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Review article

Driving the need to feed: Insight into the collaborative interaction between ghrelin and endocannabinoid systems in modulating brain reward systems

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ABSTRACT

Independent stimulation of either the ghrelin or endocannabinoid system promotes food intake and increases adiposity. Given the similar distribution of their receptors in feeding associated brain regions and organs involved in metabolism, it is not surprising that evidence of their interaction and its importance in modulating energy balance has emerged. This review documents the relationship between ghrelin and endocannabinoid systems within the periphery and hypothalamus (HYP) before presenting evidence suggesting that these two systems likewise work collaboratively within the ventral tegmental area (VTA) to modulate non-homeostatic feeding. Mechanisms, consistent with current evidence and local infrastructure within the VTA, will be proposed.

Contents

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1. Introduction

1.1. Brief overview of the ghrelin system

Ghrelin has attracted a great deal of attention since its discovery over 15 years ago, primarily due to its ability to stimulate food intake and promote adiposity (Nakazato et al., 2001; Tschop et al., 2000; Wren et al., 2001a,b). It is predominantly expressed and secreted by endocrine gastric cells of the stomach as a 28 amino-acid peptide; however, it is also secreted by other peripheral organs (*e.g.* adipose tissue, pancreas, liver) and albeit to a lesser degree, within the pituitary and hypothalamus (HYP) (Cowley et al., 2003; Date et al., 2000; Dornonville de la Cour et al., 2001; Gnanapavan et al., 2002; Gualillo et al., 2001; Kojima et al., 1999; Mondal et al., 2005; Volante et al., 2002). The capacity of ghrelin to modulate feeding and energy balance is reliant on binding to its seven transmembrane G protein couple receptor (GPCR): the type 1a growth hormone secretagogue receptor (GHSR) (Howard et al., 1996; Shrestha et al., 2009; Sun et al., 2004). In order for ghrelin to bind to its receptor it requires a post translational modification, most commonly an octanoylation, on serine-3 of its peptide (Bednarek et al., 2000; Gutierrez et al., 2008; Kojima et al., 1999; Yang et al., 2008). This reaction, which is mediated by ghrelin *O*-acyltransferase (GOAT), induces a conformational alteration in the peptide that permits efficient binding to the GHSR active site (Bednarek et al., 2000; Gutierrez et al., 2008; Yang et al., 2008). In a manner similar to ghrelin, GOAT oscillates in response to feeding status and diet and is considered the only enzyme with the ability to activate ghrelin (Drazen et al., 2006; Kirchner et al., 2009). As such, it is suggested that alterations in GOAT expression could be one of the molecular switches that conveys information about resource levels (Kirchner et al., 2009).

Surprisingly, it is estimated that only 10% of circulating ghrelin is acylated (Patterson et al., 2005). The predominant form of circulating ghrelin, des-acyl ghrelin, does not bind and activate the same GHSR as the acylated peptide at physiological concentrations (Hosoda et al., 2000; Kojima et al., 1999; but see Ref. Gauna et al., 2007). It is unknown whether des-acyl ghrelin, which has a 3 fold higher half-life, is a degradation product or a precursor of the active form (Ferrini et al., 2009; Tong et al., 2013). Des-acyl ghrelin does not stimulate release of growth hormone nor does it influence many of the other endocrine processes commonly initiated following GHSR activation by acylated ghrelin (Broglio et al., 2003a; Broglio et al., 2004; Van Der Lely et al., 2004). It is hypothesized that des-acyl ghrelin may bind to a yet uncharacterised receptor to elicit its biological effects (*e.g.* cardiovascular, metabolic, anti-proliferative) (Broglio et al., 2004; Ferrini et al., 2009; Hosoda et al., 2000; Muccioli et al., 2007; Van Der Lely et al., 2004). There is conflicting evidence with respect to how des-acyl ghrelin impacts food intake (Asakawa et al., 2005; Chen et al., 2005; Inhoff et al., 2008; Neary et al., 2006; Toshinai et al., 2006). While some report that des-acyl ghrelin decreases food intake when rodents are in their dark cycle or are food deprived (Asakawa et al., 2005; Chen et al., 2005) others find no effect of des-acyl ghrelin irrespective of feeding status or light cycle (Inhoff et al., 2008; Neary et al., 2006). Furthermore, Inhoff and colleagues have demonstrated that des-acyl ghrelin can inhibit the orexigenic effect of ghrelin while Toshinai et al. have shown increased feeding following des-acyl ghrelin administration (Inhoff et al., 2008; Toshinai et al., 2006). It is evident that more work is needed to clarify the mechanism by which des-acyl ghrelin influences feeding; however, currently the consensus is that it does so through GHSR independent processes (Asakawa et al., 2005; Chen et al., 2005; Delhanty et al., 2012; Toshinai et al., 2006; Van Der Lely et al., 2004).

GHSRs are widely distributed in many locations within the periphery (*e.g.* adipose tissue, adrenals, gonads, lungs, kidneys, pancreas, thyroid, and stomach) (Gnanapavan et al., 2002; Guan et al., 1997; Papotti et al., 2000; Shuto et al., 2001) and central nervous system (*e.g.* HYP, ventral tegmental area (VTA), hippocampus (HIP), cerebral cortex, substantia nigra, raphe nuclei, nodose ganglion, and dorsal vagal complex) (Ferrini et al., 2009; Mani et al., 2014; Zigman et al., 2006). Consistent with this, modulation of GHSR activation influences a plethora of different physiological processes including energy balance (i.e. feeding and energy expenditure) (Abizaid et al., 2006; Anderson et al., 2008; Lopez et al., 2008; Wren et al., 2001a,b), gastric acid secretion (Masuda et al., 2000), adiposity (Tschop et al., 2000), anxiety (Asakawa et al., 2001; Schellekens et al., 2012), learning and memory (Cahill et al., 2014; Diano et al., 2006; Moon et al., 2009), sleep (Tolle et al., 2002), reproduction (Farkas et al., 2013; Garcia et al., 2007; Tena-Sempere, 2008), glucose metabolism (Date et al., 2002), and insulin secretion (Broglio et al., 2003b). This review will exclusively focus on how the ghrelin system influences energy balance (see Fig. 1). For an overview of its involvement in the other aforementioned processes, please consult some excellent recent reviews (Muller et al., 2015; Stoyanova, 2014).

Given the ability of ghrelin to stimulate food intake, it is not surprising that GHSRs are expressed within important feeding related brain regions such as the HYP and VTA (Abizaid et al., 2006; Guan et al., 1997; Jiang et al., 2006; Mani et al., 2014; Zigman et al., 2006). Both GHSR transcript and protein are found within many hypothalamic nuclei (*e.g.* arcuate nucleus (ARC), ventral medial hypothalamus (VMH), and lateral mammillary nucleus) and throughout the anteroposterior axis of the VTA (Abizaid et al., 2006; Bennett et al., 1997; Cowley et al., 2003; Guan et al., 1997; Mani et al., 2014; Mondal et al., 2005; Shuto et al., 2001; Tannenbaum et al., 1998; Zigman et al., 2006). Within the ARC, GHSR mRNA co-localizes in cells that produce other important feeding peptides such as neuropeptide Y (NPY) and to a lesser degree pro-opiomelanocortin (POMC) (Willesen et al., 1999). Interestingly, ghrelin containing neurons within the HYP innervate the ARC as well as the VMH, lateral hypothalamus (LH), dorsomedial hypothalamus (DMH), suprachiasmatic nucleus (SCN) and the paraventricular nucleus (PVN) (Cowley et al., 2003; Horvath et al., 2012). In tandem with the expression profile of GHSRs, electrophysiology and ghrelin binding studies suggest that GHSRs are found

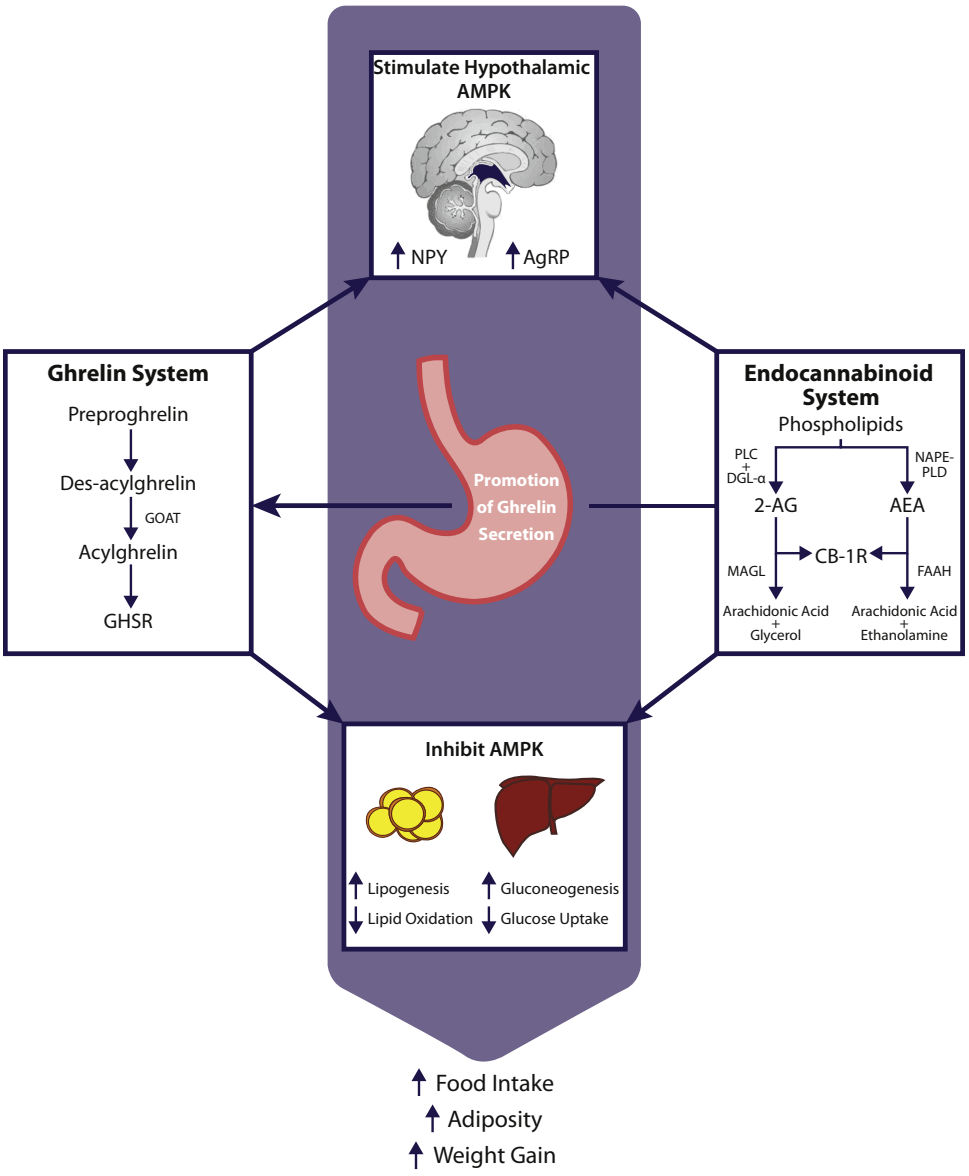

Fig. 1. Illustration highlighting important components of ghrelin and endocannabinoid systems and the regions in which these systems interact to modulate feeding and energy balance. Both systems activate hypothalamic but inhibit adipose and liver AMPK activity to promote weight gain, adiposity, and feeding. Additionally, agonism of the endocannabinoid system promotes the secretion of ghrelin. 2-AG, 2-arachidonoylglycerol; AEA, anandamide; AgRP, agouti-related peptide; AMPK, adenosine monophosphate activated protein kinase; CB-1R, cannabinoid receptor 1; DGL-α, sn-1-diacylglycerol lipase-alpha; FAAH, fatty acid amide hydrolase; GHSR, growth hormone secretagogue receptor; GOAT, ghrelin *O*-acyltransferase; MAGL, monoacylglycerol lipase; NAPE-PLD; N-acyl phosphatidylethanolamine-phospholipase D; NPY, neuropeptide Y; PLC, phospholipase C.

presynaptically and postsynaptically within the HYP (Cowley et al., 2003; Kohno et al., 2003, 2008; Yang et al., 2011). Activation of GHSRs within the hypothalamus enhances the activity of neurons that promote appetite directly and induces changes in synaptic connections (i.e. alters excitatory and inhibitory afferent profiles) to promote activation of orexigenic circuits whilst suppressing satiety promoting pathways (discussed in detail in Refs. Abizaid and Horvath, 2012; Cowley et al., 2003; Horvath, 2006; Kohno et al., 2003; Nakazato et al., 2001; Pinto et al., 2004). Similarly, within the VTA, where GHSR protein expression overlaps with that of tyrosine hydroxylase, there is also evidence that ghrelin may act at both pre and post synaptic GHSRs to activate dopamine neurons that promote feeding behaviour (Abizaid et al., 2006). This is supported by the binding pattern of ghrelin within the VTA in addition to the fact that GHSR transcript is highly expressed in VTA dopamine neurons as well as regions known to send dense projections to the VTA (*e.g.* laterodorsal tegmental nucleus and LH) (Dickson et al., 2010; Guan et al., 1997; Howard et al., 1996; Jerlhag et al., 2011a; Mitchell et al., 2001; Zigman et al., 2006). Furthermore, electrophysiology experiments likewise suggest GHSR mediated enhancement of VTA dopamine activity following ghrelin administration relies on both pre and post synaptic processes (Abizaid et al., 2006). The mechanisms in which ghrelin promotes feeding within the HYP and VTA will be discussed in more detail in subsequent sections of this review.

1.2. Brief overview of the endocannabinoid system

While the appetite inducing effects of *Cannabis sativa* have been known for centuries, the identification of Δ9-tetrahydrocannabinol (Δ^9-THC), the chemical responsible for a majority of the psychoactive and orexigenic effects of *C. sativa*,

as well as the cloning of the first two endogenous receptors to which it binds (i.e. cannabinoid receptor 1 (CB-1R) and cannabinoid receptor 2 (CB-2R)), did not occur until much later (Devane et al., 1988; Devane et al., 1992; Gaoni and Mechoulam, 1964; Matsuda et al., 1990; Munro et al., 1993). Interestingly, it is now known that CB-1Rs are one of the most abundant GPCRs in the brain (Svizenska et al., 2008). Conversely, CB-2Rs are found sparingly in the brain, yet abundantly on immune cells and in peripheral organs (*e.g.* spleen, thymus, pancreas, *etc.*) (Herkenham et al., 1991; Howlett, 2002; Mackie, 2005; Svizenska et al., 2008). Endogenous cannabinoids, aptly named endocannabinoids, are the natural ligands of CB-Rs. Arachidonic acid derivatives, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), were the first two endocannabinoids discovered and remain the two most extensively studied (Devane et al., 1992; Di Marzo and Fontana, 1995; Sugiura et al., 1995). Originally, it was thought that these endocannabinoids were solely produced "on demand" from lipids of the postsynaptic membrane in response to intracellular increases in calcium that accompany depolarization events; however, recent evidence suggests that AEA and 2-AG may also be pre-made and stored in adiposomes and intracellular pools respectively (Alger and Kim, 2011; Oddi et al., 2008; Wilson and Nicoll, 2001). Moreover, it is becoming increasingly clear that endocannabinoids do not solely bind CB-1 and CB-2 receptors but are also capable of activating other receptors such as the orphan G protein coupled receptor, GPR55, and the transient receptor potential cation channel subfamily V member 1 (TRP-V1) (Baker et al., 2006; Castillo et al., 2012; Kano et al., 2009; Starowicz et al., 2007; Zygmunt et al., 1999; Zygmunt et al., 2013). Although, endocannabinoids are most renowned for their ability to act in a retrograde manner, binding pre-synaptic CB-1Rs to discourage neurotransmitter release, AEA has been evidenced to enhance neurotransmitter release through a TRP-V1 mediated process (Alger, 2002; Lee et al., 2015; Maccarrone et al., 2008; Musella et al., 2009; Ohno-Shosaku et al., 2001; Schlicker and Kathmann, 2001; Wilson and Nicoll, 2001). Interestingly, TRP-V1 activation by AEA has been shown to oppose 2-AG actions within certain brain regions (*e.g.* striatum) by reducing 2-AG biosynthesis (Di Marzo and Cristino, 2008; Lee et al., 2015; Maccarrone et al., 2008). Together, endocannabinoids, their receptors, and the enzymes involved in their synthesis and degradation make up the endocannabinoid system (refer to Fig. 1) (reviewed in Ref. D'Addario et al., 2014). Reflective of the widespread expression of endocannabinoid signalling machinery, the endocannabinoid system influences numerous physiological processes such as neural development, immune functioning, synaptic plasticity, learning, pain, and more relevant to this review: feeding and energy homeostasis (reviewed in Refs. Bermudez-Silva et al., 2012; Fine and Rosenfeld, 2013; Lutz et al., 2015; Mechoulam and Parker, 2013; Pertwee, 2012; Viveros et al., 2008; Viveros et al., 2011).

Similar to GHSRs, CB-1Rs are appreciably expressed within important feeding related brain regions such as the HYP and VTA (Herkenham et al., 1991; Mailleux and Vanderhaeghen, 1992; Wittmann et al., 2007). Expression of CB-1R mRNA is relatively low within the HYP; however, CB-1R proteins are found ubiquitously in many hypothalamic nuclei (*e.g.* ARC, VMH, DMH, PVN, *etc.*) (Herkenham et al., 1991; Marsicano and Lutz, 1999; Matsuda et al., 1993; Wittmann et al., 2007). Consistent with the canonical retrograde signalling of endocannabinoids, hypothalamic CB-1R proteins are almost exclusively found on axon or pre-axon terminals innervating these hypothalamic nuclei (Wittmann et al., 2007). Unlike GHSRs, CB-1Rs do not seem to be found on VTA dopamine neurons but instead on excitatory and inhibitory axon terminals innervating the VTA (Herkenham et al., 1991; Mailleux and Vanderhaeghen, 1992; Matyas et al., 2008; Tsou et al., 1998; but see Ref. Wenger et al., 2003). Both electrophysiology and electron microscopy experiments confirm the presynaptic nature of CB-1Rs on afferents to the VTA (Luprica and Riegel, 2005; Matyas et al., 2008; Melis et al., 2004a,b; Szabo et al., 2002). The role of the endocannabinoid system in modulating feeding within these two regions will be discussed in more detail subsequently.

2. Described interactions between ghrelin and endocannabinoid systems

2.1. Functional overlap between ghrelin and endocannabinoid systems in regulating feeding behaviours

Ghrelin and endocannabinoid systems both play important roles in the modulation of feeding behaviours as is expected by the co-expression and prevalence of their receptors in areas of the brain important in regulating feeding (*e.g.* HYP and VTA) as well as peripheral organs associated with metabolism (*e.g.* stomach and adipose tissue) (refer to Fig. 1) (Gnanapavan et al., 2002; Guan et al., 1997; Herkenham et al., 1991; Howlett, 2002; Mackie, 2005; Zigman et al., 2006). In support of this, ghrelin secretion fluctuates with feeding status and is closely associated with scheduled meals, rising before meal onset and falling shortly after consumption (Ariyasu et al., 2001; Cummings and Foster, 2003; Drazen et al., 2006). The association between endocannabinoid serum levels and feeding status is less established (Gomez et al., 2002; Matias et al., 2012; McPartland et al., 2014); however, endocannabinoid levels in feeding related brain regions (*e.g.* HYP and limbic forebrain) do similarly oscillate with respect to feeding status (i.e. peak in the fasted state and fall post-prandially) (Kirkham et al., 2002). Furthermore, ghrelin and endocannabinoid receptor agonists (i.e. 2-AG, AEA, and Δ9-THC) independently promote food intake and body weight gain when administered peripherally or centrally (Hao et al., 2000; Jamshidi and Taylor, 2001; Kirkham et al., 2002; Tschop et al., 2000; Williams and Kirkham, 1999; Williams and Kirkham, 2002a; Wren et al., 2001a,b). These effects are primarily mediated by GHSRs and CB-1Rs as ghrelin and endocannabinoid agonists do not induce feeding in GHSR and CB-1R knockout (KO) animals respectively (Bellocchio et al., 2010; Zigman et al., 2005). Furthermore, pretreatment of rodents with sub-anorectic doses of GHSR and CB-1R antagonists mitigates the orexigenic and adipogenic action of subsequent ghrelin and endocannabinoid agonist treatments (Abizaid et al., 2006; Arnone et al., 1997; Asakawa et al., 2003; Black, 2004; Di Marzo et al., 2001; Jamshidi and Taylor, 2001; Rinaldi-Carmona et al., 1994; Shrestha et al., 2009; Simiand et al., 1998; Sun et al., 2004; Williams and Kirkham, 1999, 2002b). Lastly, independent administration of GHSR and CB-1R antagonists also decrease food intake and adiposity highlighting the importance of tonic ghrelin and endocannabinoid system activity in promoting these processes (Arnone et al., 1997; Asakawa et al., 2003; Black, 2004; Colombo et al., 1998).

2.2. Endocannabinoid system influences ghrelin secretion and action within the periphery

Given the functional overlap between ghrelin and endocannabinoid systems in promoting food intake and adiposity it is not surprising that these systems influence one another within the periphery. The stomach, which highly expresses both GHSRs and CB-1Rs, is one of the peripheral organs in which these two systems are evidenced to interact (Cani et al., 2004; Date et al., 2000; Kojima et al., 1999; Zbucki et al., 2008). The endocannabinoid system positively regulates ghrelin secretion from the stomach as exemplified by concomitant reductions in ghrelin-immunoreactivity in the gastric mucosa and heightened circulating ghrelin levels following peripheral CB-1R agonist administration (refer to Fig. 1) (Zbucki et al., 2008). Furthermore, endocannabinoid mediated

regulation of ghrelin secretion influences feeding behaviour as 24 h food deprived rats, treated with CB-1R antagonists, demonstrate quick (i.e. 15 min) and significant reductions in plasma ghrelin and blunted re-feeding compare to vehicle treated animals (Cani et al., 2004). Interestingly, blockage of peripheral CB-1Rs, using peripherally restricted CB-1R antagonists, also attenuates the orexigenic effects of intracerebroventricular (ICV) ghrelin suggesting that peripheral interactions between ghrelin and endocannabinoid systems likewise influence the orexigenic action of ghrelin in the brain (Alen et al., 2013). The nodose ganglia, may in part mediate this peripheral interplay as both GHSRs and CB-1Rs are highly expressed within the nodose ganglia and ghrelin is evidenced to modulate CB-1R expression within this region (Burdyga et al., 2006; Date et al., 2002; Gomez et al., 2002). Moreover, the orexigenic effects of peripheral ghrelin and CB-1R agonists are largely reliant on functional vagal afferents (Burdyga et al., 2006; Date et al., 2002; Gomez et al., 2002). However, there are reports that rimonabant, a CB-1R antagonist, can induce anorexia independently of vagal afferents (Madsen et al., 2009). Nevertheless many studies support the notion that ghrelin and endocannabinoid systems interact within the stomach and nodose ganglia to influence feeding (Burdyga et al., 2006; Cani et al., 2004; Date et al., 2002; Gomez et al., 2002; Zbucki et al., 2008).

2.3. Analogous regulation of AMPK by ghrelin and endocannabinoid systems within the periphery

Ghrelin and endocannabinoid systems similarly influence adenosine monophosphate activated protein kinase (AMPK), an important intracellular regulator of energy metabolism and appetite (refer to Fig. 1) (Kola et al., 2005). AMPK regulates energy levels at both cellular and whole body levels through its actions as a resource sensor (Hardie et al., 2006). AMPK is activated when energy levels are low (i.e. high AMP: adenosine triphosphate (ATP) ratio) and inhibited when energy stores are high (i.e. low AMP: ATP ratio) (Hardie and Carling, 1997). Activation of AMPK processes shifts intracellular activity away from anabolic pathways that further deplete ATP in favour of ATP producing pathways (Hardie and Carling, 1997; Hardie et al., 1998, 2006). Accordingly, once activated, AMPK increases fatty acid oxidation and glycolysis and prevents the synthesis of fatty acids and glycogen (reviewed in Ref. Hardie et al., 2006).

In agreement with the ability of ghrelin and endocannabinoid treatments to promote lipid conservation and weight gain activation of either ghrelin or endocannabinoid systems inhibits adipose tissue and liver AMPK activity (refer to Fig. 1) (Kola et al., 2005). This inhibition results in a consequential decrease in the utilization of fat and glycogen to promote adiposity (Cota et al., 2003; Daval et al., 2006; Kola et al., 2005, 2008; Osei-Hyiaman et al., 2005; Tschop et al., 2000). Given the aforementioned similarities between ghrelin and endocannabinoid systems, it is not surprising that research into their convergent action within these tissues has uncovered a mutual dependency on each other (Kola et al., 2013; Lim et al., 2013). Peripheral and ICV administration of ghrelin at doses known to potently inhibit adipose tissue and liver AMPK activity is ineffective at doing so in rimonabant treated or CB-1R KO mice (Kola et al., 2013). Likewise, the ability of cannabinoids to inhibit AMPK activity within these peripheral tissues is also reliant on a functional ghrelin system as AMPK activity is unaltered by peripheral CB-1R agonist treatments in GHSR KO mice (Lim et al., 2013). Interestingly, despite similar relative energy intake (i.e.% of body weight), CB-1R and GHSR/ghrelin double KOs gain less weight and fat compared to corresponding controls (Pfluger et al., 2008; Ravinet Trillou et al., 2004). These studies not only highlight that ghrelin and endocannabinoid systems interact within adipose tissue and the liver, they also suggest that the adipogenic effects elicited by either ghrelin or endocannabinoids are dependent on each other and involve the inhibition of AMPK signaling cascades. Accordingly, future experiments should examine downstream enzymes in the AMPK pathway in addition to body weight and fat mass in rodents chronically receiving either GHSR or CB-1R agonists, while the other system is concurrently antagonized. Based on the aforementioned studies, it is predicted that these animals would resist the adipogenic effects of the corresponding agonist treatments (Jbilo et al., 2005; Pfluger et al., 2008; Ravinet Trillou et al., 2004; Zigman et al., 2005).

2.4. Hypothalamic cooperative interaction between ghrelin and endocannabinoid systems stimulatesAMPK activity and feeding

The role of AMPK in regulating energy balance within the hypothalamus has also been extensively studied (Andersson et al., 2004; Kim and Lee, 2005; Kola, 2008; Minokoshi et al., 2004). The HYP is the most comprehensively studied brain region involved in regulating homeostatic feeding and energy balance (Abizaid and Horvath, 2008; Zeltser et al., 2012). AMPK activators and expression of constitutively active AMPK within the HYP enhances food intake and body weight; whereas, knocking down AMPK activity induces the opposite effects (Andersson et al., 2004; Minokoshi et al., 2004). Consistent with its ability to modulate appetite, hypothalamic AMPK activity fluctuates with feeding status (i.e. highest in fasted state and lowest following re-feeding) (Minokoshi et al., 2004). Accordingly, high blood glucose levels and anorexigenic peptides (*e.g.* leptin and insulin) negatively regulate hypothalamic AMPK activity while low blood glucose and orexigenic compounds (*e.g.* ghrelin and endocannabinoids) stimulate it (Kola, 2008; Xue and Kahn, 2006). Although the mechanisms in which enhanced AMPK levels promote appetite and reduce energy expenditure remain incompletely understood, enhanced expression of orexigenic peptides (i.e. neuropeptide Y(NPY) and agouti related peptide (AgRP)) within the ARC and stimulation of fatty acid β- oxidation pathways contribute (Dietrich and Horvath, 2013; Kola, 2008; Lopez et al., 2008). The independent roles of ghrelin and endocannabinoid systems in manipulating food intake and feeding circuits within many hypothalamic nuclei have been extensively studied and can be reviewed in several excellent works (Abizaid and Horvath, 2008; Cowley et al., 2003; Di Marzo et al., 2009; Kageyama et al., 2010; Malcher-Lopes et al., 2006; Muller et al., 2015; Pagotto et al., 2006; Suzuki et al., 2010). This review will recapitulate their independent ability to stimulate AMPK activity and their collaborative actions within the HYP with regards to regulating feeding behaviours.

Ghrelin's central orexigenic effects are for the most part AMPK dependent as hindering central AMPK activity obstructs the ability of ghrelin to induce feeding (Lopez et al., 2008). Within the HYP, ghrelin induced AMPK signalling cascades are thought to greatly influence nutrient sensitive fatty acid biosynthetic pathways to elicit changes in feeding behaviour (refer to Fig. 2) (Andersson et al., 2004; Kola et al., 2005, 2008; Lam et al., 2005; Lopez et al., 2008; Obici et al., 2002, 2003). This pathway consists of a series of enzymes (i.e. fatty acid synthase (FAS), acetyl-coenzymeA carboxylase (ACC), and carnitine-palmitoyl-transferase-1 (CPT-1)) and metabolites (i.e. acetyl-coenzymeA (acetyl-CoA), malonyl-CoA, and long chain fatty acids-CoA (LCFA-CoA)), many of which are believed to act as signals that modulate feeding (Andersson et al., 2004; Lam et al., 2005; Lopez et al., 2008; Obici et al., 2003). Accordingly, it has been suggested that the quantity of intracellular hypothalamic LCFA-CoA molecules acts as an index of energy stores, with low and high levels reflecting a negative and positive energy balance respectively (Andersson et al., 2004; Kola, 2008; Lam et al., 2005; Lopez et al., 2008; Obici et al., 2003). FAS is responsible for turning LCFAs into LCFA-CoAs before these molecules can be transported into the mitochondria to generate ATP via

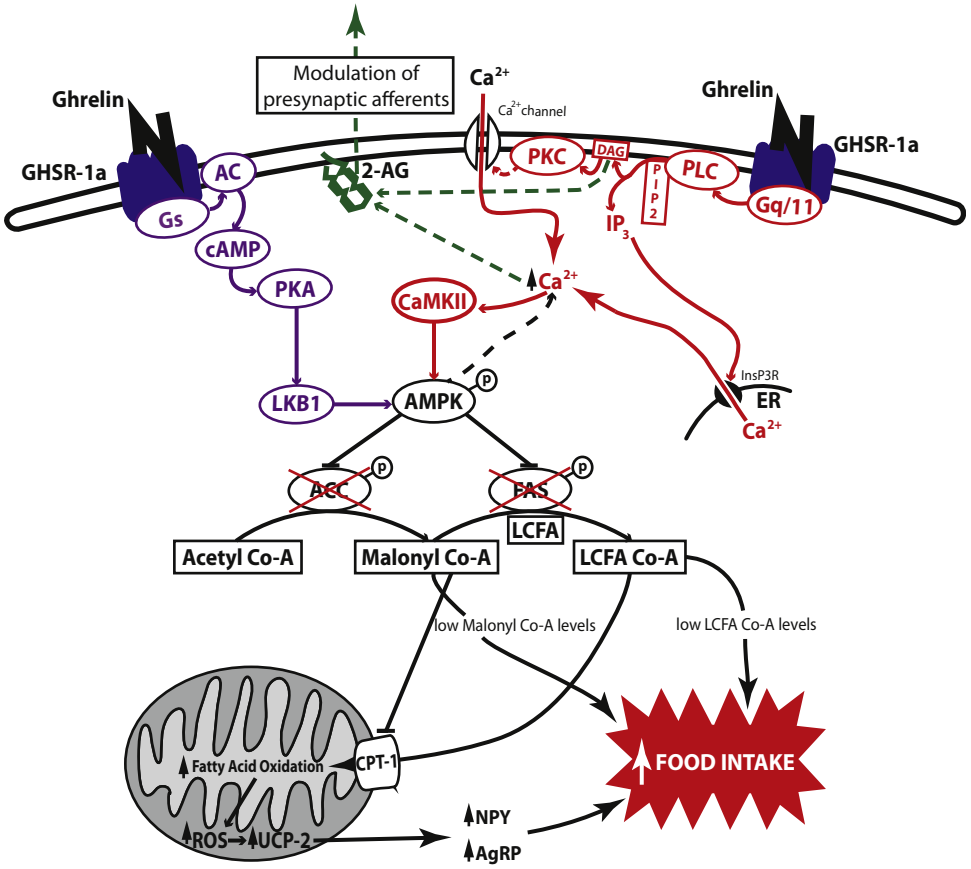

Fig. 2. Schematic diagram detailing GHSR mediated hypothalamic signaling pathways important for the promotion of food intake. Specifically, this figure highlights compounds and enzymes upstream and downstream of AMPK activation. Ghrelin mainly stimulates hypothalamic AMPK activity by activating $G_{q/11}$ mediated PLC/IP_3 signalling cascades. This pathway (shown in red) ultimately leads to a rise in intracellular calcium levels and encourages the phosphorylation and activation of AMPK by cAMKII. In addition, the ghrelin system is also evidenced to induce G_s mediated cAMP/PKA signalling cascades (shown in purple) presumably leading to the subsequent activation of AMPK by LKB1. Furthermore, it has been suggested that AMPK itself may enhance intracellular calcium ions. It is important to note that heightened intracellular Ca^{2+} and DAG are conditions that favor the production of 2-AG. Based on the predominate pre-synaptic location of CB-1R within the hypothalamus and that canonical CB-1R signalling cascades ($G_{i/o}$ mediated) do not favor AMPK activation it is likely that endocannabinoids activate hypothalamic AMPK levels indirectly by modulating presynaptic afferents. Once activated, AMPK phosphorylates and inhibits both ACC and FAS reducing cytoplasmic concentrations of malonyl Co-A and LCFA Co-A. Together the AMPK mediated decrease in cytoplasmic malonyl Co-A and LCFA Co-A and the promotion of fatty acid oxidation processes that up-regulate UCP-2, drive feeding. This illustration was drawn based on data and information from the following papers: (Andersson et al., 2004; Andrews et al., 2008; Andrews, 2011; Collins et al., 2000; Ha et al., 1994; Hawley et al., 2003; Hutchinson et al., 2008; Kohno et al., 2003, 2008; Kola et al., 2005, 2008; Kola and Korbonits, 2009; Lam et al., 2005; Lim et al., 2013; Lopez et al., 2008; McGarry et al., 1978; Minokoshi et al., 2004; Obici et al., 2002, 2003; Turu and Hunyady, 2010; Wellman and Abizaid, 2015; Yin et al., 2014). 2-AG, 2-arachidonoylglycerol; AC, adenylate cyclase; ACC, acetyl-coenzymeA carboxylase; AgRP, agouti-related peptide; AMPK, adenosine monophosphate activated protein kinase; CaMKII, calcium/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; CPT-1, carnitine-palmitoyltransferase-1; DAG, diacyl-glycerol; ER, endoplasmic reticulum; FAS, fatty acid synthase; GHSR-1a, growth hormone secretagogue receptor-1a; IP_3, inositol trisphosphate; InsP3R, inositol trisphosphate receptor; LCFAs, long chain fatty acids; LKB1, liver kinase B1; NPY, neuropeptide Y; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; ROS, reactive oxygen species; UCP-2, uncoupling protein 2.

β-oxidation processes by CPT-1 (Kola, 2008; Lopez et al., 2008; Obici et al., 2002,2003). However, CPT-1 is inhibited by malonyl-Co-A, a molecule made when ACC transfers a carboxyl group to acetyl-CoA (Ha et al., 1994; McGarry et al., 1978). Within the HYP, binding of GHSRs by ghrelin enhances intracellular calcium ions predominantly *via* phospholipase C/inositol triphosphate (PLC/IP_3) signalling cascades (Yin et al., 2014). This results in the activation of calcium/calmodulin-dependent protein kinase II (CaMKII) and the subsequent phosphorylation and activation of AMPK (Kola, 2008; Lopez et al., 2008). Ghrelin is also evidenced to engage cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) signaling cascades to activate AMPK via a GHSR-G_s dependant mechanism (refer to Fig. 2) (Andrews, 2011; Collins et al., 2000; Granata et al., 2007; Hutchinson et al., 2008; Kohno et al., 2003). Following activation, AMPK then decreases cytoplasmic LCFA-CoA in a bifurcate fashion. First, AMPK inhibits ACC reducing the conversion of acetyl-CoA to malonyl CoA (Kola et al., 2008; Lopez et al., 2008). This leads to the disinhibition of CPT-1, the promotion of LCFA-CoA molecules used for β-oxidation, and an overall diminished level of cytoplasmic LCFA-CoAs (Kola, 2008; Lopez et al., 2008). Second, AMPK likewise inhibits FAS preventing the transfer of CoA to LCFAs thus effectively attenuating the replenishment of cytoplasmic LCFA-CoA levels (Lopez et al., 2008). The consequential low concentration of LCFA-CoAs within the cytoplasm has been suggested to act as an energy depleted signal to promote food intake (Lam et al., 2005).

Further investigations into the AMPK mediated mechanism of ghrelin induce feeding has identified uncoupling protein 2 (UCP-2), an inner mitochondrial membrane protein, as an essential downstream enzyme implicated (Andrews et al., 2008). Consistent with this, UCP-2 KO animals consume significantly less food than corresponding wild types (WTs) following peripheral ghrelin administration (Andrews et al., 2008). Accordingly, UCP-2 not only is essential for buffering the effects of enhanced reactive oxygen species that accompany the increased breakdown of LCFA-CoA molecules but is also important for supporting increased mitochondrial respiration and biogenesis selectively in orexigenic neurons

of the ARC (Andrews et al., 2008). In contrast to the aforementioned studies that suggest that ghrelin induces low cytoplasmic LCFA-CoA to promote food intake, Andrews et al. (2008) report acute increases in hypothalamic LCFA-CoA levels following ghrelin administration. The authors of this study argue that this increase is integral for driving β-oxidative processes responsible for generating the ATP required for sustaining the activity of NPY/AGRP neurons within the ARC during periods of energy insufficiency (Andrews et al., 2008). Taken together, ghrelin enhances the availability of substrates required for lipid oxidation and induces AMPK intracellular cascades that favour hypothalamic fatty acid oxidation, production of orexigenic peptides, and ultimately feeding behaviours (Andrews et al., 2008; Lam et al., 2005; Lopez et al., 2008).

Although there is strong support suggesting that the orexigenic effects of ghrelin rely on the activation of AMPK signalling cascades following GHSR activation, recent evidence has challenged this notion (Verhulst et al., 2012). Verhulst and colleagues argue that upregulation of orexigenic peptides NPY and AGRP is GHSR dependent but changes in the activity of important AMPK signalling enzymes is not reliant on GHSR activation (Verhulst et al., 2012). More research is required to address these discrepancies.

As with GHSR stimulation, central and peripheral administration of CB-1R agonists also result in increased AMPK activity within the HYP (refer to Fig. 1) (Kola et al., 2005, 2008; Kola and Korbonits, 2009; Lim et al., 2013). Moreover, ICV injection of 2-AG increases the phosphorylation of ACC, a downstream target of AMPK (Kola et al., 2005). CB-1R agonists also heighten CPT-1 activity and fatty acid oxidation in cultured astrocytes (Biazquez et al., 1999). Consistent with this, injection of CB-1R agonists into various hypothalamic regions stimulates food intake (Jamshidi and Taylor, 2001; Kola et al., 2005, 2008; Lim et al., 2013; Tucci et al., 2004). However, the mechanism by which the endocannabinoid system engages hypothalamic AMPK activity remains largely unclear (Kola et al., 2005, 2008; Lim et al., 2013). CB-1Rs are GPCRs that influence a plethora of different signaling cascades when activated (*e.g.* mitogen activated protein kinase (MAPK), cAMP-PKA, phosphatidylinositol 3-kinase (PI3K)) (Bouaboula et al., 1995; Kano et al., 2009; Mackie et al., 1995; Pertwee, 1997; Sanchez et al., 1998; Twitchell et al., 1997). The signaling cascades initiated following CB-1R activation depend largely on the G-protein type coupled to CB-1Rs (Bosier et al., 2010). Most predominately, CB-1Rs associate with the $G_{i/o}$ family of G proteins, ultimately leading to the activation of inwardly rectifying K^+ currents and MAPK cascades and the inhibition of voltage-gated Ca^{2+} channels and adenylyl cyclase, following receptor activation (Bosier et al., 2010; Houston and Howlett, 1998; Howlett, 1985; Howlett et al., 2002; Kano et al., 2009; Pertwee, 1997). These CB-1R mediated effects are not consistent with those known to activate AMPK (Hardie, 2013; Lim et al., 2010; Omar et al., 2009). In contrast, activation of CB-1Rs in some instances has been reported to increase intracellular Ca^{2+} levels via a $G_{i/o}$ initiated phospholipase C/inositol triphosphate signaling cascade (De Petrocellis et al., 2007; Filipeanu et al., 1997; Netzeband et al., 1999; Sugiura et al., 1996, 1997, but see Ref. Lauckner et al., 2005). Furthermore, albeit under specific conditions (*e.g.* high CB-1R agonist concentrations, presence of forskolin or pertussis toxin, association with other GPCRs) activation of CB-1Rs can also stimulate adenylate cyclase (AC) and downstream cAMP-PKA signaling cascades through G_s GPCR mechanisms (Abadji et al., 1999; Bash et al., 2003; Calendra et al., 1999; Glass and Felder, 1997; Howlett et al., 2010; Jarrahian et al., 2004; Kearn et al., 2005; Maneuf and Brotchie, 1997; Rubovitch et al., 2002). Both the enhancement of intracellular Ca^{2+} levels and stimulation of cAMP-PKA signaling cascades promote AMPK activation (Hardie, 2013; Hawley et al., 2003, 2005; Lim et al., 2010; Woods et al., 2005). Although these processes may contribute, since canonical CB-1R mediated signalling cascades are not suggested to directly activate AMPK activity, it is likely that the endocannabinoid system indirectly affects AMPK activation within the HYP. One possibility, granted the ubiquitous expression of CB-1Rs on axon terminals innervating many hypothalamic nuclei and the ability of endocannabinoids to inhibit neurotransmitter release, is that endocannabinoids modulate synaptic afferents to these nuclei to indirectly influence AMPK activity (Kola et al., 2008; Wittmann et al., 2007). Given the inherent functional divisions within the HYP it would not be surprising to see cell type specific alterations in AMPK activity as suggested by others (Kola, 2008; Minokoshi et al., 2004). Unfortunately, all studies investigating the impact of endocannabinoids on hypothalamic AMPK activity have used whole hypothalamic abstracts; therefore, although it is known that CB-1R agonism heightens overall hypothalamic AMPK activity, it is unknown whether CB-1R mediated alterations in AMPK activity is consistent between or within nuclei of the HYP (Kola et al., 2005, 2008; Lim et al., 2013). Future studies that examine how endocannabinoids influence AMPK activity in specific nuclei and cell populations will be helpful in identifying the means by which the endocannabinoid system influences hypothalamic AMPK activity to modulate feeding behaviours.

The fact that ghrelin and endocannabinoids both stimulate feeding, have similar expression patterns, and have overlapping receptor localization in many hypothalamic nuclei, led to the investigation of their potential interaction within the HYP (Ariyasu et al., 2001; Cowley et al., 2003; Cummings and Foster, 2003; Di et al., 2003, 2005; Drazen et al., 2006; Guan et al., 1997; Herkenham et al., 1991; Jamshidi and Taylor, 2001; Kirkham et al., 2002; Mackie, 2005; Malcher-Lopes et al., 2006; Nakazato et al., 2001; Tucci et al., 2004; Verty et al., 2005; Wittmann et al., 2007; Wren et al., 2001b; Zigman et al., 2006). Tucci and colleagues provided the first substantial evidence of this interaction as they demonstrated that sub-anorectic doses of rimonabant could eliminate the orexigenic action of ghrelin administered into the PVN (Tucci et al., 2004). Interestingly, a functional endocannabinoid system is required in order for ghrelin to stimulate hypothalamic AMPK activity, an effect that as aforementioned is associated with and is important in mediating the orexigenic action of ghrelin (Kola et al., 2008). Consistent with this, genetic and pharmacological (i.e. peripheral rimonabant) disruption of CB-1Rs prevents the heightened hypothalamic AMPK activity induced by peripheral ghrelin administration (Kola et al., 2008). Furthermore, CB-1R disruption also prevents the rise in appetite induced by ICV ghrelin (Kola et al., 2008). Ensuing electrophysiology experiments confirmed the PVN as one of the hypothalamic regions in which ghrelin and endocannabinoid systems interact to modulate feeding and revealed a putative mechanism of this interaction within this region (Kola et al., 2008). Accordingly, administration of compounds that inhibit endocannabinoid signaling such as BAPTA (calcium chelator) and tetrahydrolipstatin (inhibits 2-AG synthesis) directly into PVN parvocellular neurons circumvents ghrelin induced inhibition of miniature excitatory post-synaptic currents (mEPSC) in these satiety promoting neurons (Gao and Horvath, 2007; Kola et al., 2008). Together these experiments highlight that parvocellular neurons produce 2-AG to modulate activity of afferents contacting them and suggest that 2-AG is the primary endocannabinoid mediating the effects of ghrelin within the PVN (Kola et al., 2008). This discovery complements earlier work demonstrating the capacity of leptin to reduce endocannabinoid mediated inhibition onto both PVN parvocellular and magnocellular neurons, a mechanism the authors postulated as important for influencing feeding (Di et al., 2003, 2005; Malcher-Lopes et al., 2006). Interestingly, the traditional rise in hypothalamic 2-AG content that is observed following peripheral ghrelin injections is abolished in CB-1R KOs and animals treated with rimonabant (Kola et al., 2008). This alludes to the existence of

a ghrelin sensitive positive hypothalamic feedback loop between CB-1R activation and 2-AG synthesis (Kola et al., 2008). Ultimately, the above studies suggest that a functional endocannabinoid system is required in order for ghrelin to stimulate AMPK signalling cascades and induce consequential feeding behaviours.

Ghrelin and CB-1R agonists also induce heightened hypothalamic AMPK activity in WT but not GHSR KO mice; however, the impact of GHSR disruption on cannabinoid induced feeding has not been as firmly established (Lim et al., 2013). Nevertheless, it is suspected that a functional ghrelin system is required to mediate the orexigenic effects of cannabinoids (Lim et al., 2013). Accordingly, intraperitoneal HU-210 (CB-1R agonist) injections tend to increase food intake in WTs but not GHSR KO mice (Lim et al., 2013). Future studies testing if GHSR antagonist pre-treatment can attenuate the orexigenic effects induced by intra-hypothalamic CB-1R agonist administration will be helpful in assessing whether a functional ghrelin system is likewise required for the orexigenic action of cannabinoids within the HYP.

3. Ghrelin and endocannabinoid systems promote reward feeding

3.1. Cortico-mesolimbic dopamine system important for modulating feeding behaviours

It is now well recognized that appetite is not solely regulated by homeostatic mechanisms within the HYP. Non-homeostatic or hedonic processes, which are similarly activated by both drugs of abuse and palatable foods, also play an important role (Berthoud, 2006; Liu and Borgland, 2015; Lutter and Nestler, 2009; Wellman et al., 2012, 2013). These motivational processes, which are responsible for the stimulation of appetite and sustained feeding, are driven by both the liking and wanting of food (Berridge, 2004; Berthoud, 2006). Liking responses are mediated primarily by opioid and GABA mechanisms within the brainstem, ventral pallidium (VP), and nucleus accumbens (NA); whereas, wanting processes are predominantly mediated by enhanced dopamine transmission within the cortico mesolimbic dopamine system (Alcaro et al., 2007; Berridge, 1996, 2009; Bjorklund and Dunnett, 2007). This review will largely focus on the role that ghrelin and endocannabinoid systems have in modulating the motivational or wanting aspects of food intake within the cortico-mesolimbic dopamine system. Accordingly, dopaminergic neurons that originate in the VTA and their corresponding neural projections to cortico-limbic structures such as the NA, prefrontal cortex (PFC), HIP, and amygdala (AMG) make up the cortico-mesolimbic dopamine system (refer to Fig. 3) (Alcaro et al., 2007; Berridge and Robinson, 2003; Bjorklund and Dunnett, 2007). Enhanced dopamine transmission within these target regions, induced by heightened VTA dopamine neuron activity, encourages motivational behaviors to obtain and consume foods, especially palatable or rewarding foods (Lutter and Nestler, 2009). Increased dopamine release within these regions, particularly the NA, also occur naturally in response to the incentive properties of palatable food rewards (Richardson and Gratton, 1996). Lesion studies that impair dopamine release within this pathway further emphasize its influence on feeding as lesioned animals substantially decrease their food intake and body weight (Salamone et al., 1990, 1993). Not surprisingly, the mesolimbic dopamine system has receptors for and is sensitive to many important feeding peptides and chemicals, including ghrelin and endocannabinoids (Liu and Borgland, 2015).

3.2. Ghrelin system regulates non-homeostatic feeding

The ghrelin system modulates both the liking and wanting aspects of hedonic feeding as exemplified by alterations in food preference and motivation to obtain food rewards upon its manipulation (Abizaid, 2009; Berridge, 2004; Dickson et al., 2011; Disse et al., 2010; King et al., 2011; Perello et al., 2010; Shimbara et al., 2004). Accordingly, ghrelin administration encourages the consumption of calorically balanced high fat diets over diets high in carbohydrates or proteins and induces a preferred selection of sweet sugar solutions in WT rodents (Disse et al., 2010; King et al., 2011; Shimbara et al., 2004). In contrast, mice that have disrupted ghrelin signaling, due to genetic or pharmacological GHSR disruption (i.e. GHSR KO mice or GHSR antagonist treated mice), selectively reduce their consumption of palatable foods (Egecioglu et al., 2010; Landgren et al., 2011). Moreover, ghrelin also influences more intricate reward driven behaviours as reflected in the facilitation of the development of conditioned place preferences (CPPs) and enhanced operant break points for rewards (*e.g.* food and drugs) (Davis et al., 2007; Jerlhag, 2008; Perello et al., 2010; Schuette et al., 2013; Skibicka et al., 2011). Conversely, disruption of the ghrelin system (i.e. GHSR antagonist treated and GHSR KO animals) prevents the development of CPP and decreases break points for both drugs of abuse and palatable foods (Egecioglu et al., 2010; Jerlhag and Engel, 2011; Jerlhag et al., 2009, 2010, 2011b; Perello et al., 2010; Skibicka et al., 2011). Interestingly, peripheral or central administration of ghrelin augments break points for rewarding foods in satiated rodents, demonstrating that ghrelin can engage motivational processes to drive feeding behaviour in the absence of hunger (Skibicka et al., 2012). Consistent with this, magnetic resonance imaging (MRI) studies reveal increased activity in mesolimbic dopaminergic circuits following intravenous ghrelin injections in mice (Wellman et al., 2012). Intriguingly, similar processes and brain regions are also engaged in humans, as high ghrelin levels, increased either endogenously (i.e. by fasting) or by external administration, enhance food appeal in humans and are associated with heightened cortico-limbic blood oxygen-level dependent signals (Goldstone et al., 2014). Furthermore, functional MRI studies detect augmented mesolimbic neural responses to pictures of rewarding food following intravenously administered ghrelin (Malik et al., 2008). These studies confirm the integral role that the ghrelin system plays in promoting the motivational behaviours that facilitate the obtention and consumption of palatable foods.

3.3. Ghrelin influences non-homeostatic feeding through its actions within the VTA

The VTA, also referred to as the hub of the cortico-mesolimbic system, is responsible for initiating a majority of the motivational and non-homeostatic appetite inducing effects elicited by ghrelin (Abizaid et al., 2006; Naleid et al., 2005). Compatible with this, GHSR mRNA is appreciably expressed throughout the VTA and infusion of ghrelin into the VTA potently stimulates feeding behaviours (Abizaid et al., 2006; Guan et al., 1997; King et al., 2011; Zigman et al., 2006). Conversely, administration of ghrelin antagonists into the VTA prevent the orexigenic effect of peripherally injected ghrelin (Abizaid et al., 2006). Ghrelin stimulates VTA dopamine neuron activity and dopamine turnover in the NA, consequentially engaging and enhancing motivational processes to seek rewards (*e.g.* food) (Abizaid et al., 2006; Cone et al., 2015; Jerlhag et al., 2007; King et al., 2011; Van Der Plasse et al., 2015). Accordingly, chronic intra-VTA administration of ghrelin enhances; whereas, GHSR antagonists decrease both the consumption and motivation to obtain palatable foods (King et al., 2011; Weinburg et al., 2011). These effects are shown to be dependent on striatal dopamine as VTA lesioned rodents are less motivated to search and bar press

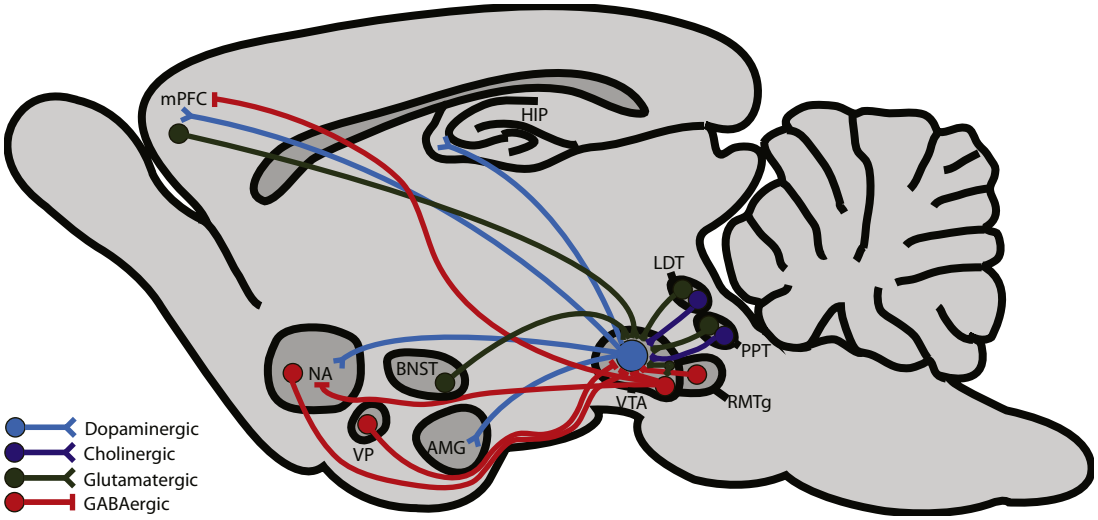

Fig. 3. Over-simplified depiction of the major afferents and efferents of the rat mesolimbic dopamine system. Note that many connections are omitted for simplicity. AMG, amygdala; BNST, bed nucleus of the stria terminalis; HIP, hippocampus; LDT, laterodorsal tegmental nucleus; mPFC, medial prefrontal cortex; NA, nucleus accumbens; PPT, pedunculopontine nucleus; RMTg, rostromedial tegmental nucleus; VP, ventral pallidum; VTA, ventral tegmental area.

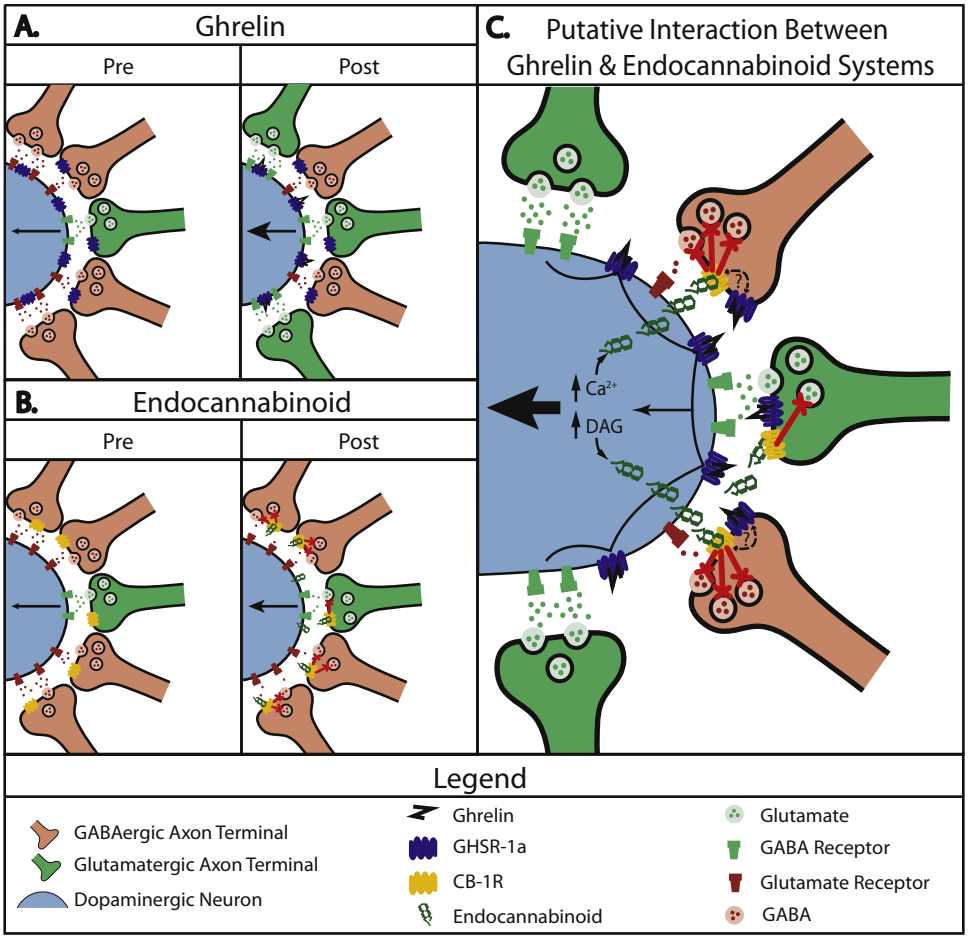

Fig. 4. Schematic representation of the putative independent (A, B) and collaborative (C) action of ghrelin and endocannabinoids within the VTA. (A) Ghrelin acts to enhance VTA dopamine activity through concomitant activation of GHSRs on VTA dopamine neurons and by augmenting the ratio of excitatory versus inhibitory synapses contacting VTA dopamine neurons. (B) Endocannabinoids increase the activity of VTA dopamine neurons by selectively or more effectively inhibiting GABA release from terminals contacting them. (C) Proposed mechanism in which ghrelin and endocannabinoid systems may interact within the VTA to promote heightened VTA dopamine neuron activity. It is hypothesized that the activation of VTA dopamine neurons by ghrelin consequentially promotes 2-AG synthesis and release which collaboratively encourages heightened VTA dopamine activity by reducing inhibitory tone onto these neurons.

for palatable foods following central ghrelin infusions compared to controls (Egecioglu et al., 2010; Weinburg et al., 2011). Ghrelin presumably enhances VTA dopamine activity via concurrent activation of GHSRs on VTA dopamine neurons and through the enhancement of excitatory versus inhibitory afferents that innervate these neurons (see Fig. 4, Panel A) (Abizaid et al., 2006). Importantly, the ability of ghrelin to heighten excitatory tone onto VTA dopamine neurons, enhance overall VTA dopamine activity, and augment dopamine turnover in the NA is mediated by GHSRs as these effects are abolished in GHSR KO rodents (Abizaid et al., 2006). Likewise, the rise in NA dopamine that accompanies presentation of palatable food rewards in WT mice is absent in mice with deficient GHSRs (Egecioglu et al., 2010). Interestingly, the ability of mice to develop CPP for palatable rewards and increase their food intake relative to GHSR KOs is rescued upon peripheral administration of ghrelin in mice that only express GHSRs on dopamine neurons (Chuang et al., 2011). These studies corroborate the important role that the ghrelinergic system has in regulating hedonic feeding behaviours within the mesolimibic dopamine system, particularly within the VTA.

3.4. The endocannabinoid system modulates non-homeostatic feeding

The endocannabinoid system also plays a significant role in regulating non-homeostatic feeding as exemplified by alterations in food preferences and in the motivation and reward associated with obtaining and consuming foods upon its manipulation (Kirkham, 2009). More specifically, the endocannabinoid system is implicated in both the liking and wanting of foods, which together, importantly influence appetite and feeding behaviours (Kirkham and Rogers, 2010). In support of this, CB-1R agonists reliably decrease the rejection of adverse solutions, increase the positive injestive responses to rewarding solutions, and promote feeding in satiated animals (Jarrett et al., 2005, 2007; Kirkham, 2009; Sinnayah et al., 2008; Solinas and Goldberg, 2005). Conversely, CB-1R antagonists increase the rejection of adverse solutions, decrease palatability of rewarding solutions and blunt re-feeding responses in food-derived rodents (Jarrett et al., 2005, 2007; Sinnayah et al., 2008; Solinas and Goldberg, 2005; Werner and Koch, 2003). Corroborating findings that pharmacological disruption of cannabinoid receptors reduces consumption of palatable foods over regular chow; CB-1 KO mice find sucrose less rewarding and reduce their consumption of sucrose compared to WTs (Arnone et al., 1997; Poncelet et al., 2003; Sanchis-Segura et al., 2004; Simiand et al., 1998). In terms of altering the motivation to feed, CB-1R agonists increase whereas CB-1R antagonists decrease the effort rodents are willing to exert in order to obtain palatable food rewards (Perio et al., 2001; Solinas and Goldberg, 2005). Similarly, CB-1R KO mice are also inherently less motivated to bar press for sucrose solutions (Sanchis-Segura et al., 2004). Intriguingly, pre-treatment of rodents with CB-1R antagonists reverses CPPs associated with classical reinforcers such as cocaine, morphine, and food thus illustrating the permissive nature that the endocannabinoid system has in regulating the perception of rewarding stimuli (Chaperon et al., 1998).

The endocannabinoid system also enhances the incentive salience of food in humans as people report heightened subjective feelings of hunger upon endocannabinoid system stimulation and hindered desire to feed following rimonabant treatment (Kirkham, 2009). Furthermore, there is evidence that a common single nucleotide polymorphism (SNP) in the gene encoding fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of AEA, modifies ventral striatum reactivity (Hariri et al., 2009). This SNP (*FAAH* 385A), which results in decreased FAAH expression and supposed enhanced AEA signalling, is associated with stronger ventral striatal activity in response to palatable food images, suggesting that these individuals may be more profoundly influenced by pleasurable food imagery (Hariri et al., 2009).

3.5. VTA endocannabinoid signalling is important for driving non-homeostatic feeding

Consistent with the influence that the endocannabinoid system has on food motivation and reward, endocannabinoids and CB-1Rs are expressed throughout the mesolimbic dopamine system (NA, VTA, HIP, *etc.*) (Herkenham et al., 1991; Kirkham et al., 2002; Mackie, 2005; Marinelli et al., 2003; Matsuda et al., 1990, 1993; Matyas et al., 2008). Accordingly, modulation of endocannabinoid elements alters dopamine release within the cortico-mesolimbic dopamine system and influences associated reward related behaviours (reviewed in Ref. Melis et al., 2012). *In vitro* and *in vivo* application of CB-1R agonists stimulates VTA dopamine neuron activity and burst firing, leading to heightened dopamine release within the NA shell (Cheer et al., 2000; Chen et al., 1990; French, 1997; French et al., 1997; Gessa et al., 1998; Gifford et al., 1997; Solinas et al., 2006; Tanda et al., 1997). These effects are mediated by CB-1Rs as they are blocked following CB-1R antagonist pre-treatment (Gessa et al., 1998; Tanda et al., 1997). Interestingly, blocking CB-1Rs or the enzyme required to synthesize 2-AG blocks the traditional rise in NA dopamine that accompanies cocaine administration (Wang et al., 2015). Similarly, the natural augmentation of NA dopamine that is induced by the presentation of novel palatable foods is also prevented by rimonabant pre-treatment (Melis et al., 2007). Further exemplifying the functional significance of the endocannabinoid system within the VTA, administration of rimonabant directly into the VTA decreases dopamine output in the NA and diminishes reward seeking behaviours in food self-administration tasks; whereas, JZL 184, an endocannabinoid degradative enzyme inhibitor, increases dopamine release and responses to obtain food rewards (Oleson et al., 2012).

The way in which the endocannabinoid system drives feeding related behaviours by modulating VTA dopamine activity and subsequent dopamine release within target regions remains incompletely understood. Nonetheless, electrophysiology and immunocytochemistry experiments have revealed the importance of presynaptic CB-1Rs in modulating neurotransmitter release from both gamma-aminobutyric acid (GABA) and glutamate afferents contacting VTA dopamine neurons (Kortleven et al., 2011; Labouèbe et al., 2013; Luprica and Riegel, 2005; Matyas et al., 2008; Melis et al., 2004a,b; Riegel and Luprica, 2004; Szabo et al., 2002; Wang et al., 2015). Accordingly, both $GABA_A$ and $GABA_B$ receptor mediated evoked inhibitory postsynaptic currents (IPSCs) onto VTA dopamine are suppressed by CB-1R agonists (Riegel and Lupica, 2004; Szabo et al., 2002; Wang et al., 2015). In support of this, bicuculline ($GABA_A$ receptor antagonists) pretreatment prevents further increases in VTA dopamine activity traditionally observed with CB-1R agonist administration (Cheer et al., 2000). Furthermore, application of AM251 (CB-1R antagonist/inverse agonist) or PIMSR1 (neutral CB-1R antagonist) increases $GABA_B$ receptor mediated IPSCs in putative dopamine neurons suggesting that endocannabinoids tonically inhibit these $GABA_B$ IPSCs in VTA dopamine neurons (Wang et al., 2015). 2-AG is suggested to be the endocannabinoid responsible for this tonic inhibition as suppression of 2-AG biosynthesis prevents; whereas, inhibition of its degradation, strengthens AM251 induced $GABA_B$ mediated IPSCs (Wang et al., 2015). On the other hand, endocannabinoids also presynaptically inhibit glutamate transmission onto VTA dopamine neurons as CB-1R agonists enhance paired pulsed ratios (indicative of presynaptic mechanism) and abolish *N*-methyl-*D*-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor mediated evoked excitatory postsynaptic currents (EPSCs) (Melis et al., 2004a,b). Inhibition of glutamate

release from extrinsic glutamatergic afferents is presumed to be the neural substrate of the reduction in VTA dopamine neuron EPSCs following CB-1R agonist treatment since these afferents are primarily responsible for maintaining glutamatergic tone onto VTA dopamine neurons (Melis et al., 2004a). The suppression of glutamate and GABA release from excitatory and inhibitory afferents is specifically mediated by CB-1Rs as CB-1R antagonists attenuate cannabinoid induced inhibition of evoked EPSCs and IPSCs respectively (Melis et al., 2004a,b; Riegel and Lupica, 2004; Szabo et al., 2002). Given that CB-1R agonists reliably induce increases in VTA dopamine activity and dopamine release within the NA, it is hypothesized that while endocannabinoids may inhibit both glutamate and GABA release onto VTA dopamine neurons, endocannabinoids ultimately suppress GABA inhibitory tone to a greater extent (discussed in more detail in subsequent sections) (refer to Fig. 4, Panel B) (Oleson and Cheer, 2012).

Recently, it has come to light that some metabolic peptides stimulate endocannabinoid signaling to modulate the activity of VTA dopamine neurons and subsequent feeding related behaviours (Labouèbe et al., 2013). Accordingly, insulin is effective in inducing long term depression at excitatory synapses contacting VTA dopamine neurons, an effect that is blocked by CB-1R antagonists (Labouèbe et al., 2013). This endocannabinoid mediated presynaptic inhibition of glutamate release onto VTA dopamine neurons relies on the induction of phosphoinositide 3-kinase activity following activation of insulin receptors on VTA dopamine neurons (Labouèbe et al., 2013). Consistent with this, intra-VTA administered insulin suppresses feeding, food anticipation, and CPP for food rewards, processes influenced by cortico-mesolimbic dopamine system activity (Bruijnzeel et al., 2011; Labouèbe et al., 2013; Mebel et al., 2012). Intriguingly, although intra-VTA leptin decreases VTA dopamine activity and food intake predominately via activation of its receptor and initiation of downstream signalling cascades (i.e. pERK1/2 and Jak-2), leptin is also reported to suppress excitatory synaptic transmission onto VTA dopamine neurons via a pre-synaptic mechanism (Hommel et al., 2006; Morton et al., 2009; Thompson and Borgland, 2013). The pre-synaptic inhibition of glutamate release following leptin administration is suggested to be primarily mediated by processes downstream of presynaptic leptin receptor (i.e. LepRb) activation; however, the possible involvement of endocannabinoid signalling should not be overlooked (Thompson and Borgland, 2013).

The opioid system, which has long been known to influence both homeostatic and hedonic feeding behaviours, likewise alters the activity of VTA dopamine neurons and subsequent dopamine release in the NA (Johnson and North, 1992; Luprica et al., 2004; Nogueiras et al., 2012; Spanagel et al., 1992). Intra-VTA μ receptor agonist administration enhances dopamine release within the NA and increases feeding; whereas, μ receptor antagonists injected within this region decrease NA dopamine release and reduce feeding under certain conditions (Badiani et al., 1995; MacDonald et al., 2003; Mucha and Iversen, 1986; Noel and Gratton, 1995; Ragnauth et al., 1997; Spanagel et al., 1992). The heightened dopamine release within the NA and increased feeding effects are thought to be primarily driven by a μ-receptor mediated disinhibition of VTA dopamine neurons (Badiani et al., 1995; Johnson and North, 1992; Spanagel et al., 1992). Accordingly, μ-receptor agonists hyperpolarize GABAergic interneurons known to negatively regulate VTA dopamine neuron activity (Badiani et al., 1995; Johnson and North, 1992; Spanagel et al., 1992). Perhaps not surprising, given that endocannabinoids and opioids both enhance VTA dopamine neuron activity, these systems influence one another. Low doses of naxolone (μ-receptor antagonist) block the rise in NA dopamine traditionally observed following peripheral injection of Δ^9-THC (Chen et al., 1990). Furthermore, opioid antagonists naloxone and naloxonazine administered peripherally and into the VTA respectively, also block augmentation of dopamine levels within the NA following peripheral injection of WIN55212 (cannabinoid receptor agonist) (Tanda et al., 1997). Consistent with this, mice lacking functional μ-opioid receptors do not show traditional place preferences for Δ^9-THC (Ghozland et al., 2002). On the other hand, cannabinoid receptor antagonism is also known to block self-administration of heroin; whereas, CB-1R agonism potentiates the rewarding properties of morphine (Navarro et al., 2001; Rashidy-Pour et al., 2013). Interestingly, opioids, like endocannabinoids, possess the ability to act as retrograde signallers, binding pre-synaptic μ and ɗ opioid receptors to inhibit neurotransmitter release within other brain regions (Iremonger and Bains, 2009; Mudge et al., 1979; Wamsteeker Cusulin et al., 2013). Although, μ-opioid receptors are predominately found post-synaptically on GABAergic interneurons, they are also expressed on excitatory and inhibitory pre-synaptic axon terminals contacting VTA dopamine neurons (Garzon and Pickel, 2001). Due to the similar described location of CB-1Rs in addition to the aforementioned evidence supporting the functional interaction between opioid and endocannabinoid systems one cannot exclude the potential interaction of their receptors in pre-synaptic afferents to the VTA (Matyas et al., 2008). Consistent with this, there is evidence that CB-1R and μ-opioid receptors may form heterodimers (Rios et al., 2006). A more detailed description of the role of the opioid system in regulating food intake as well as its relationship with the endocannabinoid system can be found in some excellent recent reviews (Befort, 2015; Le Merrer et al., 2009; Nogueiras et al., 2012; Olszewski et al., 2011; Parolaro et al., 2010).

4. Proposed collaboration of ghrelin and endocannabinoid systems within the VTA in driving feeding behaviours

4.1. Rational

It is evident that ghrelin and endocannabinoid systems both play an important role in regulating non-homeostatic feeding. Moreover, it is apparent that the VTA is an integral brain region in which these two systems act to encourage appetite and motivated behaviours to acquire food. This is corroborated by appreciable expression of appropriate ghrelin and endocannabinoid signalling proteins within the VTA in addition to the aforementioned alterations in feeding behaviours observed following intra-VTA infusion of ghrelin or cannabinoids. Despite this and evidence of their interaction elsewhere (i.e. peripheral organs and the HYP), their collaborative interaction within the VTA has not been extensively studied. This section proposes plausible mechanisms in which these two systems may interact within the VTA to drive feeding behaviours.

4.2. Anatomy of VTA and distribution of ghrelin and endocannabinoid signalling machinery

The VTA is a ventromedial midbrain region comprised of three main neuron types: dopaminergic, GABAergic, and glutamatergic (reviewed in Ref. Melis and Pistis, 2012). The VTA houses one of the largest populations of dopaminergic neurons in the brain, as the somata of mesolimbic dopamine neurons originate in this region (Bjorklund and Dunnett, 2007). Accordingly, approximately 55–65% of all neurons within the VTA express tyrosine hydroxylase (TH) (marker for dopamine neurons) (Margolis et al., 2006; Nair-Roberts et al., 2008). A majority of the remaining neurons within the VTA are thought to be GABAergic (~30–35%) (Nair-Roberts et al., 2008); however, a detectable quantity of glutamatergic neurons also reside within this region (Yamaguchi et al., 2007). The dopamine neurons of the VTA are contacted and regulated by

excitatory and inhibitory axon terminals (refer to Fig. 3) (Melis et al., 2012; Omelchenko and Sesack, 2009). These dopamine neurons receive strong GABAergic axon collateral inputs from local VTA GABAergic neurons in addition to glutamatergic inputs from the smaller resident population of VTA glutamatergic neurons (Dobi et al., 2010; Omelchenko and Sesack, 2009). Interestingly, these VTA glutamatergic neurons likewise send projections onto neighbouring GABA interneurons of the VTA (Dobi et al., 2010). In addition to these local connections, the VTA is also strongly innervated by external glutamatergic excitatory inputs of the PFC and bed nucleus of the stria terminalis (BNST), glutamatergic/cholinergic excitatory neurons of the pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT), and GABAergic inhibitory afferents of the ventral striatum, VP, and the rostromedial tegmental nucleus (reviewed in Ref. Morikawa and Paladini, 2011; Omelchenko and Sesack, 2007).

A large proportion of VTA dopamine neurons (an estimated 50–60%) also express GHSR mRNA and protein (Abizaid et al., 2006; Zigman et al., 2006). Within this region, GHSR transcript has also been reported to co-localize with about a third of GABA neurons within the VTA (Abizaid et al., 2006). Interestingly, the co-localized punctuated fluorescence immunolabelling pattern of GHSRs within the VTA is visually consistent with either pre or post synaptic localized receptor expression (Abizaid et al., 2006). Although the pattern of biotinylated ghrelin binding suggests a postsynaptic location of GHSRs, electrophysiology experiments advocate that GHSR may also be located on afferent axon terminals (Abizaid et al., 2006). Accordingly, application of ghrelin to brain slices containing the VTA significantly enhances the frequency of action potentials in dopamine neurons; however, this effect is lost when ghrelin is applied in the presence of ionotropic glutamate receptor antagonists (i.e. CNQX and AP5) (Abizaid et al., 2006). This suggests that the activation of postsynaptic GHSRs on dopamine neurons is insufficient to enhance the frequency of action potentials in the absence of presynaptic excitatory tone (Abizaid et al., 2006). This taken together with the fact that ghrelin induces synaptic rearrangements (i.e. enhances the ratio of excitatory to inhibitory synapses) onto VTA dopamine neurons in a GHSR dependent manner indicates that pre-synaptic GHSRs may also influence the capacity of ghrelin to increase VTA dopamine activity (Abizaid et al., 2006). In support of this, GHSRs are located on the presynaptic membrane in other brain regions such as the HYP and HIP (Cowley et al., 2003; Diano et al., 2006).

Initial studies investigating CB-1R localization within the VTA reported negligible expression of CB-1R mRNA as well as insignificant radioactive labelled CB-1R agonist receptor binding; however, more recent studies confirm that CB-1Rs are indeed found within the VTA (Herkenham et al., 1991; Mailleux and Vanderhaeghen, 1992; Matsuda et al., 1993; Matyas et al., 2008). Despite a few immunohistochemical studies reporting co-localization of CB-1Rs in TH expressing cells (Hernandez et al., 2000; Wenger et al., 2003), evidence suggests that CB-1Rs are not expressed directly on dopamine neurons of the VTA but rather on GABAergic and glutamatergic axon terminals contacting them (Herkenham et al., 1991; Mailleux and Vanderhaeghen, 1992; Matsuda et al., 1993; Matyas et al., 2008). The spatial separation of CB-1R mRNA, located in nuclei of neurons which project to the VTA, and protein, situated on axon terminals residing in the VTA, may partially explain the apparent disparity between CB-1R mRNA and protein expression studies (Matyas et al., 2008).

Likewise, important in supporting a role for endocannabinoid signalling within the VTA are the enzymes that synthesize endocannabinoids. 2-AG is thought to mediate a majority of endocannabinoid associated actions within the VTA as *sn*-1-diacylglycerol lipase-alpha (DGL-α), the enzyme that synthesizes 2-AG, is found appreciably within the VTA whereas *N*-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD), one of the main enzymes involved in AEA production, is not (Egertova et al., 2008; Matyas et al., 2008; Melis and Pistis, 2012). Although AEA can be produced via other enzymatic processes that do not involve NAPE-PLD, 2-AG remains the prime candidate for eliciting effects within the VTA as 2-AG levels are 100 fold those of AEA within the midbrain (Bisogno et al., 1999; Egertova et al., 2008; Matyas et al., 2008). Furthermore, manipulation of enzymes involved in the synthesis or degradation of 2-AG influences the excitability of putative VTA dopamine neurons (Wang et al., 2015). Accordingly, DGL-α transcript is highly expressed in most neurons of the VTA (Matyas et al., 2008). Interestingly, within dopaminergic and non-dopaminergic neurons of the VTA, DGL-α protein expression predominantly localizes to the inner surface of postsynaptic membranes specifically apposed to CB-1R positive axon terminals (Matyas et al., 2008). In support of the aforementioned ability of endocannabinoids to prevent neurotransmitter release from both inhibitory and excitatory inputs, DGL-α protein is positioned across from both asymmetric and symmetric synapses bearing CB-1Rs (Matyas et al., 2008).

4.3. Combined activation and disinhibition of VTA dopamine neurons by ghrelin and endocannabinoid systems likely underlies non-homeostatic feeding functional overlap

As described above, both ghrelin and endocannabinoids stimulate motivational processes to obtain and consume food following activation of their receptors within the VTA (Perello et al., 2010; Solinas and Goldberg, 2005). Accordingly, agonism of either of these systems increases the activity of VTA dopamine neurons and subsequent release of dopamine within mesolimbic dopamine system target regions to encourage these feeding behaviours (Abizaid et al., 2006; Solinas and Goldberg, 2005; Solinas et al., 2006; Tanda et al., 1997). Mechanistically, ghrelin promotes excitatory versus inhibitory inputs onto VTA dopamine neurons and activates GHSRs on the post-synaptic membrane of these VTA dopamine neurons to enhance their activity (refer to Fig. 4, Panel A) (Abizaid et al., 2006). The means by which endocannabinoids augment VTA dopamine neuron activity is not as clearly established; however, dampening down of inhibitory tone onto these neurons is thought to greatly contribute (see Fig. 4, Panel B) (Luprica and Riegel, 2005). Consistent with these two mechanisms and appropriate localization of both ghrelin and endocannabinoid signalling machinery, we propose a collaborative action between these two systems.

The most apparent mechanism in which these two systems may interact to enhance VTA dopamine activity is through concurrent stimulation and disinhibition of these neurons by ghrelin and endocannabinoid systems respectively (see Fig. 4, Panel C). Consistent with this, binding of ghrelin to its endogenous receptor induces activation and dissociation of the GHSR associated α G-protein subunit (i.e. $G_{q/11}$) consequently leading to the stimulation of PLC enzymes (Yin et al., 2014). PLC enzymes use lipids of the postsynaptic membrane to make inositol trisphosphate (IP_3) and diacylglycerol (DAG) second messengers (Yin et al., 2014). IP_3 facilitates the release of calcium from stores in the endoplasmic reticulum to enhance intracellular calcium ion levels whereas DAG, in addition to activating other intracellular signalling cascades, is the substrate that DGL-α uses to synthesize 2-AG (Yin et al., 2014). Moreover, as mentioned previously GHSR activation may also increase intracellular calcium ions through G_s induced cAMP/PKA signaling cascades (reviewed in Ref. Yin et al., 2014). Therefore, activation of GHSRs, which are located on the post-synaptic membrane of VTA dopamine neurons, enhances intracellular calcium ions and DAG, two conditions known to induce the synthesis and release of 2-AG (Wang and Luprica, 2014). Further promoting conditions that favour endocannabinoid synthesis ghrelin also drives the enhancement of intracellular Ca^{2+} levels in VTA dopamine neuron by

preferentially encouraging glutamatergic tone onto these neurons (Abizaid et al., 2006). Thus, ghrelin simultaneously increases VTA dopamine activity and triggers intracellular events that prompt endocannabinoid synthesis and release within the VTA.

Appropriately, DGL-α protein is appreciably expressed on the postsynaptic membrane of VTA dopamine neurons and large increases in endocannabinoid release are observed following heightened VTA dopamine neuron activity (Matyas et al., 2008; Riegel and Luprica, 2004). Although CB-1Rs are found on both excitatory and inhibitory synapses contacting VTA dopamine neurons, suppression of neurotransmitter release from inhibitory terminals is more efficient as the net effect of CB-1R agonism is an enhancement in VTA dopamine neuron activity (French et al., 1997; Gifford et al., 1997; Tanda et al., 1997). Compatible with this, removal of GABA inhibitory tone is sufficient to induce burst firing in dopamine neurons of the midbrain (Lobb et al., 2010). The net activation of VTA dopamine neurons by endocannabinoids may reflect a larger quantity of innate CB-1R positive inhibitory synapses relative to excitatory synapses contacting VTA dopamine neurons. Suitably, a majority of non-dopaminergic neurons within the VTA are GABAergic and the prevalence of GABA synapses onto VTA neurons has been previously described (Bayer and Pickel, 1991; Bourdy and Barrot, 2012; Grace et al., 2007; Johnson and North, 1992; Omelchenko and Sesack, 2009). Moreover, Abizaid and colleagues report higher frequencies of miniature IPSCs (mIPSCs) compared to mEPSCs and more putative GABAergic relative to glutamatergic synapses onto VTA dopamine neurons in vehicle treated animals (Abizaid et al., 2006). Alternatively or in addition to this, endocannabinoid signalling machinery may be more strongly or preferentially expressed at inhibitory versus excitatory synapses as observed in other brain regions (Uchigashima et al., 2007; Yoshida et al., 2011). Interestingly, ghrelin injections have been shown to quickly rearrange synaptic inputs onto VTA dopamine neurons, switching the inputs from a state favouring inhibition to one that encourages excitation (Abizaid et al., 2006). Given that GHSR activation encourages conditions known to promote endocannabinoid synthesis and release, it is possible that endocannabinoid signalling may facilitate the increased synaptic plasticity induced by ghrelin. Taken together, we propose that ghrelin binds to GHSRs on VTA dopamine neurons and enhances their activity, resulting in increased production and secretion of 2-AG, which further encourages heightened VTA dopamine activity by reducing overall inhibition onto these neurons.

In support of this, it has become apparent that a region once classified as part of the posterior VTA, which is functionally and neuroanatomically distinct from the VTA, is sensitive to endocannabinoids and influences VTA dopamine neuron activity (Bourdy and Barrot, 2012; Perrotti et al., 2005). This region, now referred to as the rostromedial tegmental nucleus (RMTg) or more colloquially as the tail of the VTA, contains a dense population of GABAergic neurons that strongly innervate midbrain dopamine neurons (Bourdy and Barrot, 2012; Lecca et al., 2011). Immunohistochemistry experiments conservatively estimate that approximately 60% of VTA dopamine neurons are innervated by RMTg GABAergic neurons; however, electrophysiology experiments suggest that these GABAergic projections may innervate a vast majority of dopamine neurons within the VTA (i.e. ~95%) (Balcita-pedicino et al., 2011; Hong et al., 2011; Kaufling et al., 2010). Accordingly, stimulation of the RMTg potently inhibits VTA dopamine neurons (Lecca et al., 2011). More importantly, CB-1R agonists inhibit GABAergic neurons of the RMTg consequentially leading to the disinhibition and activation of VTA dopamine neurons (Lecca et al., 2011, 2012). Initially, dampening down of glutamate release onto RMTg GABAergic neurons was thought to mediate the observed disinhibition of VTA dopamine neurons; however, recent evidence suggests that endocannabinoid mediated inhibition of GABA release from these inhibitory terminals likewise contributes (Lecca et al., 2011, 2012; Melis et al., 2014). Suitably, these inhibitory projections express pre-synaptic CB-1Rs and exhibit reduced GABA release following VTA dopamine neuron stimulation (Lecca et al., 2011, 2012). Again 2-AG is suspected to be responsible for mediating the disinhibition of VTA dopamine neurons as GABA release from RMTg inhibitory projections is unaffected following stimulation of VTA dopamine neurons in the presence of a DGL-α inhibitor (Melis et al., 2014). Together, the endocannabinoid mediated presynaptic inhibition of glutamate release onto RMTg GABAergic neurons and postsynaptic inhibition of GABA release onto VTA dopamine neurons presumably work together to remove the GABAergic brake that regulates VTA dopamine neuron activity (Lecca et al., 2011, 2012). Consistent with the aforementioned proposed relationship between ghrelin and endocannabinoid systems, activation of VTA dopamine neurons by ghrelin and consequential production and release of endocannabinoids likely dampen the release of GABA from major RMTg inhibitory projections. Together, the activation of VTA dopamine neurons by ghrelin in tandem with the associated endocannabinoid mediated disinhibition of RMTg inhibitory projections may contribute to the induction of burst firing patterns that encourage heightened dopamine release within the accumbens shell and associated motivational processes directed at obtaining and consuming food.

4.4. Possible formation of GHSR/CB-1R heterodimers within the VTA

Alternatively, one cannot ignore the possibility of a direct interaction between GHSRs and CB-1Rs within the VTA. In support of this, others studying the functional and physical overlap between ghrelin and endocannabinoid systems with respect to energy balance have hypothesized that GHSRs and CB-1Rs form heterodimers (Lim et al., 2013; Schellekens et al., 2010; Wellman and Abizaid, 2015). This notion stems from the bidirectional reliance of functional GHSRs and CB-1Rs necessary to support the orexigenic and metabolic effects (*e.g.* modulation of AMPK) elicited by agonism of either system (Kola et al., 2005, 2008; Lim et al., 2013). Further fueling speculation of a direct interaction between these receptors, GHSRs and CB-1Rs demonstrate appreciable and overlapping expression within important feeding related brain regions (*e.g.* HYP) and peripheral tissues (*e.g.* stomach) (Gnanapavan et al., 2002; Guan et al., 1997; Herkenham et al., 1991; Mackie, 2005; Matsuda et al., 1993; Zigman et al., 2006). Moreover, both GHSRs and CB-1Rs are evidenced to form heterodimers with a variety of other receptors (Turu and Hunyady, 2010; Wellman and Abizaid, 2015). GHSRs dimerize with dopamine 1, melanocortin-3, and serotonin 2C receptors; whereas, CB-1Rs are reported to form dimers with adenosine A2A, μ-opioid, and orexin-1 receptors (Carriba et al., 2008; Ellis et al., 2006; Jiang et al., 2006; Rediger et al., 2009; Rios et al., 2006; Schellekens et al., 2013). Interestingly, both GHSRs and CB-1Rs are evidenced to form heterodimers with dopamine-2 receptors (Kearn et al., 2005; Kern et al., 2012). Although GHSRs are renowned for their postsynaptic position on VTA dopamine neurons they are also expressed on presynaptic terminals impinging onto these neurons (Abizaid et al., 2006). In support of a potential direct interaction between GHSRs and CB-1Rs within the VTA, CB-1Rs are likewise densely expressed on presynaptic terminals of GABA, glutamate, and opioid expressing neurons that innervate VTA dopamine neurons (Matyas et al., 2008). Although there is no direct evidence of GHSR/CB-1R heterodimer formation, within the VTA or elsewhere, their discovery within the VTA would not be amiss given that ghrelin and endocannabinoids similarly stimulate VTA dopamine neurons and that their corresponding receptors, which are known to be able to form dimers, are both found on

presynaptic inputs converging onto VTA dopamine neurons (Abizaid et al., 2006; Matyas et al., 2008).

5. Future directions

It is evident that ghrelin and endocannabinoid systems promote the motivation to obtain and consume food in part by activating VTA dopamine neurons and subsequent dopamine release within the NA. Although this review detailed the most probable mechanisms in which these two systems presumably interact based on current behavioural, immunohistochemical, and electrophysiological experiments; there are a few critical studies that would clarify the relationship between these systems within the VTA. First, while there are a plethora of behavioural studies that have investigated the independent actions of pharmacologically stimulating or inhibiting ghrelin or endocannabinoid systems within the VTA, studies investigating the reliance and dependence of these two systems with respect to each other are lacking. Accordingly, experiments assessing overall food intake and motivation to obtain palatable food rewards following intra-VTA infusions of different combinations of GHSR and CB-1R agonist and antagonist treatments will be beneficial in elucidating if and the extent to which these systems work collaboratively to enhance feeding behaviours. In addition, future electrophysiology experiments should investigate the electrical activity of VTA dopamine neurons in response to a series of joint CB-1R and GHSR agonist and antagonist manipulations to evaluate the contributions and interdependence of these systems in manipulating VTA dopamine activity. Furthermore, in spite of the fact that GHSRs and CB-1Rs are known to be appreciably expressed within the VTA, the precise localization of these receptors within this area, especially with respect to each other, requires further clarification. Triple immunofluorescence experiments targeting different combinations of CB-1Rs, GHSRs, TH, vesicular glutamate transporter 1(VGluT1), glutamate decarboxylase, and synaptophysin would provide valuable information regarding the position and co-localization of GHSR and CB-1Rs within the VTA. In addition, these immunofluorescence experiments would allow for the approximation of the proportion of CB-1R positive excitatory versus inhibitory axonal terminals contacting dopamine and/or GHSR positive neurons within the VTA. These immunofluorescence studies are essential to prove or disprove proposed mechanisms of interaction between ghrelin and endocannabinoid systems within the VTA. Lastly, resonance energy transfer based techniques (*e.g.* FRET and BRET) investigating whether GHSRs and CB-1Rs form GHSR/CB-1R heterodimers and additional studies probing the likelihood of their presence within the VTA should be conducted pending positive results. Together these experiments will help elucidate the nature of the interaction between ghrelin and endocannabinoid systems within the VTA.

6. Concluding remarks

Ghrelin and endocannabinoid systems are undoubtedly important in regulating energy balance as demonstrated by marked alterations in feeding behaviours and body weight that accompany manipulation of either system. Within the past couple of decades, it has become apparent that ghrelin and endocannabinoid systems do not act independently to regulate adiposity and feeding but rather rely on each other both centrally and peripherally. This interaction has been best characterized within the HYP, where the appetite stimulating effects of ghrelin and endocannabinoids bi-directionally depend on the functionality of each system. Studies that discovered their collaborative actions within the HYP began with evidence of shared functional overlap and co-localized signalling machinery, two recurring situations observed within the VTA. Accordingly, recent research has uncovered that ghrelin and endocannabinoid systems similarly stimulate dopamine release within mesolimbic target regions by increasing the excitability of VTA dopamine neurons, a process demonstrated to be integral in engaging motivational behaviours to obtain and consume foods. Despite this, whether these two systems interact within the VTA and the importance of this relationship in influencing feeding behaviours requires further investigation. This review recapitulated evidence of their independent actions within the VTA and postulated putative mechanisms of their interaction consistent with current evidence and local VTA infrastructure. Presently, the concurrent activation and disinhibition of VTA dopamine neurons by ghrelin and endocannabinoid systems respectively, remains one of the most likely ways in which these two systems work together to drive the motivational processes to feed. Future studies probing the relationship between ghrelin and endocannabinoid systems within the VTA will provide a better understanding of the mechanisms that underlie non-homeostatic feeding.

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