Ghrelin signalling and obesity: At the interface of stress, mood and food reward

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Abstract

The neuronal circuitry underlying the complex relationship between stress, mood and food intake are slowly being unravelled and several studies suggest a key role herein for the peripherally derived hormone, ghrelin. Evidence is accumulating linking obesity as an environmental risk factor to psychiatric disorders such as stress, anxiety and depression. Ghrelin is the only known orexigenic hormone from the periphery to stimulate food intake. Plasma ghrelin levels are enhanced under conditions of physiological stress and ghrelin has recently been suggested to play an important role in stress-induced food reward behaviour. In addition, chronic stress or atypical depression has often demonstrated to correlate with an increase in ingestion of caloric dense ‘comfort foods’ and have been implicated as one of the major contributor to the increased prevalence of obesity. Recent evidence suggests ghrelin as a critical factor at the interface of homeostatic control of appetite and reward circuitries, modulating the hedonic aspects of food intake. Therefore, the reward-related feeding of ghrelin may reveal itself as an important factor in the development of addiction to certain foods, similar to its involvement in the dependence to drugs of abuse, including alcohol. This review will highlight the accumulating evidence demonstrating the close interaction between food, mood and the development of obesity. We consider the ghrelinergic system as an effective target for the development of successful anti-obesity pharmacotherapies, which not only affects appetite but also selectively modulates the rewarding properties of food and impact on psychological well-being in conditions of stress, anxiety and depression.

1. Introduction

Socrates famously said: “The rest of the world lives to eat, while I eat to live”. While this quote most likely refers to the fact that food fundamentally serves a nutritive purpose, within the current modern day society, in particular the Western world, food appears to be increasingly associated with aspects that exceed beyond nutrition, including behavioural reward and psychiatric disposition (i.e. mood).
Likewise, it is becoming clear that associations exist between metabolic syndrome associated co-morbidities, in particular obesity, and affective psychiatric disorders, including anxiety and depression (McElroy et al., 2004; Goldbacher & Matthews, 2007; Kaober et al., 2002; Gariety et al., 2010; Marijissen et al., 2011). Interestingly, obesity is associated with a 25% increased occurrence of anxiety and mood disorders (Simon et al., 2006). Reward signalling within the brain is mediated by the dopaminergic mesolimbic system and altered neurocircuits within this system have been postulated to play a major role in both the development of obesity as well as depression and anxiety (Wang et al., 2001; Nash & Nutt, 2004; Nestler & Carlezon, 2006; Sullivan & Dufresne, 2006; de la Mora et al., 2010; Volkow et al., 2010). Moreover, hedonic eating behaviour and addiction display overlapping reward neurocircuits and certain foods, in particular sugar, have been postulated to exhibit addictive properties (Avena et al., 2008; Kenny, 2011b). The pioneering work of Professor Bart Hoebel et al. on the neurocircuity regulating brain reward and eating behaviour has lead to fundamental discoveries in the field of eating disorders and obesity, food addiction, alcohol consumption as well as depression (Hoebel, 1985; Konturek et al., 2004; Leibowitz, 2011; Parylak et al., 2011; Xu et al., 2011). A corticostrital-lo-thalamic circuitry has been described to mediate the motivation to obtain food rewards and to promote the overconsumption of palatable foods beyond acute homeostatic needs (Kelley et al., 2005). This results in hyperphagia which combined with decreased energy expenditure, following physical inactivity, leads to an excess accumulation of body fat or adiposity and often results in an obese phenotype (Marti et al., 2004; Rokholm et al., 2011). However, it is clear that whilst genetic predisposition can increase the likelihood for the development of obesity, genetic factors cannot account for all variation in BMI. Environmental factors such as altered lifestyle, the abundant availability as well as the low cost of highly caloric foods and the exposure to chronic psychological stressors in today’s society, have equally contributed to the development of obesity (Marti et al., 2004; Swinburn et al., 2011). Both food intake and diet are closely intertwined with mood regulation and stress perception and response (Oliver & Wardle, 1999; Gibson, 2006; Morrison, 2009; Dallman, 2010). The overconsumption of calorie-dense foods extends far beyond the individual’s nutritional needs and is mediated by a natural sensitivity to food stimuli and the associated pleasurable feelings associated with eating. This hedonic signalling in response to palatable food is increasingly being recognised as an important underlying cause for the increase in obesity worldwide (Berthoud, 2006). Thus, the link between obesity, appetite and food intake, which is already extensively described, is now extended towards the reward and motivation pathways as well as to the signalling pathways involved in stress and affective disorders such as anxiety and depression.

The ghrelinergic system mediates a plethora of biological activities, including the homeostatic regulation of appetite and food intake (for review see Tschop et al., 2000; Nakazato et al., 2001; Cummings & Shannan, 2003; Korfobits et al., 2004; Kojima & Kangawa, 2005; Sun et al., 2007; Schellekens et al., 2009; Andrews, 2011). In addition, it is now becoming clear that the orexigenic peptide, ghrelin and its receptor, the growth hormone secretagogue receptor (GHS-R1a), not only play a pivotal role in the homeostatic regulation of energy metabolism but also have an impact on the non-homeostatic regulation of food intake behaviours, such as the hedonic rewarding and motivational pathways (for review see Dickson et al., 2011; Egecioglu et al., 2011; Skibicka & Dickson, 2011)). Furthermore, accumulating data suggest involvement of the ghrelin system in stress-induced food intake (Chuang et al., 2011; Diz-Chaves, 2011). This review will describe the recent advances in the understanding of ghrelin’s role in the non-homeostatic rewarding aspect of feeding and the potential obligatory role for ghrelin in stress-induced eating behaviour. In addition, circulating ghrelin levels have been shown to be elevated following stress, which correlates with its anxiolytic as well as antidepressant-like effects. Finally, a role for ghrelin in the concept of food addiction has been postulated to partly contribute to the obesity epidemic and will be discussed.

2. Ghrelin in food intake and obesity

Ghrelin is currently the only described orexigenic hormone from the periphery, which acts centrally to modulate the body’s energy homeostasis and has therefore received attention from the pharmaceutical industry as an interesting target in obesity and other eating disorders (Horvath et al., 2003; Soares et al., 2008; Depoortere, 2009; Schellekens et al., 2009; Ogiso et al., 2011; Patterson et al., 2011; Yi et al., 2011; Costantino, 2012). The hormone ghrelin is a 28 amino acid peptide (Fig. 1), primarily synthesised by gastric neuroendocrine cells (Kojima et al., 1999). The mature ghrelin peptide is activated by the enzyme, ghrelin O-acetyltransferase (GOAT) via n-octanoylation on the serine 3 residue producing acyl-ghrelin (Gualillo et al., 2008; Gutierrez et al., 2008; Yang et al., 2008a, 2008b) and functions as the endogenous ligand for the GHS-R1a receptor (Kojima et al., 1999).

Both ghrelin and its receptor are ubiquitously expressed in the periphery as well as in the central nervous system (CNS) and this abundant expression implicates its involvement in a plethora of biological functions (Guan et al., 1997; Cowley et al., 2003; Zigman et al., 2006). It must be noted that while the existence of ghrelinergic neurons remains highly controversial (Furness et al., 2011), some evidence suggests ghrelin synthesis in the brain, albeit at a much lower levels, in specific neuronal cells of the hypothalamus (Wren et al., 2000; Kojima et al., 2001; Lu et al., 2002; Cowley et al., 2003; Toshinai et al., 2003; Sato et al., 2005; Menyher et al., 2006; Niss et al., 2011). In particular a recent study shows dexamethasone-induced increases in ghrelin mRNA in a hypothalamic cell line (Kageyama et al., 2012). The primary functions of ghrelin are the secretion of growth hormone from the anterior pituitary cells (Howard et al., 1996; Kojima et al., 1999; Kamgea et al., 2004) and the central regulation of energy homeostasis through the modulation of appetite and food intake (for review see Cummings et al., 2001; Nakazato et al., 2001; Kojima & Kangawa, 2002; Castaneda et al., 2010; Andrews, 2011). The appetite-inducing effects of ghrelin are mainly linked to peripherally produced ghrelin, which exerts its effects centrally. Peripheral ghrelin signals to the brain via the blood circulation, passing the blood–brain barrier and via vagal afferents to the nucleus of the solitary tract (NTS) in the brain stem (Williams et al., 2003; le Roux et al., 2005; Banks et al., 2008). However, the requirement of vagal afferent signalling for ghrelin’s central effects has been questioned following a study by Arnold et al. (Arnold et al., 2006). Projections from the NTS convey the ghrelin signal to the arcuate nucleus (ARC) of the hypothalamus (Date et al., 2002; Zhang et al., 2004). The GHS-R1a receptor expression is highest in the ARC reinforcing its functionality in orexendocrine and appetite-stimulating activities (Fig. 2). Activation of centrally expressed GHS-R1a in the ARC leads to neuronal excitation (Dickson & Luckman, 1997) and ghrelin mediated expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP) in arcuate NPY/AgRP neurons (Asakawa et al., 2001b; Chan et al., 2004; Andrews et al., 2008). In addition to enhanced NPY and AgRP mRNA expression, ghrelin exposure was shown to induce the neuronal activity markers c-Fos and Egr-1 (Dickson et al., 1993; Dewson & Dickson, 2000; Kobelt et al., 2008). Moreover, ghrelin mediates GABA release from the NPY/AgRP neurons leading to an indirect inhibition of neurons expressing pro-opiomelanocortin and the cocaine- and amphetamine-regulated transcript (POMC/CART), which do not express the GHS-R1a receptor (Cowley et al., 2003). Subsequent increases in appetite and food intake are suggested to be mediated via centrally expressed melanocortin receptors (MC3 and MC4) expressed on hypothalamic neurons in the paraventricular nucleus (PVN) and on the lateral hypothalamic area (LHA) (Adan et al., 2006; Marston et al., 2011; Pandit et al., 2011; Xu et al., 2011). AgRP expression is mediated
by ghrelin, which further contributes to the inhibition of satiety through antagonism of the POMC-derived α-melanocyte-stimulating hormone (α-MSH) and inverse agonism of the constitutively active MC3 and MC4 receptors (Tolle & Low, 2008).

The important role of the ghrelinergic system in the regulation of appetite and satiety is well established and the orexigenic effects of peripheral or central ghrelin administration are widely documented in rodents (Tschop et al., 2000; Wren et al., 2000, 2001b; Asakawa et al., 2003; Finger et al., 2011a, 2011e; Rolland et al., 2011) as well as in (lean and obese) humans (Wren et al., 2001a; Druce et al., 2005). Plasma ghrelin levels rise prior to food ingestion and under conditions of caloric restriction and decrease postprandially, and considerable evidence supports a role for ghrelin in the sensation of hunger and meal initiation, increasing food intake and body weight (Cummings et al., 2001; Tschop et al., 2001a, 2001b). In line with this is the increased hypothalamic GHS-R expression following fasting or chronic food restriction (Kurose et al., 2005). Furthermore, ghrelin administration promotes food-seeking behaviour in both humans and rodents (Tong et al., 2011; Perello & Zigman, 2012). Aberrant circulating plasma ghrelin levels have been shown within the metabolic disorder of obesity and other eating disorders reinforcing the importance of ghrelin in the regulation of metabolic homeostasis (Tschop et al., 2001b; Cummings et al., 2002; DelParigi et al., 2002; Yildiz et al., 2004; Troisi et al., 2005). The Prader–Willi syndrome, in...
particular, is associated with high plasma ghrelin levels, which makes this disorder a logical target for ghrelin-blocking agents to promote weight reduction (Tschope et al., 2001b; DelParigi et al., 2002). Several studies using rodent models of obesity have demonstrated the role of ghrelin in the hypothalamic regulation of appetite (Cowley et al., 2003; Olzewska et al., 2003; Shrestha et al., 2009). The orexigenic effects of centrally administered ghrelin were shown to be GH-independent as food intake was still markedly increased in GH-deficient spontaneous dwarf rats (Nakazato et al., 2001). In addition, chemical ablation of the ARC and antisense GHS-R1a mRNA following central administration of ghrelin blocked food intake (Shuto et al., 2002; Tamura et al., 2002). The attenuation of ghrelin's orexigenic effects following pre-treatment with a non-peptide NPY Y1 receptor antagonist or specific antisense against NPY/AgRP confirm downstream signalling via NPY/AgRP neurons. Interestingly, GHS-R1a null mice are resistant to a high-fat diet-induced obesity (Zigman et al., 2005) and ghrelin knockout mice increased their fat utilization when fed a high-fat diet (Wortley et al., 2004; Wortley et al., 2005) (but see [Sun et al., 2008]). In agreement with these findings are the lower body weight in mice with double knockout of the ghrelin peptide and the ghrelin receptor fed a standard chow (Pfluger et al., 2008). In this study, weight loss was independent of food intake since energy expenditure and motor activity were upregulated. Taken together these data highlight the important biological relevance of the ghrelin signalling pathway in the homeostatic regulation of appetite and food intake and reinforce that the ghrelin-induced orexigenic effects are mediated via NPY/AgRP neurons in the ARC. However, the GHS-R1a receptor is expressed in hypothalamic nuclei other than the ARC, including the suprachiasmatic, anterior hypothalamic, paraventricular, anteroventral preoptic and tuberomamillary nuclei (Guan et al., 1997; Zigman et al., 2006). The GHS-R1a receptor is also expressed in extra-hypothalamic brain regions, such as the substantia nigra, the dorsal and median raphe nuclei, the ventral tegmental area (VTA) and the hippocampus. These discoveries sparked interest into the role of ghrelin in other aspects of food intake behaviour, such as the hedonic pathways leading to food intake and stress-induced food intake.

3. The link between obesity, stress, anxiety and depression

The brain-gut axis mediates the communication between the gut and the CNS, which regulates appetite and satiety and maintains the body's energy homeostasis (Stanley et al., 2005; Ahima & Antwi, 2008; Simpson et al., 2008; Blevins & Baskin, 2010; Suzuki et al., 2010). Its dysregulation is linked to metabolic imbalances leading to obesity as well as to psychological conditions such as stress, anxiety and depression (McElroy et al., 2004; Simon et al., 2006; Goldbacher & Matthews, 2007; Kloiber et al., 2007; Pallister & Waller, 2008; Gariepy et al., 2010; Marijnissen et al., 2011). Overlapping neuronal circuitries also reinforce the link between stress and feeding behaviour (Maniam & Morris, 2012). Circuitries that regulate food intake and circuitries that modulate stress, the hypothalamic-pituitary-adrenal (HPA) axis, both converge on the PVN, which contains neurons producing corticotropin-releasing hormone (CRH). Stress affects feeding behaviour in humans in both directions, with some individuals increasing their food intake while others eat less (Oliver & Wardle, 1999; Gibson, 2006; Dallman, 2010). Likewise, the diagnostic and statistical manual of mental disorders (DSM-IV) criteria include exaggerated eating patterns in both directions also (American Psychiatric Association, 1994). The question whether obesity needs to be added to the DSM-V is currently being scrutinised (Devlin, 2007; Volkow & O'Brien, 2007; Moreno & Tandon, 2011). Despite the bi-directional divergence in eating behaviour, an overall increased consumption of caloric dense and highly palatable foods following stress compared to non-stressed controls is reported, independent of stress-induced hyperphagia or hypophagia (Gibson, 2006; Dallman, 2010). Interestingly, both hyperphagia and subsequent increases in body weight and obesity are associated with major depressive disorders in humans (Novick et al., 2005; Simon et al., 2006; Kloiber et al., 2007). For example, major depression in adolescence is linked with an increased risk of obesity in adulthood (Richardson et al., 2003). Moreover, depression may lead to or exacerbate the endocrine and metabolic conditions and vice versa, indicating a reciprocal link (McElroy et al., 2004; Simon et al., 2006; de Wit et al., 2010; Luppino et al., 2010; Marijnissen et al., 2011). It is worth emphasizing the differences between melancholic and atypical depression, the former which is associated with hypercortisolism, anorexia and weight loss, while the latter is associated with high anxiety, carbohydrate craving and frequently weight gain (Jurjena & Cleare, 2007), highlighting the existence of metabolic changes in both types of depression. Furthermore, a positive correlation exists between obesity and other eating disorders and stress and anxiety (Swinbourne & Touyz, 2007; Pallister & Waller, 2008; Gariepy et al., 2010). Especially, binge eating in the form of bulimia nervosa is often associated with stress, as the bouts of eating are usually stress induced (Mathes et al., 2009). The work of Dallman et al. has been pioneering in identifying the neuroendocrine interactions between stress and diet (Dallman et al., 2003; Dallman, 2010). Following on from such work, our lab has recently shown that the selective behavioural and metabolic effects of a high-fat diet are attenuated in mice following a chronic psychosocial stress (Finger et al., 2012a, 2012b). Stress exposure caused an increase in caloric intake in mice on a low-fat diet. Interestingly, while a stress-induced increase in weight gain was observed, the chronic stress paradigm yielded an overall loss in fat mass and lower adiposity state (Finger et al., 2012a). On the other hand, stress-induced weight gain and caloric intake were inhibited in mice on a high-fat diet following the chronic stress paradigm and weight loss was observed. Markers of insulin resistance and plasma insulin levels were blunted in mice consuming a diet high in fat following exposure to chronic social defeat stress. Decreased plasma leptin levels were observed in both groups but were most apparent in mice on the high-fat diet. Interestingly, anxiety- and depressive-like behaviours were absent following the chronic social stress in mice on the diet high in fat, while stress-induced social avoidance and anhedonic behaviour were both present independent of diet. These studies demonstrate that prolonged exposure to high-fat diet selectively protects against some of the behavioural consequences of chronic unpredictable social stressors. Furthermore, the stress-induced intake of palatable foods may ultimately lead to a habitual overconsumption, following an increased emotional activity and a decreased executive function and planning (Dallman, 2010), which can further foster the unhealthy eating behaviour. In human populations obesity is associated with cognitive decline and heightened vulnerability to brain injury and accelerated age-related diseases of the CNS (Bruce-Keller et al., 2009) and animal models confirm a profile of enhanced vulnerability and decreased cognitive function. Thus, obesity-related metabolic dysfunctions may be linked with an impaired brain function, which further highlights the importance of studying the communication between the brain and the gut, the brain–gut axis, in obesity and psychological conditions. These also are important from a public health point of view as although people are made aware of the negative impact of obesogenic food they continue to make impulsive and risky choices that are detrimental to their health and ultimately survival.

4. Ghrelin in stress, anxiety and depression

Most neuropeptides regulating the homeostatic energy balance also play a key role in anxiety-like behaviour, further highlighting the importance of investigating the potential overlap in anxiety-related mechanisms and obesity. The neurobiological mechanisms between food intake and anxiety, as well as the neuronal circuitry of fear which underlies anxiety, are probably evolutionary selected as defensive survival mechanism involving neuropeptides, which regulate our response to environmental threats (Bowers et al., 2012). For example, the link between anxiety and food intake is reinforced by NPY, which has both orexigenic and anxiolytic effects (Stanley & Leibowitz, 1965; Heilig et
In both rodents and humans (Asakawa et al., 2001a; Kristensson et al., 2006), ghrelin mRNA levels demonstrated to increase in conditions of stress (Chuang & Zigman, 2010). Recently, data has accumulated suggesting a key role for ghrelin in stress-induced food intake. Plasma ghrelin levels and pre-proghrelin mRNA levels demonstrated to increase in conditions of stress in both rodents and humans (Asakawa et al., 2001a; Kristensson et al., 2006; Rouach et al., 2007; Ochi et al., 2008; Chuang & Zigman, 2010). The enhanced ghrenlin plasma levels following stress may suggest ghrelin to play a potential role in defence against the consequences of stress, including stress-induced depression and anxiety and prevent their manifestation (Lutter et al., 2008). Acylated ghrelin levels were enhanced following chronic social defeat stress (CSDS), a model of prolonged psychosocial stress, in mice and social avoidance was increased in GHS-R1a null mice, suggesting ghrelin to regulate social isolation in response to CSDS (Lutter et al., 2008). Stress-induced metabolic changes, including decreased caloric intake and body weight, were also not observed in GHS-R1a null mice (Patterson et al., 2010). The increase in ghrelin may potentially explain the phenomenon of ‘comfort eating’ observed in conditions of stress. It has been suggested that the ghrelin system functions as an energy deficit signal evolved to act in times of energy insufficiency by favouring consumption of calorie-dense palatable foods and protect the storage of fat (Wells, 2009). Moreover, mice spent more time in the open arm of the elevated plus maze and showed less time immobile in forced swim test following caloric restriction or subcutaneous ghrelin injection, suggesting anxiolytic and antidepressant-like effects of elevated plasma ghrelin. Ghrelin was suggested to reduce anxiety after acute stress by stimulating the HPA axis at the level of the anterior pituitary (Spencer et al., 2012). In line with this is the activation of CRH-producing neurons and enhanced CRH gene expression in the PVN of the hypothalamus following ghrelin administration (Cabral et al., 2012). However, administration of ghrelin has previously also been suggested to increase anxiety and depressive-like behaviour (Asakawa et al., 2001a; Carlini et al., 2002, 2004; Kanehisa et al., 2006). These differences are not easily reconciled but have been attributed to different experimental conditions (for review see (Chuang & Zigman, 2010)) as well as the type and duration of stressor used (Stengel et al., 2011). Indeed, differential circulating levels of ghrelin, as well as GOAT levels, have been observed in response to different types of stress (Stengel et al., 2011). Ghrelin levels are elevated following metabolic stressors, including cold exposure, acute fasting and caloric restriction, as well as psychological stressors, including chronic social defeat or unpredictable stress. Interestingly, reduced plasma ghrelin levels were recorded following physical stressors, such as immunological/endotoxin injection, abdominal surgery and exercise. Although the pathways underlying the changes in ghrelin plasma concentration following differential stressors are still largely unknown, it has been suggested that they are mediated via a sympathoadrenal response following activation of the sympathetic nervous system and catecholamine release (Mundinger et al., 2006; Zhao et al., 2010). Furthermore, recent evidence has suggested a potential role for ghrelin in the mediation of stress-induced food reward (Chuang et al., 2011). Food reward behaviour was assessed using conditioned place preference (CPP), which measures the time rodents spend in an environment previously paired with a palatable food reward. Following stress exposure, using the chronic psychosocial stress model of CSDS, an increased food intake was observed and an increased CPP response. Moreover, the stress-induced food reward behaviour was ghrelin dependent, as CPP was not observed in GHS-R1a null mice. Furthermore, the stress-induced ghrelin mediated orexigenic and antidepressant-like effect as well as food reward behavioural effects were mediated by catecholaminergic neurons (Chuang et al., 2011). These results identify ghrelin in a key molecular substrate in the neurocircuitry, and in particular in catecholaminergic neurons, controlling stress-induced eating. Finally, chronic stress has also been associated with functional diseases of the gastrointestinal tract and ghrelin has been linked to stress-induced gastric motility (Ochi et al., 2008). Chronic stress enhanced gastric ghrelin secretion, which mediated an accelerated gastric emptying in rats and pre-treatment with a GHS-R1a antagonist attenuated the stress-induced acceleration of gastric emptying. In contrast, gastric emptying was delayed at the acute phase of the chronic stress paradigm, which involved the sympathetic pathway. The potential role of ghrelin in stress-induced gastric motility is reinforced by the enhanced GHS-R agonist mediated increase in gastric emptying in mice (Charoenthongtrakul et al., 2009).

Data relating to ghrelin’s role in stress, anxiety and depression in humans is somewhat lacking. However, stress exposure was also shown to increase circulating levels of plasma ghrelin in humans and to correlate with cortisol levels following the standardised Trier-Social-Stress test (Rouach et al., 2007). The perception of stress and anxiety was enhanced following the stress and the increase in ghrelin was associated with the acute response of serum cortisol to stress, but was independent of BMI and eating scores. Additional studies have found that ghrelin administration increases cortisol and adrenocorticotropic hormone secretion in humans (Takaya et al., 2000; Arvat et al., 2001) as well as in rats (Ochi et al., 2008). Interestingly, in Cushing’s disease, characterised by chronic hypercortisolism and major weight gain, ghrelin is able to induce an exaggerated adrenocorticotropic hormone response while the GH response to ghrelin is reduced (Monsonego et al., 2001; Moon et al., 2011). Likewise, another study has demonstrated an enhanced ghrelin response to stress, showing that baseline ghrelin levels in low emotional eaters exceed that of high emotional eaters. In addition, ghrelin levels subsequently decline in the non-emotional eaters, but not in emotional eaters following food intake, which may explain sustained eating (Raspopow et al., 2010). Furthermore, the involvement of ghrelin in the aetiology of depressive disorders has been reinforced by a study demonstrating lower plasma ghrelin levels in depressed patients (Barim et al., 2009). However, a correlation between ghrelin and depression was absent in other studies (Schanze et al., 2008; Kluge et al., 2009). Nevertheless, a polymorphism in the ghrelin gene has been correlated with depression symptomatology (Nakashima et al., 2008) and interestingly, antidepressant effects were reported following ghrelin administration in patients with major depression (Kluge et al., 2011).

5. Ghrelin in food reward behaviour

Appetite signalling functions to initiate food intake when nutrients are low. However, food also elicits pleasurable and rewarding signals, mediated via dopamine release in the mesolimbic circuitry system, which can override satiety and stimulate appetite independently of metabolic needs (Kenny, 2011b). The non-homeostatic motivational factors to obtain a food reward increase with food palatability and caloric content and the resulting over-consumption is being recognised as a key component in the underlying causes for the increase in obesity incidence worldwide. A heightened food reward sensitivity in obese individuals, following either a hyperactivation of the hedonic system (Stoeckel et al., 2008; Stice et al., 2010) or a dopaminergic hypofunction (Reinholz et al., 2008; Johnson & Kenny, 2010) has been held responsible for the excess food consumption and weight gain. The non-homeostatic feeding involves extra-hypothalamic neurocircuitry, including cortical areas as well as areas within the mesolimbic dopaminergic pathway, including the VTA, nucleus accumbens (NAc), hippocampus and amygdala (Skibicka & Dickson, 2011). The majority of the classical peptides regulating energy homeostasis, including ghrelin, also interact with these cortical and mesolimbic circuits to modulate the reward and motivational aspects of food intake. Recent data suggest a key role for ghrelin at the interface of homeostatic control and neurobiological circuits involved in hedonic signalling (for review see (Dickson et al., 2011; Egecioglu et al., 2011; Skibicka & Dickson, 2011; Perello &
VTA (Guan et al., 1997; Zigman et al., 2006) and support a role for ghrelin in the VTA mediated reward signalling. The mesolimbic dopaminergic projections from neuronal populations in the VTA terminate in the ventral striatum and the prefrontal cortex are important for anticipatory food reward and food-seeking behaviour (Richardson & Gratton, 1998; Bassareo & Di Chiara, 1999). Ghrelin’s ability to alter food reward and enhance ingestion of palatable foods is hypothesised to be based on ghrelin’s ability to elicit rewarding effects via neuronal dopamine secretion from projections originating in the VTA (Dickson et al., 2011). Several rodent studies support ghrelin’s role in reward induced eating. Firstly, direct ghrelin administration in the VTA induced overflow of dopamine within the NAcc as measured by microdialysis in freely moving mice (Jerlhag et al., 2007). Secondly, direct microinjection of ghrelin in VTA or NAcc was shown to strongly enhance feeding behaviour (Naleid et al., 2005; Abuzaid et al., 2006). Finally, centrally administered ghrelin enhanced preference for rewarding foods and increase fat ingestion over carbohydrate intake in rats (Shimbara et al., 2004) as well as an increased consumption of saccharin solutions in mice (Disse et al., 2010). In agreement with these findings is the ghrelin-mediated shift in food preference independent of caloric content described following increased saccharin consumption in mice after peripherally administered ghrelin, while this was not observed in GHS-R1a knockout mice. Furthermore, intake of palatable food (not chow) was decreased in a free choice paradigm (chow versus rewarding food) following central ghrelin administration in mice deficient for the GHS-R1a receptor or upon GHS-R1a antagonist treatment in rats (Egecioglu et al., 2010). Recent studies demonstrating a ghrelin-dependent food CPP response reinforce the obligatory role of ghrelin in the enhancement of the rewarding value of foods (Egecioglu et al., 2010; Perello et al., 2010; Disse et al., 2011). The high-fat diet CPP response was correlated to plasma ghrelin levels and enhanced following peripheral ghrelin administration or caloric restriction (Perello et al., 2010; Disse et al., 2011). In addition, the CPP response in satiated rats, in response to chocolate, was blocked following pre-treatment with GHS-R1a antagonists (Egecioglu et al., 2010). Interestingly, pharmacologic and genetic blockade of ghrelin signalling failed to show CPP in response to a fat diet but compensatory hyperphagia, associated with chronic caloric restriction was not inhibited. This suggests that food intake to maintain homeostatic energy balance and body weight regulation is distinct from the role of ghrelin in rewarding aspects of food (Perello et al., 2010). The response to CPP following intra-VTA ghrelin administration again demonstrated the involvement of the VTA on ghrelin-mediated choice and selection of rewarding (high-calorie) foods. Likewise, consumption of rewarding foods (but not standard chow) and CPP response were attenuated following chemical VTA lesion or GHS-R1a antagonist pre-treatment (Egecioglu et al., 2010). The impact of ghrelin on the motivational aspects of food-associated reward has been investigated using operant conditioning tasks (Perello et al., 2010; Finger et al., 2011b; Skibicka et al., 2011, 2012). Direct microinjection of ghrelin into the VTA increased free feeding of chow but also enhanced motivated behaviour for a sucrose reward, as assessed in an operant conditioning paradigm in rats, demonstrating enhanced ghrelin-mediated operant lever pressing or nose poking for palatable rewards (Skibicka et al., 2011). Both peripherally and centrally administered ghrelin elevated the incentive motivation for sucrose rewards in progressive ratio operant conditioning in satiated rats and blockade of ghrelin signalling reduced the operant responding for sugar in hungry rats to the level of a satiated rat (Skibicka et al., 2012). In contrast, no effect on NAcc mediated motivated eating behaviour was seen following stimulation or blockade of the GHS-R1a receptor but regular chow intake was left intact (Skibicka et al., 2011). These results identify the VTA but not the NAcc as a direct target site for ghrelin’s action on food-motivated behaviour. These findings support the notion that ghrelin increases appetite via the NAcc, while the VTA affects the ghrelin-mediated reward and incentive motivational aspects of food intake (Dickson et al., 2011; Skibicka & Dickson, 2011). However, our lab demonstrated a reduced operant responding in diet-induced obese mice in a progressive ratio schedule of responding, which suggests a resistance to ghrelin-induced motivation to obtain a food reward following prolonged exposure to a high-fat diet. These results are reinforced by previously reported blunted orexigenic effect of ghrelin administration in this mouse model of obesity (Briggs et al., 2010; Finger et al., 2011b) It must be noted however, that individuals with obesity remain ghrelin responsive (Druce et al., 2005). This highlights the temporal interplay of diet and diet-induced obesity and reward-related behaviours and this warrants further investigation.

6. Obesity and food addiction

Although the concept of food addiction is relatively recent, the term junk food has been around for decades. Recently, it has become clear that certain foods have strong addictive properties in certain individuals (Richardson et al., 2003; Parylak et al., 2011) and the behavioural impact of abused drugs and compulsive behaviours related to food intake are no longer studied independently. The concept of food addiction is increasingly being recognised to play a key role in the overconsumption of palatable foods and may significantly contribute to the current obesity pandemic (Taylor et al., 2010). The food addiction model is reinforced by overlapping neurocircuits between drug and food reward and similar addiction-like neuroadaptive responses occur in brain reward circuits which drive the development of compulsive eating associated with food addiction (Hoebel, 1985; Wise, 2006; Davis & Carter, 2009; Wang et al., 2009; Johnson & Kenny, 2010; Volkow et al., 2010; Kenny, 2011a, 2011b; Parylak et al., 2011; Volkow et al., 2012). While evidence is accumulating suggesting that food addiction can lead to development of obesity, food addiction may equally prevail in non-obese and the link between obesity and addiction has recently been critically reviewed (Ziauddeen et al., 2012). Despite this, the fact is established that drugs of abuse as well as highly palatable, calorie-dense foods are consumed by humans or self-administered by laboratory animals because they are inherently rewarding, an effect that is mediated through their dopamine-enhancing properties in the mesolimbic circuitry system (Hoebel, 1985; Wise, 2006; Volkow et al., 2010, 2012). Many characteristics of addictive behaviour are shared with repeated overconsumption of palatable (i.e. pleasurable) foods. These include continued use and low impulse control despite negative consequences. The repeated excessive food consumption is associated with neuroadaptive changes within the central reward circuits, including altered gene expression and brain responsivity to food, similar to those occurring upon drug dependence (Richardson et al., 2003; Avena et al., 2008; Gearhardt et al., 2009a; Parylak et al., 2011; Volkow et al., 2012). Interestingly, the development of obesity is coupled with the emergence of a progressively worsening deficit in neural reward responses (Johnson & Kenny, 2010). Binge-eating disorder is characterised by periodic intermittent bouts of overeating and can occur in some obesity types but is also present in non-obese individuals. Clinical aspects of binge eating overlap strongly with the clinical aspects of addiction and binge eating has therefore been associated with the development of food addiction (Davis & Carter, 2009; Corwin, 2011; Gearhardt et al., 2011a). Evidence of lower levels of striatal dopamine D2 receptors in obese humans, where D2 levels were negatively correlated with BMI, are similar to those found in drug addiction (Wang et al., 2001). This idea of striatal hypofunction suggests a reward-deficiency in overeating. The perceived value of hedonic value is lowered and compensatory overeating ensues. In agreement with this hypothesis is the reduced D2R correlated to prefrontal glucose metabolism and reduced inhibitory control in obese subjects (Volkow et al., 2008b). Evidence from
functional neuroimaging studies, using fMRI and PET, in humans demonstrated altered brain reward responsivity to food-related stimuli in obese individuals when compared to non-obese subjects, similar to those occurring in addiction (Wang et al., 2001). Moreover, palatable food dependence was shown to activate similar brain regions implicated with substance addiction (Gearhardt et al., 2009a, 2009b, 2011b). Compulsive-like feeding behaviour with resistance to an aversive conditioned stimulus was observed in obese rats with extended access to palatable high-fat food, similar to that observed in the transition from casual use to dependence following prolonged use of cocaine or other drugs of abuse (Johnson & Kenny, 2010). The deficit in the neuronal reward response was correlated to down-regulated striatal dopamine D2 receptor levels in obese but not in lean rats. Moreover, the development of addiction-like reward deficits and the onset of compulsive-like food seeking were exacerbated following lentivirus-mediated knockdown of striatal D2 receptors. These data further demonstrate that overconsumption of palatable food triggers addiction-like neuroadaptive responses in brain reward circuits and drives the development of compulsive eating. In agreement with this hypothesis is the enhanced motivation towards food associated with the enforced abstinence from sugar (Avena et al., 2005) and the withdrawal symptoms induced by challenge with the opioid antagonist naloxone and enforced abstinence (Colantuoni et al., 2002). To date very little is known on the role of ghrelin in the neurocircuity leading to food addiction. However, considering ghrelin’s strong orexigenic effect and its involvement in reward behaviour, a role for ghrelin in the development of food addictions seems logical. In agreement with this hypothesis are the studies demonstrating that ghrelin plays an important role in self-administration of sucrose and saccharin intake in rodents (Disse et al., 2010; Skibicka et al., 2012) as well as the operant self-administration of alcohol (Landgren et al., 2012). However, evidence for sugar addiction has so far only been demonstrated in animal models and is lacking in humans. Indeed, the validity of sugar addiction in a clinical relevant setting in humans has been criticised (Benton, 2010).

7. Conclusion and future perspectives

The prevalence of obesity within the human population in today’s society continues to grow. An altered lifestyle, changes in diet and a heightened stress exposure have been suggested to fundamentally contribute to the development of the obesity epidemic in modern day society (Cecchini et al., 2010; Swinburn et al., 2011).

Primarily due to the ghrelin-mediated central regulation of feeding behaviour, interference with the ghrelin system has been and is still considered an effective means to counteract obesity (Horvath et al., 2003; Schellekens et al., 2009; Nass et al., 2011; Yi et al., 2011). However, it must be noted that ghrelin targeted anti-obesity pharmacotherapies will not be without limitations, especially since it has become evident that obesity induces ghrelin resistance (Briggs et al., 2010; Andrews, 2011; Finger et al., 2011b). Ghrelin’s effect on energy homeostasis and eating behaviour seem to be dependent on metabolic status and an obese state was shown to attenuate ghrelin’s orexigenic effects (Finger et al., 2011b). Recently, the ghrelin resistance following obesity was pinpointed to a defective NPY/AgRP neuronal function in the ARC in diet-induced obese mice (Briggs et al., 2010). Moreover, a reduced expression of both peripheral ghrelin and GOAT as well as a decreased hypothalamic GHS-R1a were all reported (Briggs et al., 2010). Regardless, central ghrelin injection in the diet-induced obesity mouse model was still able to activate PVN neurons (Briggs et al., 2010; Andrews, 2011) and to stimulate food intake in obese subjects (Druce et al., 2005). Additionally, the ghrelin system in the PVN was shown to be responsible for an increased adiposity independent of food intake (Theander-Carrillo et al., 2006; Shrestha et al., 2009). This suggests that ghrelin-mediated signalling is differentially regulated depending on separate hypothalamic nuclei, with ghrelin-induced food intake mediated by NPY/AgRP neurons in the ARC and regulation of body weight mediated by GHS-R1a expressed in the PVN (Briggs et al., 2010). The ghrelinergic system has also been implicated in antipsychotic drug-induced obesity (Davey et al., 2012) highlighting its relevance as a treatment strategy to address this important side effect of antipsychotics. Together this data reinforces the central ghrelin system as a promising target in the development of anti-obesity drugs. Additionally, restoring ghrelin sensitivity may provide a therapeutic outcome to reduce weight.

Metabolic, endocrine, cognitive and psychological functions are extensively impacted in humans experiencing chronic stress (Holsboer, 2000; McEwen, 2000; de Kloet et al., 2005). Stress often represents a driving factor in the development of both obesity and co-morbid psychiatric disorders, including anxiety and depression. In addition, a growing body of evidence has shown that depression can contribute to the cause of obesity or be a significant consequence (Richardson et al., 2003; Novick et al., 2005; Kloor et al., 2007; Luppino et al., 2010; Marijnissen et al., 2011; Landgren et al., 2012). Accumulating evidence supports the premise of feed-forward and feedback loops between stress and diet that are partly regulated by the neuropeptide ghrelin (Fig. 3). Indeed, the gut-brain hormone ghrelin integrates both stressful and rewarding stimuli to mediate food intake. Stress enhances plasma ghrelin levels, stimulating pleasurable food intake, while dietary fats will lead to increased levels of activated acylated-ghrelin in the blood circulation, an effect that is mediated by enhanced activity of GOAT (Kürcher et al., 2009; Stengel et al., 2011). Thus, the prevalence of weight-related issues in individuals with chronic stress and depression may be explained by the stress-induced elevation of circulating ghrelin, which directly lead to hyperphagia and preference of caloric dense ‘comfort’ foods. Reinforcing this hypothesis are several recent studies identifying a key role for ghrelin in stress-induced food intake and food reward behaviour (Chuang & Zigman, 2010; Perello et al., 2010; Chuang et al., 2011; Dickson et al., 2011; Skibicka & Dickson, 2011). Ghrelin modulates the hedonic aspects of food and stimulates choice and selection of palatable rewarding foods via increased dopaminergic signalling originating in the VTA (Shimbara et al., 2004; Naleid et al., 2005; Abizaid et al., 2006; Jerlhag et al., 2007; Disse et al., 2010; Egecioğlu et al., 2010). Interestingly, chronic stress increases dopamine utilization in the nucleus accumbens in wild type mice but is absent in GHS-R1a null mice (Patterson et al., 2010). Moreover, the ghrelin-mediated enhancement of pleasurable feeding on caloric dense ‘comfort’ foods has been suggested to reduce the stress-response activity and may selectively protect against stress-induced psychopathologies, including anxiety and depression (Fig. 3). In agreement with this is the protective effect against the deleterious effects of chronic stress following prolonged exposure to high-fat diet, as observed in our laboratory (Finger et al., 2012a, 2012b). This blunting effect of high-fat diet on stress has been shown before (Pecoraro et al., 2004; Dallman, 2010) and is likely mediated via enhanced corticoid expression and a reduction in activity of the HPA axis (Dallman et al., 2006; Zimmermann et al., 2007).

It is worth noting that there are similarities between stress-induced eating and the effects of stress on relapse to drugs of abuse and it has also been demonstrated that converging brain networks govern both initial liking and the learned motivation regulating these behaviours (Volkow et al., 2008a; Berrie, 2009; Kenny, 2011b). Ghrelin likely triggers cravings for pleasurable, high caloric, so-called comfort foods when exposed to psychosocial stress (Chuang et al., 2011) and a role for ghrelin in the neurobiology of food addiction may become apparent. Continuous exposure to abused drugs and potentially also palatable foods leads to a transition away from the acute pleasurable reinforcing effects towards dependence and concurrent enhancement of negative reinforcement as the rewarding properties wear off in response to stress upon withdrawal. There is a growing awareness of the role of impulsivity in drug addiction (Mello et al., 2007). Thus it is tempting to speculate that low impulse control combined with a high motivation to eat, reinforces the excessive feeding behaviour and this may similarly
contribute to the development of obesity. A specific role for ghrelin in impulsive behaviour has not been shown to date and further investigations of its role in the transition from impulsivity to compulsivity are now warranted. The diminished initial rewarding effects of pleasurable food following prolonged exposure are correlated to a down regulation of the dopaminergic system in the brain reward circuitry. Thus, prolonged stress may lead to worsening of the reward deficit leading to anxiety and depression (Fig. 3). It is hypothesised that the reward deficit is compensated for by the repeated overfeeding and overconsumption, further fostering the increased vulnerability towards overconsumption and obesity (Burger & Stice, 2011). The involvement of the ghrelinergic system in dependence-related reward deficits also awaits further investigation.

In conclusion, dietary components and chronic stress strongly impact on the regulation of food intake, body weight and the development of psychopathologies. Recent studies have highlighted the importance of ghrelin in the chronic aspects of both diet and stress and emphasise the ghrelinergic system as a promising candidate within the brain-gut-axis as a point of future therapeutic intervention in anxiety and depression related disorders. Stress-induced elevations in ghrelin represent a likely contributing factor to the increased obesity incidence following chronic stress or atypical depression. Moreover, the importance of ghrelin as a therapeutic target in reward-based eating and in addictive behaviours, such as alcohol dependence and its potential role in the development of food addiction and dependence warrants further investigation. Overall, ghrelin can be considered a master-regulator of both metabolic health and mental well-being.

Fig. 3. Model of the effect of stress on ghrelin-mediated eating behaviours in anxiety, depression and obesity. Prolonged stress increases the risk to develop psychological disorders of anxiety and depression. Increases in psychological stress elevate plasma ghrelin levels, which activates the hedonic signalling pathway and stimulates intake of calorically dense ‘comfort’ foods. Increased activity of the enzyme COAT following fat digestion and lipid availability leads to enhanced acylated-ghrelin levels further stimulating hyperphagia. Ghrelin-induced enhanced consumption of palatable foods elicits central reward pathways and increase dopamine signalling, which may act to reduce the deleterious effects of stress and minimises depression-like behaviours. However, this stress-induced food reward behaviour and hyperphagia of palatable calorically dense foods increases body weight, which in itself has been linked to major depressive disorders. While obesity generally decreases plasma ghrelin levels, the dopaminergic reward signalling is down-regulated, at the same time, following prolonged exposure to palatable foods leading to a desensitisation of reward signalling similar as observed in addiction behaviour. Thus, prolonged exposure to stress and ‘comfort foods’ may lead to worsening of the reward deficit, further fostering anxiety and depression and co-morbid obesity.

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