

Cannabinoids and appetite: Food craving and food pleasure

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Abstract

The ability of *Cannabis sativa* to promote eating has been documented for many centuries, with the drug reported by its users to promote strong cravings for, and an intensification of the sensory and hedonic properties of food. These effects are now known to result from the actions of cannabinoid molecules at specific cannabinoid receptor sites within the brain, and to reflect the physiological role of their natural ligands, the endocannabinoids, in the control of appetite. Recent developments in the biochemistry and pharmacology of endocannabinoid systems have generated convincing evidence from animal models for a normal role of endocannabinoids in the control of eating motivation. The availability of specific cannabinoid receptor agonists and antagonists raises the possibility of improved therapies for disorders of eating and body weight: not only in the suppression of appetite to counter our susceptibility to the over-consumption of highly pleasurable and energy-dense foods; but also in the treatment of conditions that involve reduced appetite and weight loss. Here, we outline some of the findings of the past decade that link endocannabinoid function appetite control, and the possible clinical applications of that knowledge.

Hyperphagic actions of the endocannabinoids

The earliest references to the hyperphagic actions of cannabis are found in the ancient Hindu *Rajaninghanta* (Chopra & Chopra, 1957), and in pharmacopoeia across the centuries. Amongst cannabis users, these effects are well known: the induction of voracious appetites, cravings, and the enhanced enjoyment of food, colloquially referred to as the ‘munchies’. Unfortunately, little empirical research has been conducted in humans to clarify the drug’s specific actions on appetite. Consequently, theorizing about the psychological and behavioural activity of the cannabinoids has been overly-reliant on anecdotal accounts from cannabis users. 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 the psychological influences on appetite. Nevertheless, recent years have produced some important insights – using animal models – into the actions of cannabis (and specifically of one of its psychoactive constituents, Δ -9-THC) and the endocannabinoids on eating motivation (Kirkham, 2005). The principal findings supporting a role for the endocannabinoid system and the control of appetite are briefly reviewed here.

At an early stage, it was demonstrated that the hyperphagic actions of THC were mediated in large part by cannabinoid CB1 receptors (Williams, Rogers, & Kirkham, 1998; Williams & Kirkham, 2002a). Subsequently, systemic anandamide administration was shown to increase food intake (Williams & Kirkham, 1999). Anandamide hyperphagia was blocked by pre-treatment with the selective CB1 antagonist rimonabant – but not by a CB2 antagonist, indicating that the overeating was specifically mediated by CB1 receptors. The feeding effects of systemic anandamide were replicated in mice (Hao et al., 2000) and rats (Gomez et al., 2002). Later experiments also confirmed that the endocannabinoids 2-arachidonylglycerol (2-AG) (Kirkham et al., 2002) and noladin ether can increase food intake in rodents (Avraham et al., 2005).

Although some workers emphasize peripheral actions of endocannabinoids in relation to appetite – and particularly modulation of afferent satiety signals (Rodriguez de Fonseca et al., 2001), this discussion is primarily concerned with the central mediation of the psychological aspects of eating. The importance of CNS endocannabinoids was first confirmed by Jamshidi and Taylor (2001), who found that rimonabant-reversible hyperphagia could be obtained by direct injection of anandamide into the ventromedial hypothalamus (VMH), one of the nuclei traditionally associated with food

intake control. Subsequently, it was demonstrated that administration of 2-AG into the shell sub-region of the nucleus accumbens (AcbSh) exerts a potent, CB1-selective, hyperphagic action (Kirkham et al., 2002). Similar effects have also been obtained with intra-accumbens anandamide treatments (Mahler, Smith, & Berridge, 2007; Soria-Gomez et al., 2007). As we will see, 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: hyperphagia follows anandamide or 2-AG administration into the lateral (LH) and paraventricular (PVN) nuclei of the hypothalamus (Kirkham & Williams, 2001a). Circuits located in feeding-relevant hindbrain areas, such as the parabrachial nucleus (PBN), dorsal motor nucleus of the vagus (DMV) and the nucleus tractus solitarius (NTS), may also be subject to cannabinoid regulation (Miller, Murray, Freeman, & Edwards, 2004; Di Patrizio & Simansky, 2008).

An essential corollary to the agonist data is the extensive database on the feeding effects of CB1 antagonists. Critically, these drugs have universally been found to suppress food intake although debate persists about the behavioural specificity of these effects (Tallett et al., 2007a, 2007b). Anorectic actions of the prototypical CB1 antagonist rimonabant were first reported by Arnone and colleagues, who argued that this effect was evidence for tonic endocannabinoid activity in feeding related systems (Arnone et al. 1997). Similar effects of rimonabant or its analogues have since been reported following systemic or central administration in satiated or fasted animals (Colombo et al., 1998; Werner & Koch, 2003; Chen et al., 2004), and dietary (Hildebrandt, Kelly-Sullivan, & Black, 2003; Ravinet-Trillou et al., 2003) and genetic models of obesity (Vickers et al., 2003). Such effects underlay the initial development of these drugs as anti-obesity agents.

The reward hypothesis of cannabinoid hyperphagia

A hypothesis that gained early currency – largely on the basis of the anecdotal accounts of cannabis users mentioned earlier (Tart, 1970) – was that endocannabinoids may provoke overconsumption by amplifying the orosensory reward, or palatability, of foods (Arnone et al., 1997). This notion was supported by studies showing that rimonabant more effectively attenuated the consumption of palatable ingesta than more bland laboratory diets (Arnone et al., 1997; Simiand et al., 1998), suggesting that tonic endocannabinoid activity mediates food reward: cannabinoid receptor agonists might increase intake by

rendering foods more palatable; while antagonists might diminish the hedonic value of foods, and so reduce consumption. However, it has become apparent that endocannabinoids are involved in the wider aspects of eating motivation; their involvement apparently encompassing the desire to eat and anticipation of food reward, as well as the enjoyment of food during ingestion. We will discuss these factors separately, using the currently accepted terminology of ‘wanting’ and ‘liking’ (Berridge, 2007), respectively reflecting the incentive processes that stimulate and guide behaviour toward food acquisition, and the subsequent hedonic evaluation of food stimuli.

Endocannabinoids and ‘wanting’

Evidence for a role of endocannabinoids in appetitive processes comes from studies using operant models, such as the progressive ratio paradigm in which rats are required to complete a progressively greater number of responses to obtain successive food rewards. The ratio at which animals cease to respond (the ‘break-point’) is taken as an index of the degree of craving, or incentive value of the food (Solinas & Goldberg, 2005). Rimonabant and other CB1 antagonists dose-dependently reduced break-point, while CB1 agonists increase break-point (Gallate & McGregor, 1999; Gallate et al., 1999; Solinas & Goldberg, 2005). These effects thus implicate endocannabinoid systems in the processes underlying the motivation to obtain food. Indeed, CB1 knockout mice have reduced sensitivity to the motivating properties of food, exhibiting reduced rates of responding for food and lower break-points than wild-type mice (Sanchis-Segura et al., 2004).

Detailed behavioural analyses of drug effects also support endocannabinoid involvement in incentive motivation. Under experimental conditions in which rats display minimal motivation to eat (such as when an animal has recently consumed a large meal), a normally long latency to the next meal is consistently reduced by THC, anandamide or 2-AG administration (Kirkham & Williams, 2001a). Crucially, once initiated, the subsequent pattern of cannabinoid-induced eating behaviour is similar to that of the spontaneous feeding in untreated rats (Williams & 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 thus begin to see the development of a model which links endocannabinoids directly to the processes that initiate feeding. The combination of CB1 ligand effects on feeding microstructure and

the motivation to work for food thus strongly implicates 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, Thomas, & Stanley, 1998). It is notable, therefore, that regional brain levels of anandamide and 2-AG 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 & Williams, 2001a; Osei-Hyiamen et al., 2005).

There are some recent human studies with THC and rimonabant that provide support for the role of endocannabinoids in appetitive processes. In addition to a significant increase of energy intake, we found that one of the principal effects of THC was a marked amplification of the normal pre-prandial rise in subjective hunger scores. This effect was associated with an earlier onset and increased incidence of snacking (Townson & Kirkham, unpublished). In a clinical trial with rimonabant, in which patients' appetite ratings were periodically assessed in laboratory test meals and home questionnaires (Blundell et al., 2006), rimonabant was found to lower subjective measures of hunger and desire to eat at the start of a meal, while having no effect on post-meal ratings of fullness. Significant reductions in hunger and the frequency and strength of food cravings were also detected over the course of the study. These complementary agonist and antagonist effects provide the most direct indications so far that CB1 receptor ligands can specifically modulate 'wanting' aspects of eating motivation.

The apparent involvement of endocannabinoids in appetitive aspects of feeding is compatible with the known effects of CB1 agonists and antagonists on mesolimbic dopaminergic incentive pathways, which terminate in the nucleus accumbens (van der Stelt & Di Marzo, 2003). Food stimuli cause dopamine release in the nucleus accumbens, especially after deprivation, or if the food is novel or palatable. Both THC and anandamide stimulate dopamine release in the nucleus accumbens (Solinas et al., 2006). Importantly, the accumbens dopamine release 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. 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.

Endocannabinoids and 'liking'

The above findings link endocannabinoids to appetitive processes in feeding. However, 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, CB1 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 CB1 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 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). We examined the actions of CB1 receptor ligands on the microstructure of sucrose drinking and found that alterations to behaviour induced by THC, anandamide and 2-AG are reminiscent of those observed in drug-free animals drinking more palatable solutions (Higgs, Williams, & Kirkham, 2003). Conversely, rimonabant alters sucrose drinking in a way that is consistent with a reduction its palatability. Additionally, CB1^{-/-} 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, Jarrett and colleagues have reported that THC produces rimonabant-reversible increases of ingestive 'liking' responses to intra-oral delivery of sucrose solutions; THC reduces the rejection of a quinine solution – an effect blocked by CB1 antagonists; antagonists alone decrease hedonic reactions to sucrose, and increases aversive reactions to quinine solutions (Jarrett, Limebeer, & Parker, 2005; Jarrett, Scantlebury, Parker, 2007). These findings support the hypothesis that endocannabinoid activity can contribute significantly to the hedonic evaluation of ingesta, and that CB1 stimulation or blockade can respectively render food more or less pleasurable.

Key components of the neural mechanisms underlying food palatability lie within the AcbSh

(Stratford, 2007) and, as already noted, 2-AG administered into this site produces a profound hyperphagic response (Kirkham et al., 2002). Anandamide 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 CB1 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 enhance the hedonic impact of sweet taste is directly supported by the finding that intra-AcbSh administration of anandamide specifically increases the number of positive ingestive responses to intra-oral infusions of sweet solutions in taste reactivity tests (Mahler et al., 2007).

A recent report also shows that the pontine parabrachial nucleus (PBN) is a sensitive site for the hyperphagic actions of 2-AG. The PBN is known to gate and information from primary gustatory sensory neurons that is ultimately transmitted to the ventral striatal areas, mentioned above, that process the hedonic aspects of food stimuli. It is notable therefore, that intra-PBN 2-AG treatment preferentially stimulates ingestion of palatable foods (Di Patrizio & Simansky, 2008).

Endocannabinoid-opioid interactions in eating motivation

Unsurprisingly, feeding effects of endocannabinoids have been linked functionally to other neurotransmitters that contribute to the control of food intake (Tucci et al., 2004; Cota et al., 2003; Di Marzo & Matias, 2005). In relation to the current argument, the strong likelihood of functional relationships between endocannabinoids and the endogenous opioid peptides are particularly pertinent. 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 (Kirkham, 1990; Kirkham & Cooper, 1988; Cooper & Kirkham, 1993; Bodnar, 2004). For example, in people, opioid antagonists reduce the perceived palatability of previously preferred foods and fluids (Drewnowski et al., 1992; Yeomans & Gray, 1996; Yeomans, 2007). 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 & Kirkham, 2002a). Importantly, the facilitatory effects of a CB1 agonist on responding for palatable solutions are reversed by both a CB1 antagonist and naloxone (Gallate & 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 & Williams, 2001b; Chen et al., 2004).

Given the established ability of opioid antagonists to reduce the hedonic evaluation of foods and to reverse CB1 agonist-stimulated ingestion, the profound anorexia induced by combined CB1 and opioid receptor blockade suggests that endocannabinoids contribute to orosensory reward through the activation of opioid processes. Moreover, administration of THC has been shown to stimulate β -endorphin release in the accumbens – a phenomenon linked to consumption of palatable foods (Solinas et al., 2004). Importantly, as with anandamide, 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 anatomical correspondence between the opioid- and cannabinoid-sensitive sites that support these effects (Pecina & Berridge, 2000; Mahler et al., 2007).

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 to activate nucleus accumbens circuits involved in the hedonic evaluation of food, 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 CB1 antagonists on the subjective experience of hunger and appetite measures in people. The emerging evidence indicates that the endocannabinoids, via their interactions with opioids, contribute substantially to the neurophysiological representation of the prospective delights of consumption that all too frequently exert a powerful influence on non-homeostatic eating.

Cannabinoids in the pathology and treatment of obesity and eating disorders

The involvement of endocannabinoids in appetite control and energy balance raises the question of whether these systems play a significant role in

disorders of eating and body weight; and can pharmaceutical interventions targeting endocannabinoids have useful therapeutic applications? Clearly, overconsumption, overweight, or heightened sensitivity to the appetite-stimulating properties of food need not be regarded as pathological conditions. They may merely reflect normal endocannabinoid function, and the effective operation of the mechanisms that have evolved to promote positive energy balance during times of plenty, in preparation for times of famine. Nevertheless, there is some evidence for deviation in endocannabinoid function in relation to obesity and other disorders of appetite (Matias, Cristino, & di Marzo, 2008).

For example, Monteleone et al. (2005) examined plasma levels of anandamide and 2-AG in women with anorexia nervosa, bulimia nervosa or binge eating disorder. They found that plasma levels of anandamide were significantly elevated in both anorexics and women with binge eating disorder, but not in bulimic patients. Endocannabinoid levels were not reliably correlated with the severity of psychological symptoms or duration of illness. Additionally, circulating anandamide levels were elevated in both restricting, underweight anorexics, and obese, overconsuming binge-eaters. These somewhat contradictory findings might suggest the possibility of some derangement in the production of anandamide in women with these particular disorders, and the authors tentatively proposed that their data reflected endocannabinoid mediation of the rewarding aspects of aberrant eating behaviours. The full significance of these findings will depend on verifying the source of anandamide that was measured, and the extent to which plasma levels can reflect altered endocannabinoid activity in the brain, as opposed to changing levels in peripheral tissues alone – which may have no ultimate significance to the psychological control of eating motivation. These complexities are multiplied by the finding that there may be genotypic differences between restricting and binge-purging subtypes of anorexia nervosa. Specifically, Siegfried et al. (2004) reported preferential transmission of different alleles of the CB1 receptor gene, *CNR1*. It was suggested that the specific alleles do not necessarily increase an individual's susceptibility to developing anorexia nervosa, but may modify the form of its expression.

Other studies have detected variations in relation to body mass and adiposity, which may bear some relationship to differences in endocannabinoid appetite processes, as distinct from potential variation in cannabinoid involvement in lipogenesis and fat accumulation. Sipe et al. (2005) reported obesity-related variations in a naturally occurring missense polymorphism in the gene encoding fatty

acid amide hydrolase (FAAH), the primary endocannabinoid-degrading enzyme. A homozygous FAAH 385 A/A genotype was significantly associated with overweight and obesity in white and black individuals, but not in a small group of Asians. Overall, the median BMI was significantly greater in the FAAH 385 A/A genotype group compared to heterozygote and wild-type groups, with a higher frequency of the FAAH 385 A/A genotype with increasing BMI: the strongest relationship was observed in the white cohort. The authors concluded that this mis-sense polymorphism could indicate an endocannabinoid risk factor in the development of overweight and obesity, potentially involving genetic malfunction of FAAH. Gazzo et al. (2007) studied the frequency of CB1 polymorphism and its relation to BMI in a Southern Italian population. They found that the CB1 1359 G/A polymorphism was associated with a significantly lower BMI, and that in similarly overweight and obese individuals those carrying have A/A allele at lower serum glucose and triglyceride levels. No such associations were found in a Brazilian population of European ancestry (Jaeger et al., 2008); although a significant association was detected between waist to hip ratio and a 4895G allele. Russo and colleagues (2007), however, failed to find any association between the 4895 A/G. variant and body fat mass and distribution in either of two European populations. They did, however, report that the 3813 G allele was associated with increased subscapular skinfold thickness and waist circumference.

Despite the conflicts between the data from these surveys, it may be that with many more thorough studies, screening for CB1 gene variants might eventually be used to indicate differences in endocannabinoid function that may be linked to a predisposition to obesity, eating disorders, or therapeutic susceptibility to CB1-acting drugs.

The possibility of manipulating endocannabinoid systems in disease is already established – not least in relation to appetite and body weight (Di Marzo, 2008). Although not specifically discussed on this article, the reader will be aware of the substantial resources have been committed in recent years to the commercial exploitation of the endocannabinoid system in an attempt to produce anti-obesity agents (Scheen et al., 2006). Unfortunately, it is now apparent that rimonabant and its sister drugs – although having beneficial therapeutic effects in relation to the metabolic syndrome – because of their penetration of the central nervous system they have a psychiatric side-effect profile that is incompatible with the requirements of regulators and patients (Christensen, Kristensen, Bartels, Bliddal, & Astrup, 2007). Some of these side-effects relate to the drugs action on the motivational/emotional systems that

we have been discussing. Although pharmaceutical companies had largely discounted direct therapeutic effects on these processes in favour of targeting peripheral metabolic factors (Van Gaal, Pi-Sunyer, Despres, McCarthy, & Scheen, 2008), it could still be possible to safely utilize CB1 antagonists as effective modifiers of appetite. New modes of administration, and perhaps combinations with other kinds of drugs to promote synergistic interactions with other feeding factors, are not beyond the scope of imagination. But it is clear that far more fundamental research into the exact role of central endocannabinoids appetite and mood processes is required.

With continuing advances, the number of therapeutic opportunities for agonists may also expand. One of the currently licensed uses of cannabinoids in the USA and elsewhere involves THC (dronabinol or its synthetic analogue nabilone) in the stimulation of appetite in cancer and HIV infection (Plasse et al., 1991; Haney, Rabkin, Gunderson, & Foltin, 2005). Cannabinoids may also have application in the wasting and appetite loss associated with ageing and the dementias (Volicer, Stelly, Morris, McLaughlin, & Volicer, 1997). Anorexia nervosa could also be a potential target for the application of cannabinoids, despite the condition's complex psychopathology. So far only a single, ineffective, study with THC has been reported, and more carefully designed studies may be more successful (Gross et al., 1983).

However, the clinical application of THC in these conditions predates the current knowledge of endocannabinoids and their behavioural and physiological functions. And, again, these applications are based on very little understanding of the psychological or behavioural actions of the drugs in healthy populations. We should, however, anticipate that better understanding of endocannabinoid function could produce enhanced treatments in future. We have the pharmacological tools whereby we could move from animal models to human experiments to gain greater insight into the potential involvement of endocannabinoids in food-craving, orosensory reward, psychophysical responses to food, hunger, etc. While it is so far impossible to administer anandamide to people, THC at relatively low doses that are devoid of unwanted intoxication represents a safe and readily available test compound. There are very many questions to ask which can only be answered through human experiments, but unless lawmakers can set aside their ignorance and prejudice in favour of supporting basic pre-clinical and clinical cannabinoid research, the pace of discovery is likely to remain slow and the likely benefits distant.

One area where basic research may provide a lead for useful medical interventions comes from recent work that suggests that endocannabinoid systems are vital to the ability of neonates to suckle. Thus when rimonabant is administered to newborn mice, milk ingestion and subsequent growth is completely inhibited, with fatal results. Similarly, CB1 knockout mice display deficient suckling at birth (Fride et al., 2005). Fride (2008) has proposed that at birth, brain 2-AG is sufficient to stimulate suckling, but that 2-AG present in maternal milk provides an essential additional stimulus to further feeding. By extrapolation, a deficient endocannabinoid-CB1 receptor system may underlie a failure to thrive in human infants. Since 2-AG has also been detected in bovine and human milk (Di Marzo et al., 1998), and dietary manipulation of essential fatty acids has been shown to affect brain endocannabinoid levels in animals (Berger et al., 2001; Artmann et al., 2008), it is possible that deficiencies in maternal nutrition may lead to underdevelopment of endocannabinoid systems in the foetus and neonate, and may possibly underlie the little understood phenomenon of 'failure to thrive'. Thus, there may be opportunities to develop nutraceutical treatments, whereby dietary manipulation of endocannabinoid precursors might effect beneficial changes in eating behaviour in infants. Such treatment might also be used to affect appetite and eating behaviour, or energy metabolism, in adults who overconsume and/or who are overweight or obese.

Future directions

As this sketch indicates, central endocannabinoid systems are implicated in the principal psychological processes that govern eating motivation, and may represent critical components of the mechanisms that lead us to overconsume, and which represent the major contributor to weight gain. As such, the endocannabinoids are potentially important therapeutic targets for pharmacological treatments designed to modify eating behaviour and attitudes/responsiveness to foods. Modification of endocannabinoid activity, or blockade of CB1 receptors may allow us to limit our susceptibility to the temptations of food and to learn to restrain our excessive appetites. As these factors contribute more than any others to the development of obesity – and may be implicated to different extents in conditions such as bulimia nervosa and binge eating disorder, there is an urgent need to define the psychological consequences of CB1 receptor manipulations in human studies. Insights obtained from the exploration of the subjective effects of CB1 ligands would shed important light on the true physiological role of

endocannabinoids in appetite control and indicate new therapeutic avenues.

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References

- Arnone, M., Maruani, J., Chaperon, F., Thiebot, M.H., Poncelet, M., Soubrie, P., & Le Fur, G. (1997). Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors. *Psychopharmacology* (Berlin), *132*, 104–106.
- Artmann, A., Petersen, G., Hellgren, L.I., Boberg, J., Skonberg, C., Nellemann, C., Hansen, S.H., & Hansen, H.S. (2008). Influence of dietary fatty acids on endocannabinoid and N-acylethanolamine levels in rat brain, liver and small intestine. *Biochimica et Biophysica Acta*, *1781*(4), 200–212.
- Avraham, Y., Ben Menachem, A., Okun, A., Zlotarav, O., Abel, N., Mechoulam, R., & Berry, E.M. (2005). Effects of the endocannabinoid noladin ether on body weight, food consumption, locomotor activity, and cognitive index in mice. *Brain Research Bulletin*, *65*, 117–123.
- Beal, J. E., Olson, R., Laubenstein, L., Morales, J. O., Bellman, P., Yangco, B., Lefkowitz, L., Plasse, T.F., & Shepard, K.V. (1995). Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *Journal of Pain Symptom Management*, *10*, 89–97.
- Berger, A., Crozier, G., Bisogno, T., Cavaliere, P., Innis, S., & Di Marzo, V. (2001). Anandamide and diet: Inclusion of dietary arachidonate and docosahexaenoate leads to increased brain levels of the corresponding N-acylethanolamines in piglets. *Proceedings of the National Academy of Sciences USA*, *98*(11), 6402–6406.
- Berridge, K. C. (2007). Brain reward systems for food incentives hedonics in normal appetite and eating disorders. In T. C. Kirkham & S. J. Cooper (Eds.), *Appetite and body weight: Integrative systems and the development of anti-obesity drugs*. Burlington, MA: Academic Press.
- Blundell, J. E., Jebb, S. A., Stubbs, R. J., Gross, H., Ebert, M.H., Faden, V.B., Goldberg, S.C., Kaye, W.H., Caine, E.D., Hawks, R., and Zinberg, N. (1983). A double-blind trial of delta 9-tetrahydrocannabinol in primary anorexia nervosa. *Journal of Clinical Psychopharmacology*, *3*, 165–171.
- Bodnar, R. J. (2004). Endogenous opioids and feeding behavior: A 30-year historical perspective. *Peptides*, *25*, 697–725.
- Chen, R., Huang, R., Shen, C., Chen, C.P., MacNeil, D.J., & Fong, T.M. (2004). Synergistic effects of cannabinoid inverse agonist AM251 and opioid antagonist nalmefene on food intake in mice. *Brain Research and Brain Research Reviews*, *999*, 227–230.
- Chopra, I.C., & Chopra, R.N. (1957). The use of the cannabis drugs in India. *Bulletin on Narcotics*, *9*, 4–29.
- Christensen, R., Kristensen, P. K., Bartels, E. M., Bliddal, H., & Astrup, A. (2007). Efficacy and safety of the weight-loss drug rimonabant: A meta-analysis of randomised trials. *Lancet*, *370*, 1706–1713.
- Colombo, G., Agabio, R., Diaz, G., Lobina, C., Reali, R., & Gessa, G.L. (1998). Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. *Life Science*, *63*, PL113–117.
- Cooper, S. J., & Kirkham, T. C. (1993). Opioid mechanisms in the control of food consumption and taste preferences. In A. Herz, H. Akil & E. J. Simon (Eds.), *Handbook of Experimental Pharmacology*, Vol. 104, part II. Berlin: Springer-Verlag.
- Cota, D., Marsicano, G., Tschop, M., Grubler, Y., Flachskamm, C., Schubert, M. et al. (2003). The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *Journal of Clinical Investigation*, *112*, 423–431.
- Di Marzo, V., Sepe, N., De Petrocellis, L., Berger, A., Crozier, G., Frider, E., & Mechoulam, R. (1998). Trick or treat from food endocannabinoids? *Nature*, *396*(6712), 636–637.
- Di Marzo, V., & Matias, I. (2005). Endocannabinoid control of food intake and energy balance. *Nature Neuroscience*, *8*, 585–589.
- Di Marzo, V. (2008). The endocannabinoid system in obesity and type 2 diabetes. *Diabetologia*, *51*, 1356–1367.
- Di Patrizio, N. V., & Simansky, K. J. (2008). Activating parabrachial cannabinoid CB1 receptors selectively stimulate feeding of palatable foods in rats. *Journal of Neuroscience*, *28*, 9702–9709.
- Drewnowski, A., Krahn, D. D., Demitrack, M. A., Nairn, K., & Gosnell, B.A. (1992). Taste responses and preferences for sweet high-fat foods: Evidence for opioid involvement. *Physiology & Behavior*, *51*, 371–379.
- Frider, E. (2008). Multiple roles for the endocannabinoid system during the earliest stages of life: Pre- and postnatal development. *Journal of Neuroendocrinology*, *20*(Suppl.1), S75–81.
- Frider, E., Bregman, T., & Kirkham, T.C. (2005). Endocannabinoids and food intake: Newborn suckling and appetite regulation in adulthood. *Experimental Biology and Medicine* (Maywood), *230*(4), 225–234.
- Gaoni, Y., & Mechoulam, R. (1971). The isolation and structure of delta-1-tetrahydrocannabinol and other neutral cannabinoids from hashish. *Journal of the American Chemistry Society*, *93*, 217–224.
- Gallate, J., & McGregor, I. (1999). The motivation for beer in rats: Effects of ritanserin, naloxone and SR 141716. *Psychopharmacology*, *142*, 302–308.
- Gallate, J., Saharov, T., Mallet, P., & McGregor, I.S. (1999). Increased motivation for beer in rats following administration of a cannabinoid CB1 receptor agonist. *European Journal of Pharmacology*, *370*, 233–240.
- Gazzerro, P., Caruso, M. G., Notarnicola, M., Misciagna, G., Guerra, V., Laezza, C., & Bifulco, M. (2007). Association between cannabinoid type-1 receptor polymorphism and body mass index in a southern Italian population. *International Journal of Obesity* (London), *31*(6), 908–912.
- Gomez, R., Navarro, M., Ferrer, B., Trigo, J.M., Bilbao, A., Del Arco, I., Cippitelli, A., Nava, F., Piomelli, D., & Rodriguez de Fonseca, F. (2002). A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. *Journal of Neuroscience*, *22*, 9612–9617.
- Gross, H., Ebert, M.H., Faden, V.B., Goldberg, S.C., Kaye, W.H., Caine, E.D., Hawks, R., & Zinberg, N. (1983). A double-blind trial of delta 9-tetrahydrocannabinol in primary anorexia nervosa. *Journal of Clinical Psychopharmacology*, *3*, 165–171.
- Haney, M., Rabkin, J., Gunderson, E., & Foltin, R. W. (2005). Dronabinol and marijuana in HIV+ marijuana smokers: Acute effects on caloric intake and mood. *Psychopharmacology* (Berlin), *181*, 170–178.
- Hao, S., Avraham, Y., Mechoulam, R., & Berry, E.M. (2000). Low dose anandamide affects food intake, cognitive function, neurotransmitter and corticosterone levels in diet-restricted mice. *European Journal of Pharmacology*, *392*, 147–156.
- Harrold, J., Elliott, C., King, P., Widowson, P.S., & Williams, G. (2002). Down-regulation of cannabinoid-1 (CB-1) receptors in specific extrahypothalamic regions of rats with dietary obesity:

- A role for endogenous cannabinoids in driving appetite for palatable food? *Brain Research*, 952, 232–238.
- Higgs, S., Williams, C. M., & Kirkham, T. C. (2003). Cannabinoid influences on palatability: Microstructural analysis of sucrose drinking after delta(9)-tetrahydrocannabinol, anandamide, 2-arachidonoyl glycerol and SR141716. *Psychopharmacology* (Berlin), 165, 370–377.
- Hildebrandt, A. L., Kelly-Sullivan, D. M., & Black, S. C. (2003). Antiobesity effects of chronic cannabinoid CB1 receptor antagonist treatment in diet-induced obese mice. *European Journal of Pharmacology*, 462, 125–132.
- Jaeger, J. P., Mattevi, V. S., Callegari-Jacques, S. M., & Hutz, M. H. (2008). Cannabinoid type-1 receptor gene polymorphisms are associated with central obesity in a Southern Brazilian population. *Disease Markers*, 25(1), 67–74.
- Jamshidi, N., & Taylor, D. (2001). Anandamide administration into the ventromedial hypothalamus stimulates appetite in rats. *British Journal of Pharmacology*, 134, 1151–1154.
- Jarrett, M. M., Scantlebury, J., & Parker, L. A. (2007). Effect of delta(9)-tetrahydrocannabinol on quinine palatability and AM251 on sucrose and quinine palatability using the taste reactivity test. *Physiology & Behavior*, 90, 425–430.
- Jarrett, M. M., Limebeer, C. L., & Parker, L. A. (2005). Effect of Delta9-tetrahydrocannabinol on sucrose palatability as measured by the taste reactivity test. *Physiology & Behavior*, 86, 475–479.
- Kirkham, T. C. (2005). Endocannabinoids in the regulation of appetite and body weight. *Behavioural Pharmacology*, 16, 297–313.
- Kirkham, T. C. (1990). Enhanced anorectic potency of naloxone in rats sham feeding 30% sucrose: Reversal by repeated naloxone administration. *Physiology & Behavior*, 47, 419–426.
- Kirkham, T. C., Williams, C. M., Fezza, F., & Di Marzo, V. (2002). Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: Stimulation of eating by 2-arachidonoyl glycerol. *British Journal of Pharmacology*, 136, 550–557.
- Kirkham, T. C., & Williams, C. M. (2001a). Endocannabinoids: Neuromodulators of food craving?. In M. Hetherington (Ed.) *Food Cravings and Addiction*. Surrey, UK: Leatherhead Publishing.
- Kirkham, T. C., & Williams, C. M. (2001b). Synergistic effects of opioid and cannabinoid antagonists on food intake. *Psychopharmacology* (Berlin), 153, 267–270.
- Kirkham, T. C., & Cooper, S. J. (1988). Naloxone attenuation of sham feeding is modified by manipulation of sucrose concentration. *Physiology & Behavior*, 44, 491–494.
- Mahler, S. V., Smith, K. S., & Berridge, K. C. (2007). Endocannabinoid hedonic hotspot for sensory pleasure: Anandamide in nucleus accumbens shell enhances 'liking' of a sweet reward. *Neuropsychopharmacology*, 32, 2267–2278.
- Marin Bivens, C. L., Thomas, W. J., & Stanley, B. G. (1998). Similar feeding patterns are induced by perifornical neuropeptide Y injection and by food deprivation. *Brain Research*, 782, 271–280.
- Matias, I., Cristino, L., & di Marzo, V. (2008). Endocannabinoids: Some like it fat (and sweet too). *Journal of Neuroendocrinol*, 20(Suppl.1), 100–109.
- Melis, T., Succu, S., Sanna, F., Boi, A., Argiolas, A., & Melis, M. R. (2007). The cannabinoid antagonist SR 141716A (Rimonabant) reduces the increase of extracellular dopamine release in the rat nucleus accumbens induced by a novel high palatable food. *Neuroscience Letters*, 419, 231–235.
- Miller, C. C., Murray, T. F., Freeman, K. G., & Edwards, G. L. (2004). Cannabinoid agonist, CP 55,940, facilitates intake of palatable foods when injected into the hindbrain. *Physiology & Behavior*, 80, 611–616.
- Monteleone, P., Matias, I., Martiadis, V., De Petrocellis, M., Maj, M., & Di Marzo, V. (2005). Blood levels of the endocannabinoid anandamide are increased in anorexia nervosa and in binge-eating disorder, but not in bulimia nervosa. *Neuropsychopharmacology*, 30(6), 1216–1221.
- Osei-Hyiamen, D., DePetrillo, M., Pacher, P., Liu, J., Radaeva, S., Batkai, S., Harvey-White, J., Mackie, K., Offertaler, L., Wang, L., & Kunos, G. (2005). Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *Journal of Clinical Investigation*, 115, 1298–1305.
- Pecina, S., & Berridge, K. C. (2000). Opioid site in nucleus accumbens shell mediates eating and hedonic 'liking' for food: Mmap based on microinjection Fos plumes. *Brain Research*, 863, 71–86.
- Pério, A., Barnouin, M. C., Poncelet, M., & Soubrié, P. (2001). Activity of SR141716 on post-reinforcement pauses in operant responding for sucrose reward in rats. *Behavioural Pharmacology*, 12, 641–645.
- Plasse, T. F., Gorter, R. W., Krasnow, S. H., Lane, M., Shepard, K. V., & Wadleigh, R. G. (1991). Recent clinical experience with dronabinol. *Pharmacological Biochemistry Behaviour*, 40, 695–700.
- Poncelet, M., Maruani, J., Calassi, R., & Soubrié, P. (2003). Overeating, alcohol and sucrose consumption decrease in CB1 receptor deleted mice. *Neuroscience Letters*, 343, 216–218.
- Ravinet-Trillou, C., Arnone, M., Delgorge, C., Gonalons, N., Keane, P., Maffrand, J. P., & Soubrié, P. (2003). Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. *American Journal of Physiological Regulation Integral and Comparative Physiology*, 284, R345–353.
- Rodriguez de Fonseca, F., Navarro, M., Gómez, R., Escuredo, L., Nava, F., Fu, J. et al. (2001). An anorexic lipid mediator regulated by feeding. *Nature*, 414(6860), 209–212.
- Russo, P., Strazzullo, P., Cappuccio, F. P., Tregouet, D. A., Lauria, F., Loguercio, M., Barba, G., Versiero, M., & Siani, A. (2007). Genetic variations at the endocannabinoid type 1 receptor gene (CNR1) are associated with obesity phenotypes in men. *Journal of Clinical Endocrinology and Metabolism*, 92(6), 2382–2386.
- Sanchis-Segura, C., Cline, B., Marsicano, G., Lutz, B., & Spanagel, R. (2004). Reduced sensitivity to reward in CB1 knockout mice. *Psychopharmacology* (Berlin), 176, 223–232.
- Scheen, A. J., Van Gaal, L. G., Despres, J. P., Pi-Sunyer, X., Golay, A., & Hanotin, C. (2006). Rimonabant improves cardiometabolic risk profile in obese or overweight subjects: Overview of RIO studies. *Reviews in Medical Suisse*, 2, 1916–1923.
- Siegfried, Z., Kanyas, K., Latzer, K., Latzer, T., Karni, O., Bloch, M., Lerer, B., & Berry, E. M. (2004). Association study of cannabinoid receptor gene (CNR1) alleles and anorexia nervosa: Differences between restricting and bingeing/purging subtypes. *American Journal of Medical Genetics B*, 125B, 126–130.
- Simiand, J., Keane, M., Keane, P., & Soubrié, P. (1998). SR 141716, a CB1 cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset. *Behavioural Pharmacology*, 9, 179–181.
- Sipe, J. C., Waalen, J., Gerber, A., & Beutler, E. (2005). Overweight and obesity associated with a missense polymorphism in fatty acid amide hydrolase (FAAH). *International Journal of Obesity* (London), 29(7), 755–759.
- Solinas, M., Goldberg, S. R., & Piomelli, D. (2008). The endocannabinoid system in brain reward processes. *British Journal of Pharmacology*, 154, 369–383.

- Solinas, M., Justinova, Z., Goldberg, S. R., & Tanda, G. (2006). Anandamide administration alone and after inhibition of fatty acid amide hydrolase (FAAH) increases dopamine levels in the nucleus accumbens shell in rats. *Journal of Neurochemistry*, *98*, 408–419.
- Solinas, M., & Goldberg, S. R. (2005). Motivational effects of cannabinoids and opioids on food reinforcement depend on simultaneous activation of cannabinoid and opioid systems. *Neuropsychopharmacology*, *30*, 2035–2045.
- Solinas, M., Zangen, A., Thiriet, N., & Goldberg, S. R. (2004). Beta-endorphin elevations in the ventral tegmental area regulate the discriminative effects of Delta-9-tetrahydrocannabinol. *European Journal of Neuroscience*, *19*, 3183–3192.
- Soria-Gomez, E., Matias, I., Rueda-Orozco, P. E., Cisneros, M., Petrosino, S., Navarro, L., Di Marzo, V., & Prospéro-García, O. (2007). Pharmacological enhancement of the endocannabinoid system in the nucleus accumbens shell stimulates food intake and increases c-Fos expression in the hypothalamus. *British Journal of Pharmacology*, *151*, 1109–1116.
- Stratford, T. R. (2007). The nucleus accumbens shell as a model of integrative subcortical forebrain systems regulating food intake. In T. C. Kirkham & S. J. Cooper (Eds.), *Appetite and body weight: Integrative systems and the development of anti-obesity drugs*. Burlington, MA: Academic Press.
- Tallett, A. J., Blundell, J. E., & Rodgers, J. R. (2007a). Grooming, scratching and feeding: Role of response competition in acute anorectic response to rimonabant in male rats. *Psychopharmacology* (Berlin), *195*, 27–39.
- Tallett, A. J., Blundell, J. E., & Rodgers, J. R. (2007b). Acute anorectic response to cannabinoid CB1 receptor antagonist/inverse agonist AM 251 in rats: Indirect behavioural mediation. *Behavioural Pharmacology*, *18*, 591–600.
- Tart, C. (1970). Marijuana intoxication: Common experiences. *Nature*, *226*, 701–704.
- Tucci, S. A., Rogers, E. K., Korbonits, M., & Kirkham, T. C. (2004). The cannabinoid CB1 receptor antagonist SR141716 blocks the orexigenic effects of intrahypothalamic ghrelin. *British Journal of Pharmacology*, *143*(5), 520–523.
- van der Stelt, M., & Di Marzo, V. (2003). The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: Implications for neurological and psychiatric disorders. *European Journal of Pharmacology*, *480*, 133–150.
- Van Gaal, L., Pi-Sunyer, X., Despres, J.-P., McCarthy, C., & Scheen, A. (2008). Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients. Pooled 1-year data from the Rimonabant in Obesity (RIO) program. *Diabetes Care*, *31*(Suppl.2), S229–S240.
- Vickers, S., Webster, L., Wyatt, A., Dourish, C. T., & Kennett, G. A. (2003). Preferential effects of the cannabinoid CB1 receptor antagonist, SR 141716, on food intake and body weight gain of obese (fa/fa) compared to lean Zucker rats. *Psychopharmacology* (Berlin), *167*, 103–111.
- Volicer, L., Stelly, M., Morris, J., McLaughlin, J., & Volicer, B. J. (1997). Effects of dronabinol on anorexia and disturbed behaviour in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *12*, 913–919.
- Werner, N., & Koch, J. (2003). Effects of the cannabinoid antagonists AM281 and AM630 on deprivation-induced intake in Lewis rats. *Brain Research*, *967*, 290–292.
- Williams, C. M., & Kirkham, T. C. (2002a). Reversal of delta 9-THC hyperphagia by SR141716 and naloxone but not dexfenfluramine. *Pharmacology Biochemistry and Behavior*, *71*, 333–340.
- Williams, C. M., & Kirkham, T. C. (2002b). Observational analysis of feeding induced by Delta9-THC and anandamide. *Physiological Behaviour*, *76*, 241–250.
- Williams, C. M., Rogers, P. J., & Kirkham, T. C. (1998). Hyperphagia in pre-fed rats following oral delta9 THC. *Physiological Behaviour*, *65*, 343–346.
- Williams, C. M., & Kirkham, T. C. (1999). Anandamide induces overeating: Mediation by central cannabinoid (CB1) receptors. *Psychopharmacology* (Berlin), *143*, 315–317.
- Yeomans, M. R. (2007). The role of palatability in control of human appetite: Implications for understanding and treating obesity. In T. C. Kirkham & S. J. Cooper (Eds.), *Appetite and body weight: Integrative systems and the development of anti-obesity drugs*. Burlington, MA: Academic Press.
- Yeomans, M. R., & Gray, R. W. (1996). Selective effects of naltrexone on food pleasantness and intake. *Physiological Behaviour*, *60*, 439–446.