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Endogenous cannabinoids and appetite

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Since pre-history, *Cannabis sativa* has been exploited for its potent and manifold pharmacological actions. Amongst the most renowned of these actions is a tendency to provoke ravenous eating. The characterization of the psychoactive principals in cannabis (exogenous cannabinoids) and, more recently, the discovery of specific brain cannabinoid receptors and their endogenous ligands (endocannabinoids) has stimulated research into the physiological roles of endocannabinoid systems. In this review, we critically discuss evidence from the literature that describe studies on animals and human subjects to support endocannabinoid involvement in the control of appetite. We describe the hyperphagic actions of the exogenous cannabinoid, Δ^9-tetrahydrocannabinol, and the endogenous CB1 ligands, anandamide and 2-arachidonylglycerol, and present evidence to support a specific role of endocannabinoid systems in appetitive processes related to the incentive and reward properties of food. A case is made for more comprehensive and systematic analyses of cannabinoid actions on eating, in the anticipation of improved therapies for disorders of appetite and body weight, and a better understanding of the biopsychological processes underlying hunger.

Endocannabinoids: Anandamide: Reward: Appetite regulation

Introduction

The past few decades have witnessed a dramatic growth in our knowledge of important central and peripheral factors affecting the regulation of appetite. This is particularly the case with respect to the neurochemical components of brain systems influencing ingestive behaviours. Each advance in pharmacological analysis has brought with it a bevy of new candidate neurotransmitters which have been found to have significant influences on what, or how much, we eat (e.g. Cooper & Clifton, 1996; Hoebel, 1997; Holst, 1999; Schwartz *et al*. 2000). Nevertheless, the growth in the number of agents known to affect feeding behaviour has not

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Abbreviations: GABA, γ-aminobutyric acid; THC, tetrahydrocannabinol.

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been fully matched by a better understanding of the psychological processes subserved by the interactions of these substances with their receptors. At a physiological level, the abundance of putative chemical 'signals' suggests either that there is considerable redundancy, or the existence of interactive systems so complex that real understanding of the role of each component is likely to take many more decades to unravel.

When considering the pharmacology of appetite, it is the case that most research effort has been diverted into the search for biochemical signals that terminate feeding. Such 'satiety signals' have been emphasized, in large part, because of the increased prevalence of obesity and the profits to be made from treatments that specifically target the physiological processes that reduce appetite. Although several neurotransmitter systems have been identified which may play a role in the stimulation of eating (e.g. Stratford *et al*. 1998; Edwards *et al*. 1999), appetite research is now largely devoted to the analysis of agents which reduce food intake. The study of the neurochemical processes that give rise to appetite has thus been overshadowed, to the detriment of progress in the broader understanding of appetite regulation and, more generally, the biological bases of fundamental motivational mechanisms.

Considering appetite for food, it seems logical to consider that man has evolved to maximize every opportunity to eat, in anticipation that times of feast will be followed by periods of famine. We have evolved a psychological predisposition to overconsume; responding to food variety, being over-sensitive to the high palatability of energy-dense foods, and possessing a seemingly limitless capacity to store excess energy in adipose tissue. Moreover, psychological factors such as conditioning and expectation seem to be far more influential in determining our eating patterns than predominant homeostatic models of energy and body-weight balance might argue (Mela & Rogers, 1998). In this context, a plethora of mechanisms designed to limit our intake, or to maintain our body weights at some arbitrary 'set point' imply a level of redundancy that is contrary to biological necessity. Similarly, arguments that widespread obesity might arise from some genetic defect seem, on the whole, unfounded. We only have to consider the average BMI of individuals in the USA compared with their cousins in the old world to see that geography and opportunity have generally been far more influential than genes.

In modern societies, it is our susceptibility to the sight, taste, or thought of food which impels overconsumption and (when matched with easy availability of food and reduced energy expenditure) gives rise to overweight and obesity. Therefore, the overshadowing of appetitive processes by the overwhelming study of satiety mechanisms is clearly deserving of some redress. A greater knowledge of the neurochemical factors underlying the urge to eat, 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 one of the most recently discovered neurochemical families: the endogenous cannabinoids. In the following text, we will present data to implicate these substances in the normal biopsychological mechanisms which create appetite and stimulate eating.

Cannabis sativa, exogenous cannabinoids and endocannabinoids

Cannabis sativa (Indian Hemp, marijuana) has been cultivated for at least 10 000 years, in part to obtain fibres for the manufacture of textiles and rope, but to an important extent because of the wide variety of pharmacological actions that follow ingestion or inhalation of the leaves or resin extracts. These pharmacological actions include ataxia, hypothermia, analgesia, short-term memory deficits, a sense of time dilation, enhanced sensation, euphoria and higher-order cognitive impairments (Dewey, 1986; Hollister, 1986). These various effects gave rise to the

historical medicinal use of cannabis and underlie its contemporary recreational abuse. Recent research has added to these, principally psychological actions of cannabis, evidence for a number of beneficial effects, including: suppression of cancer cell proliferation, analgesia, alleviation of glaucoma, antioxidant actions, stabilization of the symptoms of multiple sclerosis (e.g. Nahas *et al*. 1999; Di Marzo *et al*. 2000; Hampson *et al*. 2000; Pertwee, 2000). Even the seeds of *Cannabis sativa* have been promoted as a useful source of *n*-3 and *n*-6 fatty acids.

The chemicals within cannabis that produce biological effects in people were not characterised until 1964, when Gaoni and Mechoulam isolated Δ^9-tetrahydrocannabinol (THC) and a group of related organic 'cannabinoid' molecules in hashish (Gaoni & Mechoulam, 1964; Mechoulam *et al*. 1970). With subsequent developments in neuropharmacology, scientists were able to demonstrate that these cannabinoids exerted their effects via specific sites within the central nervous system and peripheral tissues. We now know that there is a family of G-protein linked, cell-surface cannabinoid receptors (Devane *et al*. 1988; Matsuda *et al*. 1990; Munro *et al*. 1993). Two main cannabinoid receptors subtypes have been identified and their genes cloned (Onaivi *et al*. 1996). These are classified as a 'central-type' CB1, widely distributed within the central nervous system and many peripheral tissues, and a 'peripheral-type' CB2 receptor, which is not significantly expressed in the central nervous system (Breivogel & Childers, 1998). It is generally agreed that the behavioural effects of cannabinoids are mediated by brain (CB1) cannabinoid receptors and, despite their wide distribution, the regional localization of receptors corresponds closely with their behavioural effects (Herkenham *et al*. 1990; Breivogel *et al*. 1997).

The existence of specific receptor sites mediating the effects of plant-derived exogenous cannabinoids suggested the existence of a chemical produced within mammalian tissues, for which the cannabinoid receptors are the target; endogenous ligands which compounds like THC mimic to produce their various effects. After several decades of unsuccessful searching, the 1990s saw the isolation and complete characterisation of the first 'endocannabinoid' (Devane *et al*. 1992). This compound, arachidonylethanolamide, which is synthesised within brain tissue and binds with high affinity to CB1 receptors, was named anandamide, from 'ananda', a Sanskrit word meaning inner bliss. Subsequently, the search for additional endogenous ligands selective for the CB2 cannabinoid receptor led to the identification of 2-arachidonoylglycerol (Mechoulam *et al*. 1995; Stella *et al*. 1997). Although it exhibits a lower affinity for CB1 receptors than anandamide, evidence suggests that it is present in the brain at higher levels than anandamide and is a full agonist at CB1 receptors (Stella *et al*. 1997). Both of these substances fulfil the necessary criteria for classification as neuromodulators: they are synthesised from arachidonic acid through distinct biosynthetic routes; are released from neurons in response to membrane depolarization, have specific uptake mechanisms and are hydrolysed by a selective enzyme, fatty acid amide hydrolase (Di Marzo & Deutsch, 1998; Piomelli *et al*. 1998; Reggio, 1999). Cannabinoids are also closely related to the arachidonic acid-derived eicosanoids, and may have overlapping physiological functions (Burstein *et al*. 1995; Fimiani *et al*. 1999). A number of other candidate endocannabinoids have since been characterised, but anandamide and 2-arachidonoylglycerol are considered to be the primary ligands at CB1 and CB2 receptors, with both substances capable of exerting THC-like effects in animal behavioural models (for reviews, see Pertwee, 1995; DiMarzo & Deutsch, 1998; Di Marzo *et al*. 1998). Importantly, amphibian, rodent and human CB1 receptors show a high degree of homology. Together with the occurrence of the endocannabinoids in a number of phylogenetically diverse species, a high degree of evolutionary conservation of cannabinoid signalling systems indicates that they should play an important physiological role in vertebrate brain function (De Petrocellis *et al*. 1999; Soderstrom *et al*. 2000).

Cannabinoids and appetite

The discovery of the endocannabinoids leads to the obvious question: what is their normal physiological function? As noted earlier, administration of cannabinoids induces a wide spectrum of behavioural and physiological changes. It is likely that these effects, produced by stimulation of cannabinoid receptors, reflect the normal roles of endocannabinoid systems.

Marijuana use in man has long been associated with an increase in appetite, with references to appetite stimulant properties recorded as early as AD 300 (Abel, 1975). Modern cannabis users are also very familiar with the drug's capacity to provoke eating and overconsumption, a predictable phenomenon known colloquially as 'the munchies'. However, despite the verity of hyperphagia as represented in pharmacopoeia over many centuries and in modern anecdote, there is a real paucity of detailed scientific analysis of the phenomenon. The initial discovery of the exogenous cannabinoids led to some fairly cursory examination of their therapeutic applications in the alleviation of appetite loss associated with disease states (Abel, 1971; Greenberg *et al*. 1976; Foltin *et al*. 1986, 1988). However, there has still been no comprehensive, systematic characterisation of cannabinoid effects on feeding in human subjects. Similarly, the animal literature data is very insubstantial compared with that for other drugs or neurotransmitters that affect eating. Disappointingly, there have been few consistent findings and very little research in the past 20 years. Clinical development of cannabinoid treatments, and the development of theoretical models of their actions on appetite, calls for a concerted research effort to replace our dependence on anecdotal accounts.

Contemporary progress in cannabinoid pharmacology means that we now have the proper tools to examine endocannabinoid involvement in appetite regulation, and the first real opportunity to develop effective cannabinoid therapies for disorders of appetite or body weight. In the following text, we will give an overview of the current state of knowledge concerning cannabinoids and feeding and present our own theoretical account of the role of endocannabinoids in appetite.

Exogenous cannabinoids and human appetite

As we pointed out earlier, hyperphagia following cannabis intoxication is a widely accepted phenomenon, but one which was for many years supported only by anecdotal reports (Haines & Green, 1970; Tart, 1970; Halikas *et al*. 1971). The first scientific studies we have found took place in the1970s, but since then only a handful of reports have entered the literature.

In 1971, Hollister examined the effects of oral Δ^9-THC (0·5 mg/kg) in fasted subjects, offered chocolate milk shakes at 30 min intervals over 2 h (Hollister, 1971). The drug significantly increased intake at each time point, with no evidence of the gradual fall in consumption seen after placebo. These changes were accompanied by consistently higher hunger ratings and greater appreciation of food as judged by appetite questionnaires. Similar effects on intake were obtained in a second experiment with unfasted subjects, although changes in hunger and appetite scores were more variable. Abel (1971) reported that inhalation of two cannabis cigarettes (of unknown potency) caused subjects to eat as many as fifty marshmallows, compared with only four by control subjects (the actual time over which the eating took place is not reported). As we shall see later, apparently selective effects of cannabinoids on palatable, and particularly sweet, ingesta have been very influential in later theoretical accounts of the role of endocannabinoids in feeding. But it should be noted that in the Abel (1971) experiment, there was no choice of foods, and the selection of a sweet confection as a test food was entirely serendipitous.

In the first systematic study of cannabinoid effects on feeding, Greenberg *et al*. (1976) examined long-term body-weight changes, dietary selection and energy intake in marijuana smokers tested under research ward conditions over the course of 1 month. In contrast to previous studies, dosage was well-defined, with subjects receiving marijuana cigarettes containing approximately 20 % Δ^9-THC. However, subjects were allowed to smoke freely, with the number of marijuana cigarettes smoked per d gradually increasing over the course of the experiment. In subjects who were experienced marijuana users, daily energy intake rose from a pre-drug level of 3200 (SE 200) kcal (13·39 (SE 0·84) MJ), to peak in the first few days of treatment at 3900 (SE 300) kcal (16·32 (SE 1·26) MJ), before declining to an average of 3300 (SE 200) kcal/d (13·81 (SE 0·84) MJ/d). Overeating was matched by a persistent body-weight increase, averaging 2·3 kg across the entire 21 d drug phase. In fact, body weight continued to rise despite the stabilization of energy intake. During a 5 d post-drug phase, both body weight and energy intake decreased dramatically. Subjects lost an average of 1.8 kg as daily energy intake fell by as much as 1000 kcal (4·18 MJ). Unfortunately, no data was provided on the specific changes in eating patterns or food selection associated with these changes.

The next real advance came from studies by Foltin and colleagues in the 1980s (Foltin *et al*. 1986, 1988). In their 1986 study, subjects were tested in a relatively naturalistic, residential laboratory for periods of up to 25 d. Each test day comprised three phases: a private work period, a performance task and a period of social access. Active or placebo marijuana cigarettes (containing 1·84 or 0 % Δ^9-THC respectively) were smoked before private work periods and during social access. Average daily intake increased from 2780 (SE 130) kcal (11·63 (SE 0·54) MJ) under placebo conditions to 3340 (SE 160) kcal (13·97 (SE 0·67) MJ) with the active marijuana treatment. Interestingly, the overconsumption primarily occurred during periods of social access, with subjects consuming an average of 2500 kcal (10·46 MJ) compared with 1000 kcal (4·18 MJ) under placebo conditions. Notably, this excess was obtained by an increase in the frequency and consumption of 'snack foods', rather than of the set meals provided each day.

In a subsequent experiment Foltin specifically tested the effects of smoked marijuana (1·3 or 2.3 % Δ^9-THC) on the intake of different foods (Foltin *et al*. 1988). Subjects were provided with a wide variety of different food items which they could eat at will. Marijuana increased total food intake by doubling the number of snacks. The main increase in energy intake was largely attributed to an increase in the intake of sweet solid snack items such as candy bars, cookies and cakes. The intake of sweet drinks (e.g. cola, fruit juice), or savoury solid items (e.g. potato chips) were less susceptible. Overall, the distribution of energy from carbohydrate, fat and protein did not differ between drug and placebo conditions.

Similar effects of Δ^9-THC on food selection were also reported by Mattes *et al*. (1994), who compared the relative hyperphagic potency of Δ^9-THC administered via acute oral administration, smoke inhalation or suppository. Relatively small increases in energy intake were derived principally from increased snack consumption, rather than self-selected meals.

Clinical applications of exogenous cannabinoids

While cannabinoid-induced appetite stimulation (or, more strictly, increased food intake) has been demonstrated under laboratory conditions, the few studies performed leave many questions unanswered. More controlled studies are clearly required to determine just how the motivation to eat is affected by cannabinoids, and to establish whether overconsumption is a general phenomenon or is specifically tied to particular taste modalities or specific foods. An additional

component of action of Δ^9-THC is that it exerts an antiemetic effect (Gralla, 1999) which may, or may not, be related to the drug's stimulation of appetite. Moreover, this action is not limited to Δ^9-THC. For example, Abrahamov *et al*. (1995) reported that Δ^8-THC, an analogue of Δ^9-THC with fewer psychotropic actions, was found to abolish vomiting in child patients simultaneously treated with anti-cancer drugs. Such findings indicate that broader analysis of the effects of the different cannabinoids are warranted to establish their behavioural specificity, with the possibility of developing therapeutic applications which lack some of the undesired psychological side effects of Δ^9-THC.

Despite the limitations of the human studies discussed earlier, it is clear that Δ^9-THC has potential to induce substantial elevation of food intake and promote body-weight gain, with the possible additional benefit of limiting the nausea and vomiting associated with many chemotherapy regimens. It is therefore unsurprising that clinicians were keen to assess the utility of cannabinoid treatments in relation to clinical syndromes involving appetite or weight loss. A few, somewhat limited, studies have been conducted with Δ^9-THC to examine the drug's capacity to ameliorate low appetite and wasting in clinical populations with cancer cachexia or HIV (Cat & Coleman, 1994; Gorter, 1999). One of the earliest trials, by Regelson *et al*. (1976), found that oral Δ^9-THC doses of up to 15 mg/d stimulated appetite and produced significant weight gain in advanced cancer patients. In a single-case report, Sacks *et al*. (1990) examined the effect of Δ^9-THC on food intake during a highly emetigenic chemotherapy regimen. Treatment with Δ^9-THC alone (5 mg, three times per d) had little effect on intake, but greatly attenuated the severe reduction in daily energy intake produced by chemotherapy (intake + Δ^9-THC 1453 kcal (6·08 MJ); without Δ^9-THC 764 kcal (3·32 MJ)). In contrast to the findings of Foltin and Mattes (Foltin *et al*. 1986, 1988; Mattes *et al*. 1994), this difference was attributed largely to an increase in energy derived from fat. No meaningful changes in appetite ratings were noted.

Plasse *et al*. (1991) reported the effects of chronic Δ^9-THC treatment in patients with HIV-wasting syndrome. The drug was given at total daily doses of 5–20 mg for as long as 20 weeks (administered orally at 2·5 mg twice per d, or 5 mg four times per d). Δ^9-THC not only reduced nausea, but increased both appetite and mood ratings. Of the patients who responded to the treatment, the majority gained weight, while those that continued to lose weight did so at a slower rate than previously. Drug treatment was accompanied by a weight gain of up to 5·8 kg/month (median 0·54 kg/month), compared with a median weight loss of 0·93 kg/month in the 3 months before treatment.

In a randomized double-blind study of five AIDS patients, Struwe *et al*. (1993) tested the effects of 5 mg Δ^9-THC, given twice per d before meals. Small increases in appetite scores, energy intake and body weight were accompanied by significant increases in body fat. In addition, the patients showed a marked improvement in symptom distress scores and mood. These latter effects raise a further issue which must be addressed experimentally: the extent to which changes in appetite in wasting patients are the result of specific cannabinoid actions on appetite, or to more generalized changes in their sense of well-being.

In a more comprehensive, multi-centre survey, Beal *et al*. (1995) evaluated the long-term effects of Δ^9-THC or placebo in eighty-eight patients with AIDS-related appetite and weight loss. Dronabinol (2·5 mg, twice per d before lunch and supper) was administered over 42 d. Patients who had previously suffered progressive weight loss experienced either stabilization of their body weight or a modest weight gain. In patients who were unaffected by concurrent illness, body weight increased by as much as 1·1 kg. Accompanying these changes were substantial increases (38 %) in appetite ratings across the whole course of treatment. Self-ratings of mood and nausea were also improved. Interestingly, improvements in mood preceded the

changes in appetite and nausea ratings, again indicating the need for more thorough assessment of the wider psychological and behavioural effects of these treatments.

On the basis of studies such as these, the commercial preparations of Δ^9-THC (dronabinol; trade name, Marinol) or a synthetic analogue (Cesamet) have been licensed for clinical use in the treatment of chemotherapy-induced nausea and the treatment of AIDS-associated anorexia and weight loss. It is likely that the number of therapeutic applications could be extended as beneficial effects are reported in other clinical areas. For example, it was recently reported that daily dronabinol treatment in dementia patients, whose symptoms included refusal to eat, produced significant weight gain (but not, paradoxically, significant increases in energy intake; Volicer, 1997).

However, we are still faced with a marked absence of substantial data for the efficacy of cannabinoids in reversing disease- or chemotherapy-related changes to appetite or body-weight status. It seems clear to us that medicinal application of these drugs could be optimized through a better understanding of their actions on the psychological and behavioural components of appetite. Especially important is the need for data on the extent to which the different actions of the drugs (antiemetic, appetite stimulation, mood enhancement) account for the beneficial effects; or indeed whether those effects are separable. With recent advances in cannabinoid pharmacology it is now possible to overcome some of the limitations of human studies by a detailed examination of cannabinoid interventions in animal models. As we detail later, new findings using such models are beginning to pinpoint the precise mechanisms underlying cannabinoid-induced hyperphagia.

Cannabinoid effects in animal models

Much like the literature on human subjects, the database on cannabinoids and feeding in animals is rather insubstantial. A brief spate of studies followed the isolation of the exogenous cannabinoids and the availability of Δ^9-THC, but from the late 1970s until the discovery of anandamide this was a neglected area of investigation. More importantly, the advantages of animal (predominantly rat) models in allowing manipulation of dose and test conditions were overlooked, and only the most cursory analyses of the behavioural actions of exogenous cannabinoids on feeding were carried out. Less than optimal experimental designs also resulted in the majority of studies either failing to find any effect on eating, or actually inducing anorectic effects through the use of high, narcotic doses (e.g. Sofia & Barry, 1974; Graceffo & Robinson, 1998). Abel (1975), reviewing the earliest animal experiments with cannabis extracts or Δ^9-THC, found that out of a total of twenty-five experiments published between 1965 and 1975, only three reported increased intake.

One of the first studies to demonstrate hyperphagia in rats was performed by Glick & Milloy (1972). They reported that an intraperitoneal dose of 1·0 mg Δ^9-THC/kg produced a modest increase in food intake (less than 2 g over 2 h). Unfortunately, their study was compromised through the imposition of 24 h food and water deprivation prior to testing. Under such circumstances, which represent an extreme and rather unnatural physiological challenge, it is difficult for animals to express hyperphagia above the voracious eating already induced by starvation.

Using more naturalistic methods, Brown *et al*. (1977) found that lower, orally administered doses of Δ^9-THC (0·25 or 0·4 mg/kg) significantly increased intake of both food and a palatable 0·8 M-sucrose solution. However, these increases were again very modest: food intake was increased by less than 1 g in a 1 h test; sucrose solution consumption was raised by approximately

7 ml. Like Abel's (1971) 'marshmallow effect' in people, this apparently greater effect on sweet ingesta has subsequently been cited as evidence of a preferential action of cannabinoids on palatable food intake. However, we should reiterate the fact that the increases reported by Brown *et al*. (1977) were relatively minor compared with effects that may be obtained in human subjects. Moreover, apparently selective drug effects on particular foods or flavours may reflect existing preferences rather than a particular mode of action. Indeed, it has been shown that apparently selective effects of drugs on macronutrient intake actually derive from an individual animal's preference for particular foods at the time the drug takes effect (Gosnell *et al*. 1990).

Finally, we should note that not all research has been restricted to the laboratory rat. For example, McLaughlin *et al*. (1979) found that intravenous injection of 0·5 and 1·0 mg/kg Δ^9-THC produced hyperphagia in sheep. Foreshadowing the later discovery of cannabinoid receptors, these workers also found that the effect was stereospecific: only the L-, and not the D-isomer, of Δ^9-THC induced eating (McLaughlin *et al*. 1979).

In the absence of thorough behavioural analyses of Δ^9-THC effects on feeding in rats, we undertook a comprehensive series of tests to better characterize the drug's actions. We initially adopted a pre-feed paradigm in which the rats were thoroughly sated by the provision of a palatable wet mash meal before drug administration. This procedure ensures low baseline intakes and so maximizes our ability to detect hyperphagia. We also conducted our tests during the dark period of a daily 12 h light–dark cycle, as rats are predominantly nocturnal feeders. After oral Δ^9-THC administration, the animals were given unrestricted access to their normal maintenance diet (more usually referred to as 'lab chow' (g/kg): protein 163, fat 29, carbohydrate 460). As can be seen in Fig. 1, a wide range of doses stimulated eating (Williams *et al*. 1998). Furthermore, the maximum effect of the drug was far greater than any previously reported. A 1·0 mg/kg dose produced a greater than 4-fold increase in consumption over 1 h. After administration of the highest dose, non-specific behavioural effects of the drug were evident, such as impaired motor coordination and sedation. Above this dose, the acute, motoric and sedative side effects are such that animals are incapable of overeating.

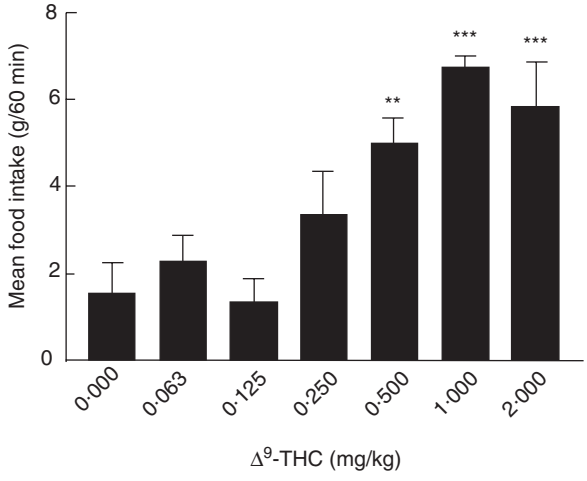

Fig. 1. Orally administered Δ^9-tetrahydrocannabinol (THC) exerts a dose-dependent hyperphagic action in pre-satiated rats (rats consumed approximately 30 g palatable wet mash during 2 h before drug administration). The eating produced by this exogenous cannabinoid can be attenuated by pre-treatment with the selective CB1 receptor antagonist, SR141716 (Williams *et al.* 1998). Values are means with standard errors shown by vertical bars. Mean values were significantly different from vehicle condition: $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$.

Subsequent experiments confirmed that these hyperphagic effects of Δ^9-THC were mediated by central CB1 cannabinoid receptors. Specifically, we found that hyperphagia was significantly attenuated by SR141716, a selective CB1 receptor antagonist, but not by SR144258, a selective antagonist of the peripheral type, CB2 receptor (CM Williams and TC Kirkham, unpublished results).

One aspect of these data that deserves particular emphasis is the magnitude of the overconsumption that was induced by Δ^9-THC. Our pre-fed animals were thoroughly satiated, having already eaten an amount of wet mash equivalent to their normal daily food intake (> 20 g). The substantial intake that followed Δ^9-THC treatment thus signifies that stimulation of CB1 receptors can provoke an exceptionally powerful stimulus to eat. Moreover, the extent of Δ^9-THC-induced overeating was similar, if not in fact greater than, that induced by central administration of the neurotransmitter neuropeptide Y (for example, see Clark *et al*. 1984), widely regarded as being a key component of the brain mechanisms that promote ingestive behaviour. The remarkable potency of Δ^9-THC, and the attenuation of its hyperphagic effects by CB1 blockade, thus provides a very convincing case for involvement of the endocannabinoid systems in the normal regulation of feeding.

An important aspect of modelling cannabinoid effects in animals is the examination of chronic effects of the drug. If we are to obtain an adequate understanding of the behavioural changes that might affect clinical applications of the cannabinoids, long-term studies are essential. Again, the literature on chronic Δ^9-THC administration generally relates to the use of relatively high doses of the drug, and the most consistent report is of anorectic consequences. A typical finding is that food intake is persistently suppressed with a consequent reduction in body weight (Manning *et al*. 1971; Sjoden *et al*. 1973; Sofia & Barry, 1974). These effects are probably due to the narcotic properties of the doses employed (Drewnowski & Grinker, 1978). Chronic cannabinoid treatment thus remains an important, and currently neglected, area of study. In our own pilot experiments, mimicking typical clinical treatment regimens, we have found that while Δ^9-THC will produce acute increases of food intake rats tend to display rebound hypophagia, compensating for their initial overconsumption. Consequently, over 24 h, total intake may be suppressed relative to controls. When measured over several days, the net consequence of daily (single or multiple) Δ^9-THC doses is to actually retard the normal weight gain in rats fed *ad libitum*. Further experiments are thus required to determine the optimum level and frequency of dosing to obtain persistent elevation of intake and body weight.

While the potent CB1-mediated hyperphagic effects of Δ^9-THC provide strong evidence of endocannabinoid involvement in appetite, this possibility necessitates the demonstration that the endogenous cannabinoids, themselves, will also exert hyperphagic actions. The contemporary literature provided no support for this possibility, with the only previous test of anandamide effects on eating being unsuccessful (Crawley *et al*. 1993). We nevertheless conducted our own investigation, using the same pre-feed design as had been so effective for THC. In our tests, anandamide was indeed found to significantly increase chow intake in pre-fed rats (Williams & Kirkham, 1999*a*), over a range of peripherally administered doses (Fig. 2). Although the degree of overeating was quite modest compared with the effects of Δ^9-THC, the most effective dose (1 mg/kg) produced a doubling of intake over a 3 h test. Moreover, anandamide hyperphagia was entirely prevented by pre-treatment with SR141716, while the CB2 antagonist SR144258 was without effect (Fig. 3), indicating that the overeating was specifically mediated by central CB1 receptors.

More intriguingly, anandamide effects were apparent over a much longer time course than those of Δ^9-THC. Whether this reflects continued bioavailability of the exogenously administered endocannabinoid (which is very susceptible to enzymic degradation once within neurons),

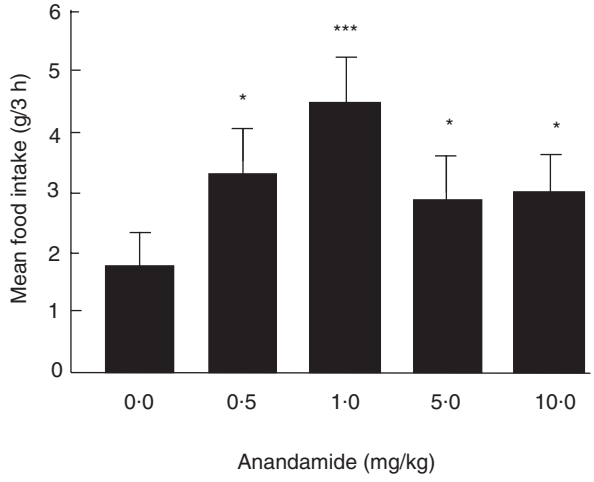

Fig. 2. Subcutaneous injection of the endogenous cannabinoid, anandamide, produces significant overeating in pre-fed rats. The degree of hyperphagia is modest compared with the effects of Δ^9-tetrahydrocannabinol, but has a much longer duration (Williams & Kirkham, 1999). Values are means with standard errors shown by vertical bars. Mean values were significantly different from vehicle condition: $^*P < 0{\cdot}05$, $^{***}P < 0{\cdot}001$.

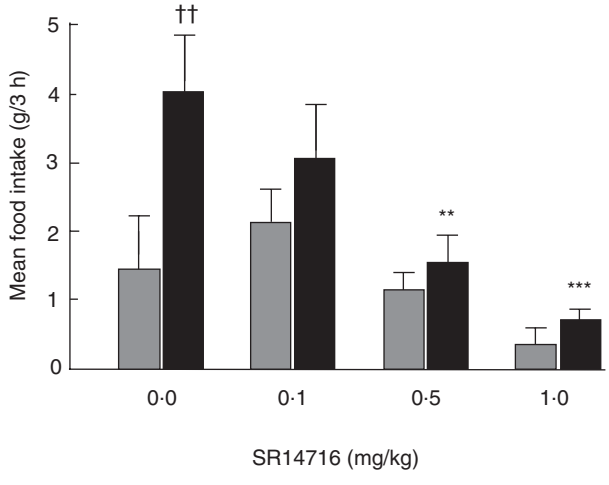

Fig. 3. Hyperphagia in anandamide-treated, pre-fed rats (■) is prevented by pretreatment with the selective CB1 antagonist, SR141716 (▒), indicating that the effects are mediated by central cannabinoid receptors. The grey bars display weak effects of SR141716 when administered alone. Values are means with standard errors shown by vertical bars. Mean value was significantly greater after subcutaneous anandamide (1·0 mg/kg): $\dagger\dagger P < 0{\cdot}01$. Mean values showed significant attenuation of anandamide hyperphagia: $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$.

or involves the initiation of a cascade of physiological events remains to be determined. However, what was striking was that the largest effects occurred at times when, under control conditions, animals were most likely to engage in substantial feeding. Thus, early in the test when the satiating effect of the pre-feed was apparent as an almost complete suppression of

feeding, anandamide produced only very weak effects. Only when the inhibitory effects of the pre-feed began to wane did the stimulatory actions of the endocannabinoid become easily apparent. We are tempted to speculate that our data represent an amplification, or potentiation, of endocannabinoid activity associated with the normal, episodic pattern of meal-taking in rats.

Importantly, anandamide-induced feeding has also been replicated in mice by Hao *et al*. (2000) with a very low dose of the cannabinoid (0·001 mg/kg, intraperitoneally). In addition, as a corollary to these agonist data, we should also note that repeated, daily administration of the CB1 antagonist, SR141716, has been shown to suppress appetite and induce persistent weight loss in rats (Colombo *et al*. 1998). Although tolerance to the drug's effect on appetite was apparent after 5 d, the resultant suppression of body-weight gain was evident across the full course of a 14 d experiment. These combined agonist and antagonist data thus provide the first clear indications that endogenous cannabinoid systems may play a normal role in the physiological regulation of appetite.

Behavioural characterization of cannabinoid hyperphagia: the reward hypothesis

The preceding findings do provide evidence for some role of endocannabinoids in appetite regulation. However, increases in food intake alone tell us little about what aspect, or aspects, of the motivation to eat are actually altered to affect behavioural change. Indeed, given the wide pharmacological spectrum of cannabinoids, it is essential to demonstrate that hyperphagia follows from a natural adjustment to feeding motivation, and not through some non-specific action (we will return to this issue later). Certainly, the very limited insights provided by the early cannabinoid research demand far more detailed analyses of behavioural modifications induced by CB1 ligands before detailed hypotheses can be formed.

Despite the lack of precise information about cannabinoid actions, one hypothesis has gained particular influence. As we noted earlier, early reports from some studies with animals and human subjects were suggestive of a more marked susceptibility of palatable foods to the stimulant effects of Δ^9-THC. While those data are not wholly convincing (and may be artifactual), they have given rise to the notion that cannabinoids may provoke overconsumption by amplifying the orosensory reward, or palatability, of foods (Arnone *et al*. 1997).

A common feature of drugs of abuse is their activation of the brain pathways which normally subserve the appetitive and consummatory aspects of natural rewards, such as food and sex. There is convincing evidence to suggest that the exogenous cannabinoids can also influence these brain reward systems (for review, see Gardner & Vorel, 1998). Reward circuitry can be also be activated by electrical stimulation of the brain: animals will actually perform complex instrumental tasks to obtain such stimulation. Moreover, with appropriate environmental stimuli, electrical brain stimulation can also induce and sustain those behaviours, such as eating, which normally produce reward. It is significant then that Trojniar & Wise (1991) were able to show that Δ^9-THC will facilitate feeding induced by electrical stimulation of the lateral hypothalamus (a brain region long associated with feeding and reward processes). These effects imply that Δ^9-THC amplifies the rewarding properties of food with a consequent increase in the motivation to eat.

Endocannabinoids are also implicated in food reward by the behavioural effects of CB1 blockade. Arnone and colleagues reported that in rats and marmosets SR141716 selectively attenuated the consumption of palatable ingesta (Arnone *et al*. 1997; Simiand *et al*. 1998), while having little or no effect on bland food intake (of the kind normally provided to laboratory animals for their general maintenance). These workers suggested that such preferential

effects of CB1 blockade indicate important tonic endocannabinoid activity underlying food reward. Thus, cannabinoid agonists could increase food intake by rendering foods more palatable, while antagonists might tend to diminish the hedonic value of foods, and so reduce consumption.

With these data in mind, we began a series of studies to directly address the cannabinoid-reward hypothesis and, more generally, to obtain more thorough details of cannabinoid effects on feeding behaviour. As a starting point, we began by measuring the effects of SR141716 on sucrose sham-feeding. In this model, rats are surgically implanted with a chronic gastric fistula (a sealable cannula through which gastric contents may be drained). The animals ingest palatable sucrose solutions, which are recovered within seconds directly from the stomach. Under these circumstances, normal satiation mechanisms are minimized and ingestion is motivated exclusively by food palatability (Weingarten & Watson, 1982). In the absence of normal satiety, 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 hypothesized that, if endogenous cannabinoids directly mediate food reward, sham-feeding should be disrupted by CB1 blockade. More specifically, we anticipated that suppression of sham-feeding by SR141716 would produce changes in behaviour which resemble the effect of diluting the sucrose solution (Kirkham & Cooper, 1988; Kirkham, 1990). A precedent for such an effect comes from our previous work with opioid antagonists. Opioids are heavily implicated in orosensory reward (see later), in part through the demonstration that opioid receptor antagonists reduce sucrose sham-feeding in a manner which exactly mimics the changes in ingestion produced by 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 & Cooper, 1988; Kirkham, 1990; Leventhal *et al*. 1995).

Contrary to our expectations, SR141716 failed to affect sucrose sham-feeding at all (Kirkham & Williams, 1998). Even doses ten times greater than those that reverse Δ^9-THC- or anandamide-induced feeding (Williams & Kirkham, 1999*a*; CM Williams, PJ Rogers and TC Kirkham, unpublished results), or reportedly suppress sucrose drinking in intact animals (Arnone *et al*. 1997) were ineffective. The failure of SR141716 to attenuate sham-feeding argues strongly against significant endogenous cannabinoid activity within the pathways which maintain sucrose ingestion. In other words, endocannabinoids do not seem to be primarily involved in food reward during ingestion, and are not crucial to the pleasure derived from orosensory characteristics of food.

However, while our sham-feeding data do not support endocannabinoid mediation of the consummatory aspects of food reward, our data do not entirely preclude their involvement in some other aspect of feeding-related reward processes. It is possible, for example, that endocannabinoids are associated with appetitive, or incentive, aspects of feeding motivation, related to the anticipation of food or the desire to eat.

Going beyond the feeding literature to studies of endocannabinoid involvement in alcohol craving, we can find convincing evidence that cannabinoid interventions do indeed modify appetitive–incentive processes. McGregor and his colleagues have reported several experiments using an operant, lick-based, progressive ratio paradigm as a model of craving. Rats are required to complete a progressively greater number of responses (licks at a spout) to obtain successive reinforcements of small volumes (0·1 ml) of some liquid (typically alcohol or sucrose solutions). The reinforcement ratio at which animals cease to respond (the ‘break-

point') is taken as an index of the degree of craving. Gallate & McGregor (1999) found that the CB1 antagonist SR141716 produced a dose-related reduction in break-point to obtain beer reinforcers. By contrast, they found that a CB1 agonist, CP 55940, would increase break-points in rats licking for beer or sucrose solutions; i.e. rats would work harder to obtain reinforcement (Gallate *et al*. 1999). These effects, which were also reversed by SR141716, strongly implicate endocannabinoid systems in the processes underlying the motivation to obtain palatable ingesta.

Returning to feeding, we have also obtained data to support endocannabinoid involvement in incentive motivation. Using an open-field apparatus, we observed the behaviour of satiated rats following administration of Δ^9-THC and anandamide. 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 (Fig. 4). 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 Δ^9-THC- and anandamide-treated rats in the open field is identical to that of untreated rats feeding freely in their home cages (Williams & Kirkham, 1999*b*; CM Williams, unpublished results). At this stage of our investigations, we cannot entirely preclude non-specific actions of the cannabinoids which might account for these latency effects (for example, an anxiolytic action which could suppress exploratory activity in favour of eating). However, in no case was there any evidence of unnatural activities (such as stereotypy) that might otherwise account for the increased feeding. With these cautions in mind, we feel that these data are compatible with an action of cannabinoids to increase the incentive value of the food and advance the species-typical sequence of feeding behaviours.

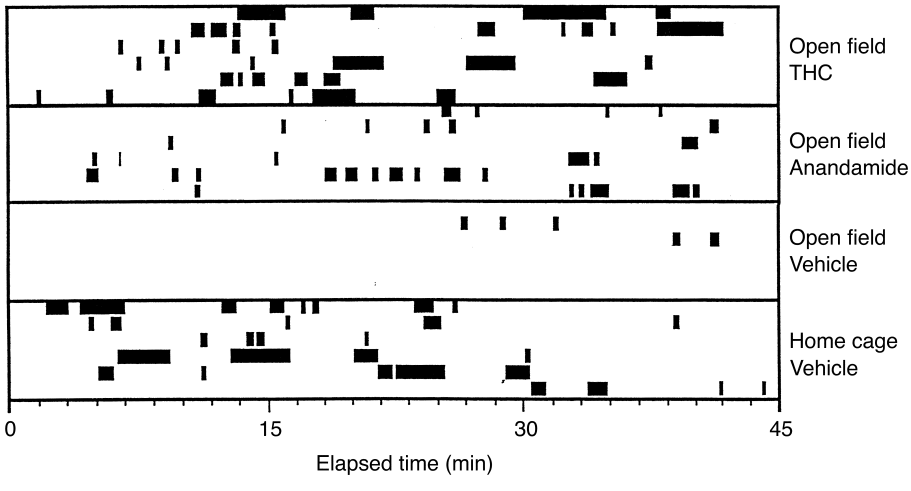

Fig. 4. These charts represent the occurrence of eating episodes in groups of pre-satiated rats, observed either in their home cage after saline injection, or in an open field arena following administration of hyperphagic doses of Δ^9-tetrahydrocannabinol (THC), anandamide or vehicle. For each condition, behavioural traces are presented for six rats, allowing comparison of feeding behaviour after vehicle and each drug dose. In a relatively novel open field, vehicle-treated rats show little motivation to eat. However, both Δ^9-THC and anandamide actively promote eating: reducing the latency to begin eating and inducing a pattern of feeding which is very similar to that seen in the untreated rats under home cage conditions.

We have also observed these effects using a more naturalistic, continuous meal pattern monitoring technique, where moment-to-moment feeding is monitored in the animals' home cages (for review of meal pattern methodology, see Clifton, 2000). Under these circumstances, the latency to the first meal of pre-satiated or free-feeding rats is consistently reduced after endocannabinoid administration; often by more than 1 h compared with the control values.

Interestingly, a similar action of Δ^9-THC on eating latency was reported by Trojniar & Wise (1991) in their experiments on eating induced by electrical stimulation of the lateral hypothalamus. Together with the Gallate *et al*. (1999) break-point data, such findings imply that stimulation of CB1 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 intrameal palatability factors which maintain sham-feeding, these data tend to support a specific endocannabinoid involvement in the inter-meal motivational processes that culminate in meal taking.

Further support for this notion comes from our pilot experiments examining interactions between food deprivation and the anorectic potency of SR141716 on the intake of bland laboratory chow (TC Kirkham and CM Williams, unpublished results). The antagonist was administered to rats which had been food deprived for 18 h or maintained on a schedule of restricted access to food. We found that whereas rats fed *ad libitum* were unaffected by the drug, restricting food availability resulted in significant intake suppression by SR141716. These preliminary results suggest that deprivation induces, or enhances, endocannabinoid activity. As SR141716 acts as a competitive antagonist at CB1 receptors, the behavioural effects of CB1 blockade will only become apparent if there is endogenous cannabinoid release and receptor stimulation. The greater the level of cannabinoid activity, the greater will be the behavioural consequences of SR141716 treatment.

In effect, the stimulatory actions of the cannabinoids on eating resemble the physiological changes which occur with food deprivation, since both manipulations reduce eating latency and promote short-term increases in meal size (Bivens *et al*. 1998). Unfortunately, this aspect of our story is complicated by a report that SR141716 fails to affect operant responding for food pellets in food-restricted rats (Rodriguez de Fonseca *et al*. 1999); precisely the circumstances where antagonist-induced reduction of responding might be expected. There is clearly much more work to be done to resolve these issues, but it is interesting that Hao *et al*. (2000) have recently reported that doses of anandamide that can provoke overeating in mice also reverse some of the changes in brain neurotransmitter turnover that are induced by food restriction.

Nevertheless, on the basis of our data, we might propose that endogenous cannabinoid activity gradually increases during intermeal intervals to reach some critical level when motivation to eat is triggered. Accordingly, the longer the time that has elapsed since the last meal, the greater will be the activity in relevant endocannabinoid circuits, and the higher the motivation to eat. We might also assume that there are natural rhythms in such activity which are correlated with normal patterns of meal taking, so that the optimal demonstration of CB1 agonist or antagonist effects on feeding will be obtained by carefully synchronizing drug administration with these endogenous cycles.

Interactions between cannabinoids and brain reward systems

The notion that endocannabinoids are involved in appetitive aspects of feeding is compatible with the known effects of Δ^9-THC on brain reward pathways. Central to these pathways are the

mesolimbic dopaminergic neurons, arising in the ventral tegmental area and projecting to the nucleus accumbens (Spanagel & Weiss, 1999). Natural rewards, including food, together with many drugs of abuse, have been found to stimulate dopamine release from terminals in the nucleus accumbens. Researchers now emphasize a specific role for these pathways in incentive motivation, i.e. the generation of emotional arousal and behavioural activation in response to stimuli, which predict reward (Ikemoto & Panksepp, 1999; Spanagel & Weiss, 1999; Berridge, 2000).

Ingestion of food causes dopamine release in the nucleus accumbens, especially after deprivation, or if the food is novel or palatable. In addition, food restriction is known to enhance the rewarding properties of food and of drugs of abuse (Berridge, 1991; Cabeza de Vaca & Carr, 1998). It is perhaps not coincidental, then, that doses of Δ^9-THC which we have found to produce hyperphagia have also been found to stimulate dopamine release in the nucleus accumbens (Gardner, 1992; Tanda *et al*. 1997; Gardner & Vorel, 1998; Williams *et al*. 1998).

Other data indicate that the various behavioural effects of CB1 agonists can be modified by dopamine receptor antagonists (Souilhac *et al*. 1995; Sanudo-Pena *et al*. 1996), and that cross tolerance can occur between CB agonists and dopamine agonists (Rodríguez de Fonseca, 1994). In addition, CB1 receptors have been found to be co-localized, and to interact, with dopamine D1 and D2 receptors (Bidaut-Russell & Howlett, 1991; Glass *et al*. 1997). Overall, there is growing support for functional relationships between endocannabinoid and dopaminergic activity in the brain. Therefore, it is entirely feasible that brain dopaminergic systems implicated in general incentive processes and drug craving could also be involved in the feeding effects of cannabinoids. It will be important, therefore, to assess the extent to which feeding effects of CB1 ligands can be affected by treatments modifying dopamine function.

In addition to dopamine, the endogenous opioid peptides are also linked to central reward processes. For example, in the accumbens, dopamine neurons synapse with enkephalinergic neurons that are critical to the expression of reward- or incentive-related behaviours (Gardner & Vorel, 1998). In the ventral tegmental area, opioids are thought to remove mesolimbic dopaminergic neurons from γ-aminobutyric acid (GABA)-mediated inhibition (Spanagel & Weiss, 1999).

Evidence has also accumulated to support overlapping endogenous opioid and endocannabinoid mechanisms in relation to a wide range of physiological processes (Fuentes *et al*. 1999), including reward and appetite. For example, CB1 receptor knockout mice are not only unresponsive to cannabinoids, but display a reduced sensitivity to the rewarding properties of opiate drugs (Ledent *et al*. 1999). In addition, in the same strain of mice, morphine administration fails to stimulate the nucleus accumbens dopamine release found in animals that do express the CB1 receptor, suggesting that CB1 receptors regulate mesolimbic dopamine transmission (Mascia *et al*. 1999).

Gardner *et al*. (1988) reported that enhancement of brain-stimulation reward by Δ^9-THC was blocked by the general opioid receptor antagonist, naloxone. Importantly, the facilitation by Δ^9-THC of feeding induced by stimulation of the lateral hypothalamus is also blocked by naloxone (Trojniar & Wise, 1991). Finally, Gallate *et al*. (1999) found that the facilitatory effects of a CB agonist on responding for palatable solutions were reversed by both a CB1 antagonist and naloxone. Such findings imply that cannabinoids modulate the motivation to ingest via actions on both cannabinoid and opioid systems.

Opioids are firmly implicated in the mediation of food reward in their own right by the ability of opioid receptor agonists and antagonists to increase or reduce food intake respectively. These effects have been shown to involve changes in the hedonic evaluation of foods

(for reviews, see Kirkham & Cooper, 1991; Cooper & Kirkham, 1993). For example, opioid antagonists are reported by human subjects to reduce the perceived palatability of previously preferred foods and fluids. Since food palatability is one of the principal determinants of the persistence of eating, it is important that opioid manipulations primarily affect the duration of meals and are most apparent in tests with palatable foods.

Although our analyses are in their preliminary stages, the meal pattern analyses referred to earlier suggest that there may be a secondary action of anandamide. In addition to the marked effects on eating latency, there may also be a tendency for agonist administration to increase the size and/or duration of meals. If this latter effect can be confirmed, it would suggest that the behavioural consequences of cannabinoid treatments may not, after all, be restricted solely to intermeal incentive processes. Given the potent influence of food palatability on the maintenance of eating, any tendency of cannabinoids to increase meal duration would suggest some enhancement of orosensory reward. However, it is also possible that any effect of cannabinoids on intrameal factors may be indirect, and mediated through interactions with other important neurochemical systems mediating food palatability. Some of our recent experiments do indeed provide convincing evidence for interactions between cannabinoids and endogenous opioids in relation to feeding.

To investigate this possibility, we first attempted to block the hyperphagic actions of Δ^9-THC with naloxone. We found that even low, subanorectic doses of the opioid antagonist effectively blocked cannabinoid-induced overconsumption (CM Williams and TC Kirkham, unpublished results). Subsequently, we examined whether combined administration of the CB1 antagonist SR141716 with naloxone could provide further evidence of co-operative interactions between cannabinoid and opioid systems. We chose a range of doses of each antagonist which, alone, are capable of reversing the actions of agonists at their respective binding sites but exert no significant effect on chow intake. As can be seen in Fig. 5, neither naloxone alone, nor

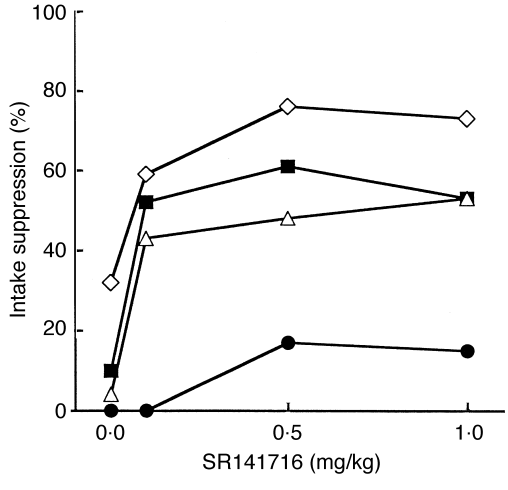

Fig. 5. Subanorectic doses of the opioid antagonist naloxone and the CB1 antagonist, SR141716, were given alone or in combination to non-deprived rats. Each line indicates the effect of a single dose of SR141716 with increasing doses of naloxone (NX). (●), 0·0 mg NX/kg; (△), 0·1 mg NX/kg; (■), 0·5 mg NX/kg; (◇), 1·0 mg NX/kg. The data are presented as intake suppression (%) relative to the vehicle–vehicle control condition. The graph illustrates how combined doses of both drugs, which were ineffective independently, interacted to produce significant intake suppression.

SR141716 alone, produced any reliable effects on food intake. However, when given in combination, every dose of SR141716 potentiated the effects of all doses of naloxone. Significant intake suppression occurred with every combination of the two drugs, relative to the vehicle–vehicle, SR141716–vehicle or vehicle–naloxone conditions (Kirkham & Williams, 2001).

These data seem to indicate a synergistic interaction between the effects of opioid and cannabinoid receptor antagonists, and go a long way to support an important functional relationship between cannabinoid and opioid systems in the normal regulation of appetite. The dramatic nature of the combined effects of these drugs compared with their very weak independent effects are difficult to explain. However, given what we already know about opioids and feeding and CB1 agonist effects on eating microstructure, it is possible to argue that the suppression of feeding by combined opioid and cannabinoid receptor blockade may involve distinct actions on both appetitive (cannabinoid) and consummatory (opioid) aspects of eating motivation. If SR141716 acts to reduce the incentive value of food, while naloxone reduces food palatability once the animals begin to eat, we might predict that joint administration of the two drugs would act to delay the onset of feeding and, once initiated, lower the palatability of the test food and so reduce meal duration. Each effect alone may be insufficient to significantly affect intake, being obscured by the low resolution of measurement in our tests (i.e. by only measuring total intake after 1 h), but easily detectable when occurring contiguously. We are currently testing this hypothesis using observational analyses.

Whatever the behavioural alterations underlying these effects, our findings may have particular importance in the light of the proposed existence of a cannabinoid receptor subtype that is differentially linked to opioid systems (Welch & Eads, 1999). A further possibility is that these combinatorial effects reflect similar actions on ventral tegmental dopamine neurons. These neurons are under the inhibitory influence of GABAergic neurons in the ventral tegmental area. Endogenous opioids act to increase dopamine release in the accumbens by disinhibiting GABA neurons in the ventral tegmental area (Johnson & North, 1992). In addition, many of the neurons which express CB1 receptors are GABAergic, and the effect of CB1 agonists on these cells is again to reduce the release of GABA (Marsicano & Lutz, 1999). The marked effects of combined administration of opioid and cannabinoid receptor blockers might thus be explained in terms of enhanced GABAergic inhibition of mesolimbic dopamine activity. Obviously, a wide range of detailed pharmacological analyses are necessary to shed further light on these phenomena.

Another aspect of our research, which may shed further light on the mechanisms by which endocannabinoids influence appetite, involves mapping the brain sites mediating their actions. As we discussed earlier, CB1 receptors are expressed throughout the brain and the number of potential targets is extensive. However, one particular brain region has been increasingly linked to feeding and reward processes: the nucleus accumbens, and especially the shell sub-region of this nucleus (Kelley, 1999). We have obtained pilot data showing that several CB1 agonists, including anandamide, can induce feeding in this region (Kirkham & Williams, 1999). In our most recent experiments (TC Kirkham and CM Williams, unpublished results) we have also shown that hyperphagia can be obtained in freely-feeding rats by bilateral accumbens shell infusion of the endocannabinoid 2-arachidonoylglycerol. This latter finding represents the first demonstration of the ability of 2-arachidonoylglycerol to increase food intake, and provides compelling evidence for a natural role of this endocannabinoid in appetite regulation. Interestingly, short-term increases in food intake following 2-arachidonoylglycerol were almost wholly attributable to a reduction in meal latency, rather than increases in meal size. More experiments are obviously required to explore the brain sites sensitive to cannabinoid treatments, but the demonstration that

the accumbens is a sensitive target for endocannabinoid-induced feeding further strengthens the link between these neuromodulators and the reward processes outlined earlier.

Conclusion

The historical association between the effects of exogenous cannabinoids and appetite has provided scientists with an important lead to one of the possible physiological roles for the newly discovered endocannabinoid systems. While the potential of the exogenous cannabinoid, Δ^9-THC, to stimulate eating has been an accepted fact for many years, our review of the past literature shows that there are many questions about its action which remain unanswered. Work in our laboratory has shown that Δ^9-THC can induce a degree of overeating that matches that produced by other hyperphagic pharmacological manipulations. We have also demonstrated that these effects are due to interaction with central, endocannabinoid systems. In addition, we have now obtained very strong evidence that the endocannabinoids contribute to the normal mechanisms regulating appetite, through the demonstration that anandamide and 2-arachidonoylglycerol can also induce hyperphagia. Importantly, animals work harder to obtain food after CB1 stimulation, and eat sooner in a test, and more frequently than normal. Moreover, the changes to feeding behaviour induced by the endocannabinoids are entirely compatible with specific adjustments to eating motivation. Strengthening this hypothesis, we have seen that blockade of CB1 receptors reduces the willingness of laboratory animals to work for ingesta. Together with the other behavioural effects of exogenous or endogenous cannabinoids, these findings suggest that endocannabinoid systems are actively involved in the processes which drive us to eat.

In addition, we have presented evidence to suggest that endocannabinoid activity is not essential to the maintenance of ingestion, particularly ingestion maintained by palatability. However, we have also seen evidence of interactions between endogenous cannabinoids and the opioid systems which are intimately associated with orosensory reward. Such interactions suggest that, in addition to making food stimuli more salient, cannabinoid administration may also indirectly amplify the hedonic evaluation of foods. We have proposed that these combined actions on appetitive and consummatory aspects of feeding motivation may reflect modulation of classical, dopaminergic and opioidergic reward pathways. In line with this notion, we have demonstrated that the nucleus accumbens shell is a sensitive site for cannabinoid-induced hyperphagia. Overall, these different findings tend to confirm endocannabinoid involvement in the critical motivational processes underlying the stimulation of appetite. Experiments that we are currently conducting will attempt to establish the extent to which endocannabinoid activity contributes to the normal cyclicity of feeding and whether it may constitute a component of a normal ‘hunger signal’.

Despite recent advances in cannabinoid pharmacology and a growing interest in the potential of cannabinoid-based therapies, current knowledge is severely handicapped by the lack of fundamental research into the behavioural actions of these substances. A willingness to accept essentially anecdotal accounts about cannabinoid actions, and to build hypotheses without access to even the most basic phenomenological data has slowed progress in this area considerably. However, we hope that our first steps in characterizing the behavioural actions of, and motivational processes served by endocannabinoids will soon give rise to both a better understanding of the neurochemical mechanisms regulating appetite and the promise of improved therapies for the treatment of disorders of eating and body weight.

The demonstration that cannabinoid receptor ligands can stimulate eating, and the possibility

that endocannabinoids could play an important role in the processes which give rise to hunger or appetite, may also help redress the current outlook on eating as merely a process to be limited. We hope that our research will contribute to a resurgence of interest in the biopsychological processes underlying so much of our individual and cultural approaches to food and eating. Our innate responsiveness to food stimuli and our capacity to overconsume are likely to be understood and managed more easily through analysis of the mechanisms that provoke appetite, rather than by pursuing yet more putative satiety factors. There are many more experiments to do, and many more avenues to follow. But we anticipate that future research will only consolidate our view of endocannabinoid systems as essential components of appetite regulation.

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