Caenorhabditis elegans* sleep-like state. Nature, 451(7178): 569–572

Sarzani R, Strazzullo P, Salvi F, Iacone R, Pietrucci F, Siani A, Barba G, Gerardi M C, Dessì-Fulgheri P, Rappelli A (2004). Natriuretic peptide clearance receptor alleles and susceptibility to abdominal adiposity. Obes Res, 12(2): 351–356

Sengenès C, Berlan M, De Glisezinski I, Lafontan M, Galitzky J (2000). Natriuretic peptides: a new lipolytic pathway in human adipocytes. FASEB J, 14(10): 1345–1351

Shibakusa T, Iwaki Y, Mizunoya W, Matsumura S, Nishizawa Y, Inoue K, Fushiki T (2006). The physiological and behavioral effects of subchronic intracisternal administration of TGF-β in rats: comparison with the effects of CRF. Biomed Res, 27(6): 297–305

Sikder D, Kodadek T (2007). The neurohormone orexin stimulates hypoxia-inducible factor-1 activity. Genes Dev, 21(22): 2995–3005

Stroebele N, De Castro J M (2004). Effect of ambience on food intake and food choice. Nutrition, 20(9): 821–838

Suo S, Kimura Y, Van Tol H H (2006). Starvation induces cAMP response element-binding protein-dependent gene expression through octopamine-Gq signaling in *Caenorhabditis elegans*. J Neurosci, 26(40): 10082–10090

Takei Y (2001). Does the natriuretic peptide system exist throughout the animal and plant kingdom? Comp Biochem Physiol B Biochem Mol Biol, 129(2-3): 559–573

Tsai V W, Macia L, Johnen H, Kuffner T, Manadhar R, Jørgensen S B, Lee-Ng K K, Zhang H P, Wu L, Marquis C P, Jiang L, Husaini Y, Lin S, Herzog H, Brown D A, Sainsbury A, Breit S N (2013). TGF-b superfamily cytokine MIC-1/GDF15 is a physiological appetite and body weight regulator. PLoS ONE, 8(2): e55174

Valentino M A, Lin J E, Snook A E, Li P, Kim G W, Marszalowicz G, Magee M S, Hyslop T, Schulz S, Waldman S A (2011). A uroguanylin-GUCY2C endocrine axis regulates feeding in mice. J Clin Invest, 121(9): 3578–3588

Ward A, Liu J, Feng Z, Xu X Z (2008). Light-sensitive neurons and channels mediate phototaxis in *C. elegans*. Nat Neurosci, 11(8): 916–922

Weingarten H P (1983). Conditioned cues elicit feeding in sated rats: a role for learning in meal initiation. Science, 220(4595): 431–433

Woods S C (2005). Signals that influence food intake and body weight. Physiol Behav, 86(5): 709–716

Yau K W, Hardie R C (2009). Phototransduction motifs and variations. Cell, 139(2): 246–264

You Y J, Kim J, Raizen D M, Avery L (2008). Insulin, cGMP, and TGF-β signals regulate food intake and quiescence in *C. elegans*: a model for satiety. Cell Metab, 7(3): 249–257

Zhang M, Su Y Q, Sugiura K, Xia G, Eppig J J (2010). Granulosa cell ligand NPPC and its receptor NPR2 maintain meiotic arrest in mouse oocytes. Science, 330(6002): 366–369