Endocannabinoids and the Non-Homeostatic Control of Appetite

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Abstract The usual physiological perspective on appetite and food intake regards control of eating simplistically, as merely the reflexive behavioural component of a strict homeostatic regulatory system. Hunger is seen to arise in response to energy deficit; meal size is determined by the passage of nutrients into the gut and the stimulation of multiple satiety signals; and overall energy intake is modified to reflect the balance of fuel reserves and energy expenditure. But everyday experience shows that we rarely eat simply through need. Rather, food stimuli exert a powerful influence over consumption through their appeal to innate and learned appetites, generating the psychological experiences of hunger, craving and delight independently of energy status. That these important and influential subjective experiences are mediated through complex neurochemical processes is self-evident; but the chemical nature of our infatuation with, and subservience to, the motivating

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properties of foods are overshadowed by mechanistic, peripherally anchored models that take little account of psychological factors, and which consequently struggle to explain the phenomenon of obesity. This chapter discusses recent developments that suggest the endocannabinoids are key components of the central mechanisms that give rise to the emotional and motivational experiences that lead us to eat and to overconsume.

Keywords Appetite • Craving • Hyperphagia • Orexigenic

1 Obesity and the Problem of Homeostasis

When considering the orthodox position that energy intake and body weight are homeostatically regulated in reference to energy expenditure and levels of available fuel reserves, the early twenty-first century provides us with some problems. Specifically, if efficient homeostatic mechanisms have evolved to maintain energetic constancy, how do we explain the increasing prevalence of obesity? Are overconsumption and obesity a consequence of the failure of energy/body weight homeostasis due to powerful psychological factors that can override regulation for the sake of indulgence; or are they actually evidence of the lack of adequate regulatory systems that function to modulate appetite against energy reserves?

The past few decades have witnessed a dramatic increase in the number of central and peripheral chemical factors proposed to control food intake. But with the general acceptance of homeostatic models in this field, the predominant theme of research and theorising centres on the determination of the negative feedback signals that such a model requires to regulate feeding. Neurocrine, endocrine and adipokine messengers have been identified and proposed, through hypothalamic integration, to provide the neural brake to ingestion; arguably to prevent unnecessary overconsumption, and to maintain a stable internal energetic milieu and body weight constancy. The list of these "satiety" factors grows annually: most, by dint of their ability to suppress food intake (naturalistically or otherwise), are seen as key to the regulation of energy intake and to directly serve the homeostatic imperative (Konturek et al. 2005; Maljaars et al. 2007; Valassi et al. 2008; Wren and Bloom 2007). With such an armoury of inhibitory feedback signals it is surprising that overconsumption, let alone obesity, is ever expressed. Yet people continue to overconsume and to gain weight – and to become massively obese. And a typical, but less-than-satisfactory theoretical response is that negative regulation fails due to excessive demand on one or more of these multiple inhibitory systems (Scarpaci and Zhang 2007; Kalra 2008).

By contrast, the mechanisms that promote eating motivation, and the signals that may act to instigate feeding have received far less attention (Beck 2007). However, the systems that underlie hunger, and particularly food-craving and hedonic

responses to food, represent considerably greater influences on the frequency, quantity and variety of consumption. Consequently, should we wish to pursue the totality of any homeostatic influences on feeding, or be set on the development of pharmaceutical interventions to restrict food intake, these positive motivational factors represent crucial targets for investigation. There is, however, an unfortunate tendency for researchers to ignore their own, common experience of the power of food to engender appetite, or to consider the possibility that this phenomenon represents more than an accident of psychology and an inconvenient interference to homeostatic regulation. This, in turn, leads to neglect of the evolutionary parsimony of the pre-eminence of the psychological processes that maintain positive energy balance and adequate nutritional status in the face of potentially unreliable nutrient sources.

The concept of satiation of a motivated behaviour was initially invoked to explain its eventual cessation. This conceptualization may, however, be distinguished from the existence of dynamic mechanisms that actively suppress the desire to eat. Satiation of eating may be a phenomenon that, acutely, is influenced by food intake and the bodily recognition that reserves are being restored or replenished. But, given the unpredictability of food availability in the world of our evolutionary antecedents, control of eating should not be wholly dependent upon such short-term considerations. An adaptive organism in an unpredictable food environment requires the control of eating motivation to be responsive to the immediate vagaries of that environment, and also to reflect the need for long-term energetic security. The central integration of oro-oesophageal and gastrointestinal sensory inputs resulting from the ingestion of food may act to dampen the urgency of eating motivation, but it is unlikely that the rate of passage of food through the gut during a meal can provide sufficiently rapid calculation of nutrient or utilisable energy content to accurately control meal size in relation to homeostatic constraints. Rather, physico-chemical stimuli have predictive, partly learned, qualities that signal later energy absorption (Gibson and Brunstrom 2007). These qualities are permissive in that they allow attention to be diverted to other aspects of the environment that may then gain motivational impact in relation to the satisfaction of other bodily needs. Satiety, then, need not be considered as a condition that will only wane with the passage of time and the expenditure of recently consumed calories, according to some immutable energetic equation – but is rather a reflection of the relative valence of competing stimuli for alternative motivational imperatives.

Indeed, appetite for food, itself, provides a prime example of such motivational lability: evident in the all too common experience whereby the sight or smell of food can provoke the desire to eat in the absence of any pre-existing, conscious yearning for food – or even, as with some tantalising dessert, when we may actually be at the point of physical discomfort from the recent consumption of a large meal, and should presumably already be subject to the inhibitory actions of manifold homeostatic satiety signals. Similarly, eating may be disrupted and terminated by the appearance of more urgent, environmental stimuli. The primacy and potency of external stimuli to promote eating should not be considered as incidental to the physiological investigation of how food intake is controlled.

From an evolutionary perspective, eating may be considered to be an opportunistic activity (albeit a pre-eminent factor for survival), arguably developed to suit an ancestral environment of periods of plenty alternating with limited food availability (Speakman 2007). We might perhaps retain a weak homeostatic model, whereby specific physiological influences reflecting nutritional state can operate on behaviour – in the short- or long-term – to affect the relative priority of food seeking and consumption. Examples of these would include responses to enforced fasting, maintaining sufficient energy/nutrient levels for fecundity, or the necessity to consume essential amino acids to allow the synthesis of certain neurotransmitters. However, observing modern people, there is less than compelling support for the short-term regulation of energy intake relative to short-term energy expenditure. Certainly, there appears to be no strong case that excessive energy intake manages to counteract eating motivation sufficiently to prevent obesity. Thus, Levitsky has discussed the apparent "non-regulation" of human eating behaviour, and the fact that "in the vast literature on human feeding behaviour, there is very little evidence eating behaviour is tightly coupled to biological mechanisms involved in energy balance" (Levitsky 2005). Indeed, his research provides convincing demonstrations of how energetic manipulations fail to elicit compensatory behavioural responses, contrary to the predictions of a homeostatic system that couples feeding to body weight regulation (Levitsky 2002).

1.1 Eating for Survival

To consider the governance of eating solely in terms of the instantaneous maintenance of finite levels of key factors such as glucose availability or glycogen stores, or longer-term adjustments correlated with adiposity levels, is to avoid the realities of the ancestral environment that shaped the evolution of the motivational and behavioural processes controlling ingestion. In the sense used by Cannon (1932), homeostasis as "a condition which may vary, but which is relatively constant" may be easily applied to the demonstrable physiochemical processes that maintain the immediate availability of sufficient energy and nutrient levels to the cells of the body. But long-term survival requires both the persistence of sufficient reserves to support the regulation of the milieu interne, and the development of behavioural processes that will maintain those reserves in anticipation of probable – but unpredictable – shortfall. Hence, maintaining too fine a balance of energy reserves against expenditure renders an organism unnecessarily subject to the consequences of privation.

Meal-taking represents a punctuation between our other daily activities, its regularity – or otherwise – reflecting food availability, lifestyle and a host of individual and environmental factors. For our early ancestors, meal frequency must have been largely determined by the relative availability and nutritional quality of food. An opportunistic grazing and scavenging style would have consumed much time and energy in relatively impoverished pre-agrarian environments;

even the acquisition of more sustaining, meat-containing diets through hunting would have entailed considerable energy expenditure and irregular meals. Only in relatively recent times, with the development of social structures built around agriculture and industrialisation, did predictable food supplies enable a formalised ritual of regular daily meals. These were coordinated to match the demands of laborious, energy-costly lifestyles, the expediencies of food preparation and the cycles of working and social life. For modern people, the occurrence of the psychological and visceral components of hunger at pre-determined meal times merely reflects conditioned, cephalic responses to the imminent, expected arrival of food: a bodily adaptation for maximising the efficient absorption and utilisation of a predictable supply of nutrients, rather than – except under extremis – a response to actual energetic deficit. In a healthy individual, hunger will eventually subside if a mealtime passes but no food is eaten. This motivational lapse does not appear to be the signature of a truly homeostatic system, responding on an instantaneous basis to the demands of finely tuned energetic requirements. Individuals with similar physiques, activities and energy requirements may have very disparate styles of eating, in terms of the distribution and size of meals. In fact, eating patterns may be seen to be largely subject to habit and conditional influences (Gibson and Brunstrom 2007). Moreover, dietary styles and patterns of consumption can shift very quickly, depending on factors such as the availability and palatability of supplies, and these changes will occur in the absence of altered energetic demands.

Of course, hunger and voracious eating may be engendered in response to weight loss under extreme environmental conditions, such as starvation (as is the predominant mode in animal research), or by dramatic experimental manipulations that reduce the availability of cellular fuels (but which barely reflect physiological conditions). Under these circumstances, appetite arises from a real and urgent energy deficit – or some neuroendocrine representation that simulates that deficit – and consequently provokes the behaviours necessary to defend critical adipose mass and fuel availability. But so much (if not all) of our eating arises in the absence of any such urgency: seemingly defying the long-term defence of a critical level of adipose stores, and overcoming the apparent redundancy of the putative inhibitory controls of meal size and meal frequency.

The pre-potency of external food-related stimuli in determining the recrudescence of the desire to eat and the provocation of overindulgence, particularly apparent in modern societies, should not be considered accidental. We have clearly evolved systems that are acutely sensitive to environmental signals and which, under modern conditions, allow us to feel hungry when replete, overconsume in response to variety, and be particularly desirous of high calorie, sweet, fatty foods (Yeomans 2007). As many of us know to our cost, regular consumption of the latter diet will easily produce substantial weight gain, clearly provoking deviations from hypothetical, finely gauged, homeostatic set-points – or even less-finite "settling" points – for adiposity or body weight. And, acutely, an individual snacking on relatively small quantities of junk foods can easily and quickly ingest calories far in excess of any immediate need – and do so long before any inhibitory, satiating, regulatory gut signals might be invoked. The extensive literature on sensory-specific

satiety also indicates that subjective feelings of being replete can be overridden by the simple presentation of a new, palatable food (Rolls 1986).

Authors who view homeostasis more flexibly argue that feeding is not necessarily tied to the authority of negative feedback signals and is, in fact, not a regulated variable in the traditional homeostatic sense. Rather, to quote Woods and Ramsay, "eating is a behaviour that functions to *stabilise* adiposity over long intervals" (Woods and Ramsay 2007, p. 393). It is possible to further question the notion of even approximate long-term stabilisation of adiposity, at least in the sense that food intake might decline once a certain, surplus, level of fat storage has been achieved. Judging by the increasingly common examples of morbid obesity, any regulatory influences that might be predicated to counter "excess" fat accumulation may be considered ineffectual. Is this ineffectuality brought about by the extreme "obesogenic" environment in which we live, and a failure of normal feedback mechanisms (implicit, for example, in the notions of leptin resistance or leptin insufficiency syndrome; Kalra 2008) – or is there a more straightforward explanation?

1.2 Gluttony and Externality

Given the fact of obesity, and that – self-evidently – the obese do not appear to display significant automatic regulatory changes in eating behaviour to sufficiently counter the accrual of adipose stores, parsimony would indicate that there are simpler accounts. More specifically, we can argue that evolution has provided us with a "greedy" phenotype. The premise here is that, in all but a very few pathological instances, the obesity epidemic that confronts us reflects the fact that we are biologically programmed for gluttony. While the modern environment now provides us greater opportunity to indulge in the pleasure from varied, energy-dense foods, it is reasonable to assume that the underlying neural mechanisms mediating these cravings and delights represent a deep-time relationship between our world and the neural mechanisms that reinforce behaviours that lead to food acquisition (Sullivan et al. 2008). Eating is absolutely fundamental to survival, and mechanisms that encourage us to eat in order to maintain buffering reserves of fuel might therefore be considered essential. In reward systems, natural selection has seemingly given us the necessary apparatus to ensure that we respond positively to opportunities to acquire nutrients and supplement our fuel reserves. Some argue that our modern susceptibility to greed is more akin to the development of addictions subsumed by the same incentive and reward pathways that can drive food consumption (Lowe and Butryn 2007; Acosta et al. 2008). But as the hedonic processes that underlie the anticipation or experience of pleasure and satisfaction are such profound and fundamental components of general motivational systems, can we reasonably argue that efficient feeding control mechanisms could have evolved without their integration (Figlewicz Latteman et al. 2007)?

Should we not question, therefore, the notion that evolutionary pressures would have given us multiple mechanisms to prevent the storage of excess

calories, or actively redress accidental overconsumption, when the most pertinent challenge to survival was the lack of food, not its surfeit? If our opportunistic susceptibility to overconsumption does constitute a component of a regulatory regime, then it may most easily be regarded as one that increases the likelihood that future energetic demands will be met – to support the truly homeostatic, moment-to-moment maintenance of cellular fuel availability. Overeating then is not counter-regulatory, but represents the most effective behavioural mechanism for ensuring that energy input can match future requirements. The ease with which appetite can be engendered, the hedonic processes that promote overconsumption, and the efficiency and remarkable capacity of fuel storage in adipose tissues all provide evidence that the ready development of obesity reflects the evolution of highly effective, persistent mechanisms to ensure positive energy balance. From this perspective, the development of cuisines and eating styles, and the overwhelming variety of foods provided through the industrialisation of food production are the consequence of our proclivity for enjoyment of tastes and flavours. Modern food manufacturers only exploit that proclivity, reflecting centuries of use of salt, herbs, spices and sugars invoked to overcome the bland monotony of our staple diets.

As described by Cannon in his *Wisdom of the Body* (1932), ". . . the person beset by an appetite is tempted, not driven, to action – he seeks satisfaction, not relief." He also observed, however, that ". . . the two motivating agencies – the pang and the pleasure" may not always be separable. Lowe has coined the term "hedonic hunger" to describe eating arising from a pre-occupation with "thoughts, feelings and urges about food in the absence of any short- or long-term energy deficit" (Lowe and Butryn 2007). But whatever the descriptor, the desire for food in the absence of energy deficit, and in particular the craving and enjoyment of the most palatable, highly calorific foods is a fundamental aspect of eating motivation – and may be viewed as a quintessential component of normal, non-pathological mechanisms that promote survival through the maintenance of positive energy balance. Modern overindulgence is merely a reflection of the indulgent nature of motivational processes, and the critical importance of hedonic factors in energising and guiding behaviour.

Notwithstanding the preceding arguments on the validity of homeostatic models in the control of eating, the contribution of the processes that give rise to appetite in overconsumption, overweight and obesity is all too evident. The overshadowing of appetitive processes by the overwhelming study of satiety mechanisms and lipostatic negative feedback is therefore clearly deserving of some redress. A greater knowledge of the neurochemical factors underlying the urge to eat, food anticipation, or the pleasure derived from eating will have crucial implications for understanding general motivational processes, as well as having far-reaching clinical implications. To this end, we now turn our discussion to the endogenous cannabinoids, and address the evidence for their role in the normal biopsychological mechanisms that create appetite and stimulate eating. More specifically, the following sections will address their contribution to incentive processes and the hedonic evaluation of food stimuli – or what Berridge (2000) has respectively described as "wanting" and "liking".

2 Endocannabinoids in Food Craving, Anticipation and Palatability

The appetite-stimulating action of the cannabis plant (*Cannabis sativa*) and its extracts has been documented for many centuries (Abel 1971; Kirkham and Williams 2001a). This effect is attributable to Δ^9-tetrahydrocannabinol (THC), one of a large group of "cannabinoid" molecules characterised in the 1960s (Gaoni and Mechoulam 1971). As described in other chapters, the actions of these phytocannabinoids in people were explained by the discovery of cannabinoid (CB) receptors and their endogenous ligands, the "endocannabinoids" (Pertwee 2008). The psychoactive effects of THC are thus explained by its ability to mimic the neural actions of the endogenous agonists at their receptors.

2.1 THC Hyperphagia

The earliest references to the hyperphagic actions of cannabis are found in the ancient Hindu writings of the *Rajanirghanta* (1,700 BP). Surprisingly, however, very little empirical research has been conducted in humans to clarify the plant's specific actions on appetite. The same limitation applies to exploration of the actions of THC or other phytocannabinoids, in people or in animal models. As a consequence of governmental paranoia about the use of these compounds, theorising about the psychological and behavioural activity of the cannabinoids has been overly reliant on anecdotal accounts from cannabis users and a limited number of, often poorly designed, animal studies. Even with the recent enthusiasm for endocannabinoid systems as therapeutic targets for obesity, metabolic syndrome and cardiovascular disease, relatively little work has been conducted to explore the critical actions of cannabinoid receptor agonists on appetite. Nevertheless, recent years have produced some important insights into the actions of THC and the endocannabinoids (Kirkham 2005). Here, we shall discuss the principal findings that guide us to the likely mechanisms whereby CB_1-specific drugs affect eating motivation and the role for endocannabinoid systems in the normal control of ingestive behaviour.

Much early research failed to obtain THC hyperphagia in rats, or reported only relatively weak effects. However, by adopting a pre-feed paradigm in which the rats were thoroughly sated before drug administration, we found that oral THC administration would reliably stimulate nocturnal feeding (Williams et al. 1998). We also demonstrated that THC hyperphagia is mediated by CB_1 receptors, being attenuated by rimonabant (SR141716), the selective CB_1 receptor antagonist, but not by SR144258, a selective antagonist of the CB_2 receptor (Williams and Kirkham 2002a).

One aspect of our data that deserves particular emphasis is the magnitude of the overconsumption induced by THC. Our animals were thoroughly satiated, having

already eaten a quantity of a palatable wet mash diet equivalent in weight to their normal daily food intake. The substantial intake that followed THC treatment thus signifies that stimulation of CB1 receptors can provoke an exceptionally powerful stimulus to eat (and, arguably, overriding any supposed inhibitory feedback that arises from meal consumption). Moreover, the extent of THC-induced overeating easily matched that induced by central administration of neuropeptide Y, commonly regarded as one of the most potent orexigens (Chee and Colmers 2008). The remarkable hyperphagic potency of THC, and its mediation by CB_1 receptors, thus provided strong support for involvement of the endocannabinoid systems in the normal control of feeding.

2.2 Orexigenic Actions of the Endocannabinoids

This possibility necessitated the demonstration that the endocannabinoids, themselves, will exert hyperphagic actions. Using our pre-feed design, we found that systemic anandamide (AEA) administration significantly increased food intake (Williams and Kirkham 1999), although the degree of overeating was modest compared with the effects of THC. Moreover, AEA hyperphagia was blocked by rimonabant pre-treatment – but not by a CB_2 antagonist, again indicating that the overeating was specifically mediated by CB1 receptors. Subsequently, the feeding effects of systemic AEA were replicated in mice (Hao et al. 2000) and rats (Gómez et al. 2002). Later experiments also confirmed that 2AG can exert a potent stimulus to eat (Kirkham et al. 2002). More recently, a third endogenous CB_1 agonist, noladin ether, has been shown to increase food intake in food-restricted mice (Avraham et al. 2005) and free-feeding rats (Rogers and Kirkham, unpublished results). Remarkably, there has been very little subsequent investigation of the orexigenic actions of these compounds (with only five publications in a decade directly exploring their feeding effects).

The first published demonstration of a central site of action of endocannabinoids was by Jamshidi and Taylor (2001), who found that modest, rimonabant-reversible hyperphagia could be obtained by direct injection of AEA into the ventromedial hypothalamus (VMH). Subsequently, we demonstrated (so far uniquely) that administration of 2AG into the shell sub-region of the nucleus accumbens (AcbSh) exerts a potent, CB_1-selective, hyperphagic action (Kirkham et al. 2002). Similar effects have also been obtained with intra-accumbens AEA treatments (Mahler et al. 2007; Soria-Gomez et al. 2007). As we shall discuss below, the sensitivity of the AcbSh as a locus for endocannabinoid-induced feeding is critical to current hypotheses concerning their role in eating motivation. However other brain regions are also implicated in endocannabinoid effects. We have shown increases in food intake after AEA or 2AG administration into the lateral (LH) and paraventricular (PVN) nuclei of the hypothalamus (Kirkham and Williams 2001c), while others have obtained reliable hyperphagia following lateral ventricular administration of THC

(Koch and Matthews 2001). Circuits located in feeding-relevant hindbrain areas, such as the dorsal motor nucleus of the vagus (DMV) and the nucleus tractus solitarius (NTS), may also be subject to cannabinoid regulation, with the synthetic CB_1 agonist CP55940 reported to enhance milk intake when administered into the fourth ventricle (Miller et al. 2004).

An essential corollary to the agonist data, of course, is the extensive investigations of the feeding effects of CB_1 antagonists. Critically, these drugs have universally been found to suppress food intake (although debate persists about the actual specificity of the suppression to direct interruption of eating motivation (Tallett et al. 2007a, b). An anorectic action of rimonabant was first reported by Arnone and colleagues, providing evidence for tonic endocannabinoid activity in feeding-related systems (Arnone et al. 1997). Reliable anorectic actions of rimonabant, or its analogues (e.g. AM281, AM251, surinabant), have since been reported, following systemic or central administration in satiated or food-deprived animals, and after acute or chronic treatments (e.g. Colombo et al. 1998; Shearman et al. 2003; Werner and Koch 2003; Chen et al. 2004; Rutkowska 2004; Wiley et al. 2005; Rinaldi-Carmona et al. 2004). Several studies have also reported anorectic effects of CB_1 blockade in dietary (Hildebrandt et al. 2003; Ravinet Trillou et al. 2003) and genetic models of obesity, often with greater effects than in lean littermates (e.g. Vickers et al. 2003; Zhou and Shearman 2004).

3 Behavioural Characterization of Cannabinoid Hyperphagia: The Reward Hypothesis

These findings provide evidence for some role of endocannabinoids in feeding. However, increases or decreases in food intake alone tell us little about what aspects of eating motivation are altered to affect behavioural change. Indeed, given the wide pharmacological spectrum of cannabinoids, it is essential to demonstrate that these changes follow from a natural adjustment to feeding motivation, rather than some non-specific action. (Until recently, the behavioural pharmacology of cannabinoids was largely the study of high, non-selective, frankly sedative doses of agonists – and for many years, anorectic actions of THC were the most frequently reported in feeding experiments, leading to suggestions of "species differences" between animals and rodents to explain the consequences of inappropriate choice of dose.)

An hypothesis that gained early currency – on the basis of the anecdotal accounts of cannabis users described earlier (Tart 1970) – was that endocannabinoids may provoke overconsumption by amplifying the orosensory reward, or palatability, of foods (Arnone et al. 1997). Initially, this notion was supported by studies that were interpreted as indicating a more marked susceptibility of palatable foods to the stimulant effects of THC. Arnone and colleagues reported that in rats and marmosets rimonabant selectively attenuated the consumption of palatable ingesta

(Arnone et al. 1997; Simiand et al. 1998), while having little effect on intake of bland food. These workers suggested that such preferential effects of CB_1 blockade indicated important tonic endocannabinoid activity underlying food reward. Thus, cannabinoid agonists might increase food intake by rendering foods more palatable, while antagonists might tend to diminish the hedonic value of foods, and so reduce consumption. As we shall see, there are data that support this notion but the specifics are a little more complex.

With these antagonist data in mind, we began a series of studies to directly address the cannabinoid-reward hypothesis. Initially, we measured the effects of rimonabant on sucrose sham-feeding to explore drug effects on ingestion maintained entirely by palatability. In this model, rats are surgically implanted with a chronic gastric fistula and ingest palatable sucrose solutions, which are recovered within seconds directly from the stomach – thus avoiding the normal inhibitory consequences of gastric distension or of nutrient entry into the duodenum. Sham-feeding rats will consume many times the amount of sucrose solution ingested by intact, normally feeding rats. Moreover, the rate of sham-feeding is proportional to the palatability of the sucrose: the sweeter the solution, the more avid the ingestive response. Consequently, the model is particularly sensitive to manipulations that affect orosensory reward.

We hypothesised that, if endocannabinoids directly mediate food reward, sham-feeding should be disrupted by CB1 blockade. More specifically, we anticipated that suppression of sham-feeding by rimonabant would produce changes in behaviour which resemble the effect of diluting the sucrose solution (Kirkham 1990; Kirkham and Cooper 1988). A precedent for such an effect comes from our previous work with opioid antagonists. Opioids are heavily implicated in orosensory reward (see Sect. 4, below), and opioid receptor antagonists reduce sucrose sham-feeding in a manner which exactly mimics the changes in ingestion produced by mere sucrose dilution, and hence the palatability, of the sucrose. In addition, attenuation of sham-feeding by opioid antagonists can be reversed by increasing the palatability of the sucrose during a sham-feeding test (Kirkham and Cooper 1988; Kirkham 1990; Leventhal et al. 1995).

Contrary to our expectations, rimonabant failed to affect sucrose sham-feeding (Kirkham and Williams 2001b). Even doses of the drug ten times greater than those required to reverse cannabinoid-induced feeding (Williams and Kirkham 1999), or doses which suppress sucrose drinking in intact animals (Arnone et al. 1997), were ineffective. This failure argued against significant endogenous cannabinoid activity within the pathways that *maintain* sucrose ingestion. In other words, endocannabinoids did not seem to be primarily involved in food reward during ingestion, and might not be considered crucial to the pleasure derived from orosensory characteristics of food ("liking"); we shall return to this issue later. However, while our data did not support endocannabinoid mediation of the consummatory aspects of food reward, they did not preclude their involvement in some other aspect of feeding-related, emotional processes. For example, endocannabinoids could still be associated with appetitive, or incentive, aspects of feeding motivation, related to the anticipation of food or the desire to eat ("wanting").

3.1 *Endocannabinoids and "Wanting": Primary Motivational Actions*

Evidence for such a role of endocannabinoids comes from studies using progressive ratio paradigms as a model of craving. In these, rats are required to complete a progressively greater number of responses to obtain successive rewards of small amounts of liquid or food (typically sucrose solutions or pellets). The ratio at which animals cease to respond (the "break-point") is taken as an index of the degree of craving. Gallate and McGregor (1999) found that rimonabant dose-dependently reduced break-point, while after administration of the CB_1 agonist CP55,940 rats would work harder to obtain reinforcement, resulting in increased break-points (Gallate et al. 1999). THC will also produce rimonabant-reversible increases in responding for food (Solinas and Goldberg 2005). Recently, we have shown that systemic administration of a hyperphagic dose of noladin ether will also increase break-point (Rogers and Kirkham, unpublished data). These effects, which were reversed by the CB_1 antagonist surinabant, strongly implicate endocannabinoid systems in the processes underlying the motivation to obtain palatable ingesta. In line with these studies are reports that CB_1 knockout mice have reduced sensitivity to the motivating properties of food. Thus, $CB_1^{-/-}$ animals show lower levels of responding for sweet food and exhibit lower break-points than wild-type mice (Sanchis-Segura et al. 2004). Interestingly, however, antagonist effects on operant responding are also evident with more bland foods (Freedland et al. 2000; Pério et al. 2001), and rimonabant has proved equi-anorectic when tested with foods of differing macronutrient content and intrinsic palatability (Verty et al. 2004a, b). This generality of effect suggests that endocannabinoids modulate appetitive processes per se, to provide a general gain in the incentive value of all food (and is, incidentally, therefore supportive of the notion that common incentive processes are engaged by external food quality or internal deficit stimuli).

We have obtained further data to support endocannabinoid involvement in incentive motivation. Using an open-field apparatus, we observed the behaviour of pre-satiated rats following administration of THC or AEA. Under control conditions, rats generally displayed little motivation to eat: when eating did occur, it did so only after many minutes engaged in exploratory behaviours. By contrast, both exogenous and endogenous cannabinoid treatments stimulated feeding, dramatically reducing the latency to eat. Crucially, once initiated, the subsequent pattern of feeding behaviour displayed by THC- and AEA-treated rats in the open field was similar to that of untreated rats feeding freely in their home cages (Williams and Kirkham 2002b). These data are again compatible with an action of cannabinoids to increase the incentive value or salience of the food, and importantly, indicate that cannabinoids provoke feeding through adjustments to natural feeding control mechanisms.

We have also observed these effects using a more naturalistic, continuous meal pattern monitoring technique, where moment-to-moment feeding is monitored in

animals' home cages. Under these circumstances, the latency to the first meal of pre-satiated or free-feeding rats is consistently reduced after central AEA and 2AG administration, often by more than an hour compared with the control condition (Kirkham and Williams 2001b). Indeed, in all experiments where we have measured the temporal distribution of feeding episodes, increases in total food intake over a finite test interval derive principally from the advance of eating onset. Together with the break-point data, such findings again imply that stimulation of CB_1 receptors increases the salience of food and hence the motivation to eat. We thus begin to see the development of a model which links endocannabinoids directly to the processes that lead to the initiation of feeding. Recalling the lack of effect of cannabinoid receptor blockade on the intra-meal palatability factors that maintain sham-feeding, most data support specific endocannabinoid involvement in the motivational processes that culminate in meal taking. The combination of CB_1 ligand effects on feeding microstructure and the motivation to work for food thus strongly implicate endocannabinoids in "wanting" processes.

In effect, the stimulatory actions of the cannabinoids on eating resemble the changes that occur with food deprivation, since both increase food salience, reduce eating latency and promote short-term hyperphagia (Marín Bivens et al. 1998). We might therefore expect to see activation of endocannabinoid systems under conditions where the incentive value of food is naturally raised. Some support for this comes from our finding that regional brain levels of AEA and 2AG increase after fasting (Kirkham et al. 2002), and that the anorectic action of rimonabant is significantly enhanced in food-deprived rats compared to non-deprived animals (Kirkham and Williams 2001b; Osei-Hyiamen et al. 2005). By contrast, levels of AEA or 2AG in animals re-feeding after fasting, or in rats eating a palatable diet, did not show any increase – again indicating only an indirect role for endocannabinoids in the maintenance of feeding once it has been initiated. It remains to be seen whether direct measures of brain endocannabinoids will support their activation by external food stimuli of high valence (such as the presence, or promise, of highly palatable foods).

In addition to the animal literature, there are some indications from recent human studies with a CB_1 agonist and antagonist that provide support for the role of endocannabinoids in appetitive processes. For example, we explored the acute effects of oro-mucosally administered THC on eating in healthy volunteers. In addition to a significant increase of energy intake, we found that one of the principal effects of the drug was a marked amplification of the normal pre-lunch rise in subjective hunger scores. Compared to placebo, hunger was seen to increase far earlier in the morning after THC, with significantly higher pre-prandial peak levels. This effect was associated with an earlier onset and increased incidence of snacking (Townson and Kirkham, unpublished results). Complementary data from CB_1 blockade are provided by a clinical trial with rimonabant. Over the course of 3 months of daily dosing, patients' appetite ratings were periodically assessed by laboratory test meals and home questionnaires (Blundell et al. 2006). Critically, rimonabant was found to lower hunger and desire to eat at the start of the meal, while having no effect on post-meal ratings of hunger or fullness. Significant reductions in hunger and the frequency and

strength of food cravings were also detected over the course of the study, while rimonabant had no reliable effect on ratings of food pleasantness. These agonist and antagonist effects provide the most direct indications so far that CB_1 receptor ligands can specifically modulate "wanting" aspects of eating motivation, and are clearly worthy of further investigation.

Importantly, the apparent involvement of endocannabinoids in appetitive aspects of feeding is compatible with the known effects of CB_1 agonists and antagonists on mesolimbic dopaminergic neurons, arising in the ventral tegmental area (VTA) and projecting to the nucleus accumbens. This pathway is linked to incentive motivation, and the generation of emotional arousal and behavioural activation in response to stimuli that predict reward (Berridge 2007). Food stimuli cause dopamine release in the nucleus accumbens, especially after deprivation, or if the food is novel or palatable. There is growing support for an influence of endocannabinoids on mesolimbic dopaminergic activity. For example, CB_1 receptors are co-localised, and interact, with dopamine D1 and D2 receptors (Pickel et al. 2006; Meschler and Howlett 2001). Moreover, both THC and AEA have been reported to stimulate dopamine release in the nucleus accumbens (Gardner and Vorel 1998; Solinas et al. 2006). And Verty et al. (2004b) have shown that a behaviourally silent dose of the D1 antagonist SCH23390 prevents THC hyperphagia. It is therefore noteworthy that the accumbens dopamine release that is provoked by presentation of a novel, palatable food is blocked by rimonabant (Melis et al. 2007), suggesting that endocannabinoids normally facilitate the mesolimbic dopamine signalling that can give rise to appetite. This may occur in part through a disinhibitory action of endocannabinoids, whereby stimulation of accumbens CB_1 receptors suppresses glutaminergic activity and inhibits GABAergic medium spiny neurons that normally constrain the firing of VTA dopamine neurons (van der Stelt and Di Marzo 2003). Riegel and Lupica (2004) have suggested that, through independent pre- and post-synaptic mechanisms, endocannabinoids and dopamine in the VTA-accumbens pathways may co-operate to dynamically fine-tune the activity of incentive pathways in response to salient environmental stimuli. Endocannabinoids may thus be essential for the orientation to motivationally significant stimuli, the attribution of incentive salience and reward anticipation, and the elicitation of appropriate behavioural responses such as food seeking and eating initiation.

One might expect that endogenously entrained eating patterns (and perhaps also those arising from conditioned hunger) might show some linkage to changes in endocannabinoid activity. So far, there is little evidence for such specific associations, but circadian rhythms in endocannabinoid levels have been detected in the brains of rats. For example, Valenti et al. (2004) demonstrated clear diurnal variations, albeit with differential changes evident for AEA and 2AG. Thus, AEA levels were highest in the dark phase, when most eating occurs, while 2AG exhibited peak levels during daylight. These opposing variations (which may reflect changes in synthesis or metabolism of endocannabinoids) indicate the urgent necessity to explore the individual roles of each endocannabinoid in behavioural processes. It is also a priority to explore such changes with higher temporal resolution, to more precisely match behaviour to endocannabinoid activity.

3.2 *Endocannabinoids and "Liking": Secondary Motivational Actions*

The above findings link endocannabinoids to appetitive processes in feeding. However, despite our sham-feeding data, their role may also be extended to involvement in food "liking". As we have noted, such a role is clearly suggested by the anecdotal reports of cannabis users (Tart 1970), and recent animal studies have provided support for a specific interaction of endocannabinoids with food palatability.

In early reports, CB_1 receptor blockade was reported to preferentially attenuate the intake of palatable, sweet foods (Arnone et al. 1997; Simiand et al. 1998) and reduce operant responding for sweet food (Pério et al. 2001); while CB_1 knockout mice consume less sucrose than wild types (Poncelet et al. 2003). We have observed that central injection of endocannabinoids can induce modest increases in meal duration and, consequently, meal size. Although these effects are weak in relation to the effects on the latency noted above, they are compatible with an action of the agonists to enhance food palatability (i.e. eating may persist for longer as a consequence of increased food palatability/liking). More definitively, we examined the actions of CB_1 receptor ligands on the microstructure of sucrose drinking and found that alterations to licking behaviour induced by THC, AEA and 2AG are reminiscent of those observed in drug-free animals drinking more palatable solutions (Higgs et al. 2003). Conversely, rimonabant alters drinking in a way that is consistent with a reduction in the palatability of the sucrose solution. Additionally, $CB_1^{-/-}$ mice are less responsive to sweet taste, consistently drinking less of a range of sucrose solutions than the wild type (Sanchis-Segura et al. 2004). Moreover, these differences are abolished when sucrose solutions are adulterated with bitter quinine, indicating that they arise from differences in the rewarding consequences of palatable ingesta rather than from any sensory impairment.

Further support for an endocannabinoid role in palatability is provided by experiments employing a taste reactivity paradigm to gauge hedonic reactions to flavours by monitoring innate ingestive responses. Thus, Jarret and colleagues have reported that: THC produces rimonabant-reversible increases in ingestive "liking" responses to intra-oral delivery of sucrose solutions; THC reduces the rejection of a quinine solution – an effect blocked by the CB_1 antagonist AM251; AM251 alone both decreases hedonic reactions to sucrose, and increases aversive reactions to quinine solutions (Jarrett et al. 2005, 2007). These important findings thus support the hypothesis that endocannabinoid activity can contribute significantly to the hedonic evaluation of ingesta, and that CB_1 stimulation or blockade/deletion can respectively render food more or less pleasurable. That these effects on liking responses can be obtained under conditions where tastants are delivered directly into the mouth, independently of any volition on the part of the animal (and presumably also of activation of incentive mechanisms), suggest that endocannabinoid modulation of liking can occur separately from their effects on wanting processes.

Consistent with this notion is the fact that key components of the neural mechanisms underlying food palatability lie within the AcbSh (Stratford 2007) and, as already noted, 2AG administered into this site produces a profound hyperphagic response (Kirkham et al. 2002). AEA is also an effective orexigen in this region, as are agents that increase endocannabinoid levels by blocking their enzymatic breakdown or reuptake (Soria-Gomez et al. 2007). Moreover, Harrold and colleagues (2002) showed that accumbens CB_1 receptors are down-regulated in rats that overconsume palatable food supplements. This latter effect is consistent with increased activation of these receptors by endocannabinoids, and again suggests that they mediate the hedonic evaluation of palatable foods. That accumbens endocannabinoids can indeed enhance the hedonic impact of sweet taste is directly supported by the finding that intra-AcbSh administration of AEA specifically increases the number of positive ingestive responses to intra-oral infusions of sweet solutions in taste reactivity tests (Mahler et al. 2007).

4 Endocannabinoid–Opioid Interactions in Eating Motivation

Opioid receptor agonists and antagonists respectively increase or reduce food intake, and these effects have been shown to involve changes in the hedonic evaluation of foods (Cooper and Kirkham 1993; Bodnar 2004). For example, in people, opioid antagonists are reported to reduce the perceived palatability of previously preferred foods and fluids (Drewnowski et al. 1992; Yeomans and Gray 1996). There is now convincing evidence for interactions between endocannabinoids and opioids in relation to feeding, and that cannabinoids modulate the motivation to ingest via actions on both cannabinoid and opioid systems. For example, the hyperphagic action of THC is significantly attenuated by sub-anorectic doses of naloxone (Williams and Kirkham 2002a). Importantly, the facilitatory effects of a CB_1 agonist on responding for palatable solutions are reversed by both a CB_1 antagonist and naloxone (Gallate and McGregor 1999). Moreover, low doses of rimonabant and opioid antagonists that are behaviourally inactive when administered singly, combine synergistically to produce a profound anorectic action when co-administered – far outweighing the suppressive effects of even large doses of either drug given separately (Kirkham and Williams 2001b; Chen et al. 2004).

Given the established ability of opioid antagonists to reduce the hedonic evaluation of foods and to reverse CB_1 agonist-stimulated ingestion, the marked anorexia induced by combined CB_1 and opioid receptor blockade suggests that endocannabinoids also contribute to orosensory reward through the activation of opioid processes. Mesolimbic dopamine neurons synapse with accumbens enkephalinergic neurons that are critical to the expression of reward-related behaviours (Solinas et al. 2008), and there is ultrastructural evidence that cannabinoid–opioid interactions are mediated by activation of CB_1 and -opioid receptors within the same, or synaptically linked, reward-relevant neurons in the AcbSh (Pickel et al. 2004). Moreover, systemic administration of THC has been shown to stimulate β-endorphin release in the

accumbens – a phenomenon that has been previously linked to consumption of palatable foods (Solinas et al. 2004). Importantly, as with AEA, administration of morphine into the AcbSh increases the liking of sweet solutions in taste reactivity tests, and it is notable that there is a very close correspondence between the opioid- and cannabinoid-sensitive sites (Pecina and Berridge 2000; Mahler et al. 2007).

Independent manipulations of endocannabinoid or opioid processes produce distinct behavioural/motivational consequences. As we have seen, cannabinoids principally reduce eating latency without dramatic effects on meal duration (i.e. primarily actions on appetitive processes); while opioids typically do not alter eating latency but extend meal duration by enhancing palatability (i.e. they primarily exert actions on consummatory processes). However, a closer temporal relationship, or merging, of direct cannabinoid influences on appetitive motivation and their secondary facilitation of opioid consummatory components may be revealed by a study by Solinas and Goldberg (2005). They reported that THC and morphine dose-dependently increased break-points for food reinforcement, while rimonabant and naloxone dose-dependently decreased break-points. Confirming our findings in free-feeding rats, THC effects on break-point were blocked by naloxone. But more surprisingly, morphine's effects were also blocked by rimonabant.

These data support interactive cannabinoid–opioid mediation of eating motivation, potentially linking the two systems in the reciprocal modulation of hedonic factors that control appetitive and consummatory behaviour. Certainly, the known effects of exogenously administered cannabinoids to promote activation (or disinhibition) of mesolimbic incentive circuits and activate nucleus accumbens circuits involved in hedonic evaluation could account for the heightened intensity of food craving and enhanced appreciation of food reported by cannabis users. It would therefore be extremely instructive to more fully explore the actions of THC or CB_1 antagonists on the subjective experience of hunger and appetite measures in people. The emerging evidence indicates that – as one might expect from personal subjective experience of food's attractiveness – the neurochemical systems that mediate the anticipation or actual experience of the pleasure derived from eating may interact in complex ways. However, it is not too radical to consider that expectation of food (or "hedonic hunger") should incorporate some neurophysiological representation of the prospective delights of consumption. The relationship between endocannabinoids and opioids in modulating activity of incentive-reward circuits may be key to this – reinforcing the primacy of pleasure (or its anticipation) as a key factor in the normal generation of eating motivation.

5 Endocannabinoids and Interactions with Other Orexigens

As might be expected, functional interactions between endocannabinoids and systems implicated in feeding are not restricted to the opioids. Indeed, there is a growing body of evidence for endocannabinoid interactions with a wide range of other factors that are currently implicated in the control of appetite, including

putative orexigens (Cota et al. 2003; Matias et al. 2008). So far, much of this evidence is based on histological or in vitro studies, and research is heavily weighted to interactions with feeding-inhibitory agents; the few behavioural studies relevant to appetite-stimulation are outlined below.

In the first description of rimonabant's anorectic action, Arnone et al. (1997) also reported that the drug could block the ability of neuropeptide Y (NPY) to increase the intake of a palatable sucrose solution. Despite this finding, the considerable potency of NPY as an orexigen, and its key interactions with other feeding-related hypothalamic neuropeptides, subsequent analysis of potentially important relationships between this peptide and the endocannabinoids has been limited. Further investigation is warranted however, since Poncelet et al. (2003) reported that rimonabant can prevent NPY hyperphagia, and that the peptide's ability to stimulate feeding is abolished in $CB_1^{-/-}$ mice; although rimonabant is as effective in reducing food intake in NPY knockout mice as in wild-type (Di Marzo et al. 2001).

Very little is presently known about the interaction of the endocannabinoids with other neuropeptides implicated in stimulating food intake. However, Cota and colleagues (2003) have shown co-localization in the PVN of the CB_1 receptor with the orexigenic melanin-concentrating hormone (MCH). Importantly, the very potent and naturalistic hyperphagic actions of centrally administered MCH are sensitive to cannabinoid receptor blockade. Thus, we have found that the eating induced by intra-ventricular MCH is prevented by pre-treatment with behaviourally silent doses of the CB_1 antagonists rimonabant and surinabant (Cooper, Rogers, and Kirkham; unpublished data).

Evidence has also been obtained for significant interactions between endocannabinoids and the orexigenic peptide, and putative hunger signal, ghrelin. Ghrelin is a gut–brain peptide that is synthesised in gastric tissues and the hypothalamus. Circulating levels of gastric ghrelin are closely correlated with meal taking: rising in advance of meals and declining rapidly post-prandially. We found that feeding stimulated by intrahypothalamic (PVN) ghrelin injection is blocked by pre-treatment with sub-anorectic doses of rimonabant, suggesting that expression of ghrelin hyperphagia is dependent on an intact endocannabinoid system (Tucci et al. 2004). Additionally, plasma levels of ghrelin are suppressed by systemic rimonabant treatment (Cani et al. 2004). Importantly, ghrelin hyperphagia is abolished in CB_1 knockout mice, indicating that an intact cannabinoid signalling pathway is required for the peptide to exert its effects on food intake – possibly through the involvement of hypothalamic AMP-activated protein kinase, a key enzyme in the regulation of metabolism (Kola et al. 2008).

6 Conclusion

The preceding discussion has questioned whether homeostatic models of food intake control can adequately account for the actual nature of human appetite and eating behaviour, and particularly their susceptibility to external influences. It has

been argued that overconsumption provoked by the anticipated and actual pleasures to be derived from food does not represent an aberrational, counter-regulatory phenomenon. Instead, such "hedonic" eating should be considered as a core component of specialised motivational mechanisms that have evolved to engage us in food-seeking, ensure consumption of the foods most likely to sustain us, and thereby to provide long-term energetic security. Current problems of obesity may in fact be seen to arise from the sheer effectiveness of the hedonic processes guiding appetitive and consummatory components of eating. Traditionally, motivation and emotion have been regarded as being intimately related – with desire, pleasure and satisfaction acting as guiding principles in the arousal and direction of behaviour. To view intake control in the absence of these factors, and solely in terms of instantaneous input:output calculations about energy balance regulation, denies the evidence of our own experience and the record of centuries. The contribution of hedonic factors in determining food intake needs to be more fully acknowledged by physiologists and neuroscientists, and must become the focus of a more concerted effort to determine their neurochemical underpinnings. The well-documented actions of cannabis on appetite must now be integrated with rigorous, detailed investigations in humans of the motivational and emotional actions of endocannabinoid receptor agonists and antagonists. Building on what we have seen in the animal data, the availability of selective CB_1 ligands provides us with an important opportunity to further our understanding of the neurochemical controls of eating behaviour in people, and particularly of the neural underpinnings of the psychological experience of hunger, food craving, eating pleasure and satisfaction.

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