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Review

# Endocannabinoids and food consumption: comparisons with benzodiazepine and opioid palatability-dependent appetite

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**Abstract**

The endocannabinoid system consists of several endogenous lipids, including anandamide and 2-arachidonoyl-glycerol (2-AG), and constitute a retrograde signalling system, which modulates neurotransmitter release and synaptic plasticity. Specific brain-type cannabinoid receptors ($CB_1$) are widely distributed in the central nervous system, and are localized presynaptically. Mounting evidence, reviewed here, indicates that cannabinoids can act to increase food consumption, and cannabinoid $CB_1$ receptor antagonists/inverse agonists reduce food intake and suppress operant responding for food rewards. Hence, endocannabinoids provide the first example of a retrograde signalling system, which is strongly implicated in the control of food intake. Benzodiazepine and opioid palatability-dependent appetite are well-established processes supported by several sources of convergent evidence; they provide pharmacological benchmarks against which to evaluate the endocannabinoids. To date, evidence that endocannabinoids specifically modulate palatability as an affective evaluative process is insufficient and not compelling. Endocannabinoids may have important clinical utility in the treatment of human obesity and forms of eating disorders.


*Keywords:* Appetite; Benzodiazepine; Endocannabinoid; Obesity; Opioid; Palatability

**Contents**



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## 1. Introduction

It is widely recognised that there is a rapidly growing prevalence of obesity and diabetes, with obese individuals being at greater risk for high blood pressure, high cholesterol levels, asthma and arthritis. Within the United States, there have been consistent increases in obesity and overweight for both sexes, all ages, all races, all educational levels, and all smoking levels, for the periods 1991–1998 (Mokdad et al., 1999), 1999–2000 (Flegal et al., 2002), and 2000–2001 (Mokdad et al., 2003). In 2001, the prevalence of obesity in US adults stood at 20.9%, using a body mass index (BMI) criterion of ≥30 (Mokdad et al., 2003). Similar data also indicate an increasing prevalence of overweight in US children and adolescents (Ogden et al., 2002). For 12–19-year olds, the prevalence of overweight was 15.5%. However, this is not a problem which is restricted to the US, and the prevalence of overweight is also increasing in almost all Western European countries, Australia and China (Silventoinen et al., 2004).

There has been debate about the respective contributions of decreased energy expenditure and increased energy intake in determining overweight and obesity. A recent large international study has found a close association between increasing energy supply and increasing overweight and obesity (Silventoinen et al., 2004). The Pima Indians living in Southwestern Arizona are amongst the most obese populations in the world; a recent investigation has demonstrated that in this population total energy intake is a determinant of changes in body weight (Tataranni et al., 2003). High-energy intake is a risk factor for human obesity.

Faced with these seemingly inexorable trends, two fundamental questions arise: What are the determinants of high-energy intake? What interventions are possible which will be effective in reducing human overweight and obesity? Perhaps surprisingly, despite the attention paid to palatability as a factor determining overconsumption of energy-dense foods (Drewnowski, 1990), there is a paucity of evidence linking sensory properties of food, related to palatability, with human food selection and consumption (Sørensen et al., 2003). In respect of pharmacological interventions, there are few available long-term studies of the effectiveness of anti-obesity drugs. Of currently approved medications, orlistat and sibutramine appear to be modestly effective in helping to reduce body weight (Padwal et al., 2003). Quite clearly, considerably more research is needed urgently, if the current obesity and diabetes epidemic is to be controlled successfully, while answers to such fundamental issues remain elusive.

Within this general context, I shall focus on the recent evidence, derived in the main from animal studies, which shows that the endocannabinoid system (defined below) plays a significant role in the control of food intake. More specifically, I shall consider the idea that cannabinoids and cannabinoid receptor antagonists modulate food and taste palatability, which is a popular way to construe their actions on ingestive response. However, we need to adopt criteria for judging the issue, and the most practical means to do this is to review evidence for classes of drugs where strong cases have been made that they modulate food and taste palatability. For this reason, I have chosen benzodiazepines and opioids, since there is strong evidence that they modulate the positive hedonic evaluation of tastes and foodstuffs. Even with these examples, the evidence is far from complete, but they at least provide important benchmarks against which to consider the currently available evidence for the cannabinoids. At a basic science level, we should consider the possibility that a range of drug classes may have convergent effects to moderate the activity of an extended palatability system, involving a number of interconnected brain structures. A number of earlier reviews on endocannabinoids in relation to food intake and body weight are available (Berry and Mechoulam, 2002; Cota et al., 2003; Kirkham and Williams, 2001a).

## 2. The endocannabinoid system

### 2.1. Discovery

Forty years ago, Gaoni and Mechoulam (1964) reported the isolation and identification of $\Delta^9$-tetrahydrocannabinol{(−)-*trans*-(6*aR*,10*aR*)-6*a*,7,7,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol} (THC), the main active psychotropic ingredient of *Cannabis sativa*. This discovery (Mechoulam, 2002) promoted an enormous volume of research, and recent developments have placed $\Delta^9$-THC and cannabinoids at the centre of increasingly interesting insights into neural functions, and of associated behavioural and physiological systems. Howlett and Fleming (1984) observed that cannabinoids inhibit adenylyl cyclase, and this was followed by the discovery of a specific receptor in the brain for cannabinoids (Devane et al., 1992). It is described as the cannabinoid $CB_1$ receptor (Howlett et al., 2002). The rat brain receptor was cloned by Matsuda et al. (1993), followed by the human (Gérard et al., 1990, 1991) and mouse homologues (Chakrabarti et al., 1995). A second

receptor, found in peripheral tissue (Munro et al., 1993), is referred to as the cannabinoid $CB_2$ receptor (Howlett et al., 2002). These important developments set the scene for the discovery of endogenously occurring ligands for the cannabinoid $CB_1$ receptor in brain tissue, and the unfolding of a novel, and quite unsuspected, neuronal signalling system. Viewed in its several aspects, there is considerable justification in referring to an endocannabinoid system, comprising endogenous signalling entities associated with specific receptors, and widely distributed throughout brain tissue. One can anticipate the critical involvement of such an extended system in a wide variety of behavioural functions (Chaperon and Thiébot, 1999).

### 2.2. Cannabinoid receptors

Cannabinoid $CB_1$ receptors belong to the superfamily of G protein-coupled receptors (metabotropic receptors), regulating adenylyl cyclase, and leading to an inhibition of cyclic AMP production (Pertwee, 1997). They are much more densely expressed in the rat brain than any other G protein-coupled receptor, and, indeed, compare with levels found for common ionotropic receptors. Studies that have employed quantitative autoradiography, in situ hybridization, and immunocytochemistry have yielded detailed information about the distribution of cannabinoid $CB_1$ receptors in the brain. Autoradiographic studies (Glass et al., 1997; Herkenham et al., 1990, 1991) demonstrated that high levels of receptors were found in cerebral cortex, hippocampus, basal ganglia and cerebellum; lower levels were found in hypothalamus and spinal cord (Freund et al., 2003; Pertwee, 1997). In situ hybridisation studies broadly corroborated the earlier autoradiographic studies, and confirmed that the cannabinoid receptors were found on axon terminals (Mailleux et al., 1992; Matsuda et al., 1993). Immunocytochemical and detailed electron microscope studies have confirmed that cell-surface cannabinoid $CB_1$ receptors are found almost exclusively on pre-synaptic terminals (Egertová and Elphick, 2000; Hájos et al., 2000; Katona et al., 2000; Tsou et al., 1998). In hippocampus, cannabinoid $CB_1$-receptor-immunoreactive neurones are γ-amino butyric acid (GABA)-containing interneurones; in cerebellar tissue, cannabinoid $CB_1$-receptor-immunoreactivity has been found on axon terminals of granule cells and basket cells, presynaptic to Purkinje cells; cannabinoid $CB_1$ receptor-immunostaining has been found on cortico-striatal glutamatergic terminals, and terminals of medium spiny GABAergic neurones. In general, presynaptically localized cannabinoid $CB_1$ receptors contribute to the modulation of neurotransmitter release, including glutamate and GABA (Pertwee and Ross, 2002).

### 2.3. Cannabinoid $CB_1$-selective receptor antagonists

The discovery of specific cannabinoid $CB_1$ receptors led to the introduction of competitive cannabinoid receptor antagonists. A number of compounds have been synthesised (Pertwee, 1997), but the most extensively employed has been the potent antagonist, SR14176A {*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride} (Rinaldi-Carmona et al., 1994). It shows selectivity for the $CB_2$ receptor, and antagonises typical effects of cannabinoids. There is some evidence that SR14176A may exhibit some inverse agonist activity (Landsman et al., 1997; Pan et al., 1998).

### 2.4. Endogenous cannabinoid receptor ligands

The presence of a specific cannabinoid receptor in the brain initiated a search for endogenous ligands. Initially, two endocannabinoids were identified: anandamide (*N*-arachidonoyl-ethanolamine, AEA), and 2-arachidonoyl-glycerol (2-AG) (Devane et al., 1992; Mechoulam et al., 1995; Sugiura et al., 1995). Anandamide resembles $\Delta^9$-THC in behaving as a partial agonist at cannabinoid $CB_1$ receptors. 2-AG functions as an agonist at both cannabinoid $CB_1$ and $CB_2$ receptors. More recently, other candidate endocannabinoids have been identified: noladin (2-arachidonyl-glyceryl ether, 2-AGE) (Hanuš et al., 2001), virhodamine (*O*-arachidonoyl-ethanolimine), which acts as a partial agonist/antagonist at cannabinoid $CB_1$ receptors (Porter et al., 2002), *N*-arachidonyl-dopamine (AA-DA), one of a series of *N*-acyl-dopamines (NADAs) (Bisogno et al., 2000), and oleamide (*Cis*-9,10-octadecanoamide) (Leggett et al., 2004). Oleamide is a full cannabinoid $CB_1$ receptor agonist.

### 2.5. Retrograde signalling

One of the most important newer developments in our understanding of chemical signalling at synapses in the mammalian central nervous system is the existence of "retrograde signalling" (Tao and Poo, 2001). This stands in contrast to the classical picture of synaptic transmission in which neurotransmitters are synthesized in the presynaptic neurone, stored, and released in response to increased $Ca^{2+}$ flux consequent upon action potential propagation to axon terminals. In the case of retrograde signalling, membrane-permeable, diffusible messengers (e.g. gases like nitric oxide and carbon monoxide, and lipids) are produced on demand in postsynaptic neurones and exert their effects in a retrograde sense through actions at receptors localized pre-synaptically. It has now emerged that the endocannabinoids constitute the most thoroughly investigated class of retrograde signals in the brain (Alger, 2002; Elphick and Egertová, 2001; Freund et al., 2003; Pertwee and Ross, 2002; Wilson and Nicoll, 2002). They are rapidly synthesized in response to postsynaptic activity, travel backwards across synapses, and through activation of cannabinoid $CB_1$ receptors bring about a suppression of neurotransmitter release. Hence, endocannabinoids mediate a rapid negative feedback control on

presynaptic release of a variety of neurotransmitters (Schlicker and Kathmann, 2001). The interesting phenomenon of "depolarization-induced suppression of inhibition", which occurs presynaptically to inhibit GABA release in the hippocampus, arises through effects of a retrograde messenger, which can be blocked by a cannabinoid $CB_1$ receptor antagonist (Alger, 2002). In the cerebellum, a retrograde messenger affects excitatory glutamatergic neurotransmission to produce a phenomenon called "depolarization-induced suppression of excitation" (Alger, 2002). This, too, is mediated by an endocannabinoid retrograde messenger.

### 2.6. Synaptic plasticity and synaptic homeostasis

Synaptic plasticity is fundamental to neural processes of adaptation, learning and memory (Martin et al., 2000). Two models of long-term synaptic changes which have been subject to considerable investigation over the past 30 years have been long-term potentiation and its complement, long-term depression (Malenka and Nicoll, 1999; Martin et al., 2000). Since it is now apparent that retrograde signalling is closely associated with both long-term potentiation and long-term depression (Tao and Poo, 2001), it would be expected that endogenous cannabinoids would be involved in these and other synaptic plasticity phenomena (Gerdeman and Lovinger, 2003). Recent evidence indicates that endogenous cannabinoids are involved in the induction of long-term depression in the striatum (Gerdemanm et al., 2002), nucleus accumbens (Robbe et al., 2002), and hippocampus (Chevaleyre and Castillo, 2003), and induction of long-term potentiation in hippocampus (Carlson et al., 2002).

It is now recognized that several forms of *synaptic homeostasis* are involved in neurotransmission; without homeostatic feedback, plastic processes like long-term potentiation and long-term depression would lead to extremes of synaptic excitability or depression, respectively. Effective synaptic signalling would be severely impeded (Burrone and Murthy, 2003; Turrigiano and Nelson, 2004). Retrograde signalling is likely to play a critical role in synaptic homeostasis, to stabilize neuronal activity, and therefore one should expect to see endocannabinoids involved not only in processes involved in synaptic plasticity but also, and perhaps as importantly, in the negative feedback signals mediating synaptic homeostasis. Suppression of neurotransmitter release by retroactively acting endocannabinoids is consistent with this view.

## 3. Cannabinoids and food consumption

### 3.1. Cannabinoid receptor agonists

Although there are observations that marijuana may stimulate human appetite and food consumption (Abel, 1971; Foltin et al., 1986), the evidence for cannabinoid-induced hyperphagia in animal studies has been equivocal, at least until comparatively recently. For example, Sjödén et al. (1973) noted that daily treatment with either $\Delta^9$-THC or its congener $\Delta^8$-THC decreased body weight in female Wistar rats. Sofia and Knobloch (1976) reported that $\Delta^9$-THC decreased food and water consumption in rats, although concurrent sucrose consumption was spared. Drewnowski and Grinker (1978) also found that chronic treatment with $\Delta^9$-THC led to suppression of food intake in obese and lean Zucker rats, although they attributed these effects to a non-specific reduction in arousal level. Graceffo and Robinson (1998) found that acute treatment with $\Delta^9$-THC has no effect on palatable food consumption. Giuliani et al. (2000) recently reported that sub-chronic treatment with the cannabinoid receptor agonist HU210, (−)11-hydroxy-$\Delta^8$-tetrahydrocannabinol-dimethylheptyl, produced loss of body weight in male Wistar rats.

In contrast to these results, there are studies which have succeeded in demonstrating that cannabinoids can stimulate food consumption in animal studies. Baile and his colleagues demonstrated that intragastric administration of $\Delta^9$-THC increased short-term food intake in ad lib fed rats (Anderson-Baker et al., 1979). Using the paradigm of feeding elicited by electrical stimulation of the lateral hypothalamus, Trojniar and Wise (1991) reported that 0.4 mg/kg, i.p. $\Delta^9$-THC reduced the threshold for feeding, and reduced the latency to eat. Recent interest in cannabinoid-induced hyperphagia was aroused with the study of Williams et al. (1998). Under their procedure, rats were prefed a highly palatable diet before $\Delta^9$-THC was administered. Subsequent measurement of nocturnal consumption of standard food pellets revealed that in doses of 0.5–2 mg/kg, p.o., $\Delta^9$-THC significantly increased food intake in a 2-h period. A further study confirmed that $\Delta^9$-THC-induced hyperphagia in pre-satiated rats was blocked by the cannabinoid receptor antagonist SR141716 (Williams and Kirkham, 2002b). Koch (2001) demonstrated that 0.5 and 1.0 mg/kg, i.p., $\Delta^9$-THC increased food consumption in free-feeding male Lewis rats. With these positive results, it is interesting that the endocannabinoid anandamide has been shown to increase food consumption in pre-satiated rats (Williams and Kirkham, 1999), and that a small dose of anandamide (0.001 mg/kg, i.p.) increased food intake in diet-restricted mice (Hao et al., 2000). Berry and his colleagues have also shown that a small dose of $\Delta^8$-THC increases food intake in diet-restricted mice, an effect which is reversed by SR141716 (Avraham et al., 2004).

Taken together, these positive data indicate that, under certain conditions at least, cannabinoids can produce some increases in food consumption. There is insufficient evidence here to identify the important factors in achieving a hyperphagic response, although the degree of pre-satiation or food restriction may not be relevant. More significantly, for present purposes, the data so far reviewed provide almost no clues as to the mechanisms (neural or behav-

ioural) which account for the hyperphagic outcomes following cannabinoid treatments. I shall turn to these questions later.

### 3.2. Cannabinoid antagonists/inverse agonists and food consumption

The introduction of a selective brain cannabinoid receptor antagonist, SR141716A (*N*-(piperidin-l-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide HCL) provided an important tool with which to investigate the endogenous cannabinoid system in the brain (Rinaldi-Carmona et al., 1994). Subsequent work also identified SR141716A as an inverse agonist at the human cannabinoid $CB_1$ receptor (Landsman et al., 1997). So far, as ingestive behaviour is concerned, Arnone et al. (1997) showed that SR141716A has a selective effect to reduce consumption of sucrose pellets in food-restricted rats, and reduced sucrose drinking in non-deprived rats. Daily administration of SR141716A reduced food intake and body weight in Wistar rats (Colombo et al., 1998). Simiand et al. (1998) reported that SR141716A reduced consumption of a highly palatable sweetened food in the marmoset, and suggested that endogenous cannabinoid activity may modulate "the appetitive value of food". However, Freedland et al. (2000) showed that SR141716A dose-dependently reduced responding maintained under a fixed-ratio schedule of food reinforcement (normal food pellets), and suggested that appetitive value or enhanced palatability was not necessary to the anorectic effect of the antagonist. The rate-reducing effect of SR141716A was confirmed by De Vry et al. (2004), although they cautioned that the drug might induce some aversion or malaise.

Two recent studies have demonstrated that chronic oral administration of SR141716A decreased food intake and gain in body-weight in lean and obese Zucker rats (Vickers et al., 2003), and reduced food intake and body weight in diet-induced obese mice (Ravinet Trillou et al., 2003). SR141716A had no effect in cannabinoid $CB_1$ receptor knockout mice (Ravinet Trillou et al., 2003). In comparable studies, chronic treatment with the cannabinoid $CB_1$ receptor antagonist AM-251{*N*-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide} reduced food intake and body weight in diet-induced obese mice (Hildebrandt et al., 2003). AM-251 has also been shown to reduce food intake in overnight-fasted mice (Shearman et al., 2003). Like SR141716A, AM-251 has been shown to reduce food consumption in rats, and also to produce dose-dependent reductions in operant responding maintained under fixed-ratio schedules of reinforcement (McLaughlin et al., 2003). Werner and Koch (2003) reported that intracerebroventricular injection of the cannabinoid $CB_1$ antagonist/inverse agonist AM281{*N*-(morpholin-4-yl)-5-(4-iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide} blocked food deprivation-induced intake of rat chow.

Taken together, these data indicate that cannabinoid $CB_1$ receptor antagonists/inverse agonists reduce not only food consumption, but also appetitive responding for food rewards, and appear effective in reducing body weight, or weight-gain, in animal models of obesity. However, one has to caution again that these data in themselves do not identify neural or behavioural mechanisms, which may mediate the changes in appetite.

## 4. Palatability-dependent appetite

For Young (1961), "palatability refers to the hedonic value of a foodstuff that depends upon taste, aroma, texture, temperature, appearance, and other sensory properties, and upon the (...) environmental setting." Too often, the term palatability is treated as if it were a sensory property of foodstuffs itself; but as Young (1961) emphasises, it is the hedonic evaluation of the experience which constitutes palatability, and can be distinguished into positive and negative evaluations. Young (1961) also defined palatability as an affective process, as distinct from a sensory process. In human subjective experience, palatability equates to "pleasure" or "liking", but it is important to recognize that hedonic evaluation may be a largely unconscious process, and is also a central neural function of non-human animals which determines food preferences and consumption (for an extended discussion, see Berridge, 1996, 2000, 2003). Young could also have mentioned developmental experience, conditioning history and genetic factors, but his principal assertion is accepted here, that palatability is shorthand for central processes, which evaluate and assign the affective sign and magnitude of the sensory characteristics of ingested foodstuffs and liquids.

It is not possible to go into great detail, but it is conventional to distinguish palatability-dependent appetite from depletion- or deprivation-induced feeding and drinking. Interactions between the two no doubt occur, but we recognize that we may consume food not because we are hungry but because the food is attractive and eating it gives pleasure. Palatability serves a number of important functions, but it has the characteristic of being a positive feedforward factor, set, therefore, to promote persistence or maintenance of ingestive behaviour, in the face of competing demands to engage in other behavioural activities. Left to itself, therefore, there would be runaway food consumption (e.g. the sucrose sham-feeding rat; Weingarten and Watson, 1982), and there have to be counterbalancing homeostatic controls to stabilize and limit its influence. These homeostatic feedback controls operate over a range of time-scales, and are mediated by a variety of mechanisms; sensory-specific satiety (Rolls et al., 1983) is an example of pre-absorptive feedback limiting palatability, while satiation develops within a meal and determines inter-meal intervals, and depends on post-absorptive factors (Smith and Gibbs, 1979). I would argue that these homeostatic feedback

signals serve not merely to inhibit palatability (and to bring about cessation of eating), but significantly to stabilize the influence of palatability and to maintain its responsiveness to other determining events, including cognitive factors. These, then, are the physiological analogues at a systems level of the concepts of synaptic retrograde signalling and homeostasis discussed above.

Palatability displays plasticity; although some flavour preferences may be innate, most are acquired, and we are familiar with examples of acquiring liking for coffee, tea, hot chilies, and many other liquids and foodstuffs which initially are not acceptable (Rozin, 1996). Hence, hedonic evaluation is malleable, and not a fixed function of the sensory characteristics of foodstuffs and liquids. The paradigms of conditioned taste aversions (Bernstein and Borson, 1986; Riley and Tuck, 1985) and conditioned taste preferences (Booth, 1991; Sclafani, 1990) are well-established animal models which demonstrate the plasticity of hedonic processes.

Since we are far from sure what the neural and functional features of the central palatability system are, in their entirety, experimental work on palatability is best advised to rely upon convergent data from a number of different approaches to arrive at preliminary conclusions. To characterize the effects of drug treatments in terms of specific changes in the hedonic evaluation of foodstuffs and liquids, therefore, it is necessary to adopt a variety of experimental approaches, and to ensure that results are not susceptible to a range of alternative behavioural explanations. In the two following sections which deal with benzodiazepines and opioids, examples will be given from animal studies which illustrate putative measures of palatability in terms of: palatable food consumption in nondeprived animals; food preferences; sweet- and salt-taste preferences; sham-feeding in gastric-fistulated rats; taste-reactivity measures; licking microstructure studies. This list is not exhaustive, but is sufficient to indicate sources of potentially convergent data.

## 5. Benzodiazepines, food consumption and palatability

Considerable evidence shows that benzodiazepine receptor agonists, acting at specific central-type benzodiazepine receptors, promote increased food consumption (Cooper, 1980; Cooper and Estall, 1985), leading to increased meal size (Clifton and Cooper, 1996). This hyperphagic effect has been shown in a great variety of mammalian species, including primates (Foltin et al., 1985, 1989), and in human laboratory studies (Evans et al., 1999; Haney et al., 1997). Pharmacologically, the hyperphagic effect is not restricted to benzodiazepines, but also includes non-benzodiazepine compounds which act as agonists at benzodiazepine receptors, e.g. certain β-carbolines, and the pyrrolopyrazine derivative, zopiclone (Cooper, 1986; Cooper and Moores, 1985). Taking full account of the structural diversity of benzodiazepine receptor ligands, Filizola et al. (2000) used a computational procedure to obtain a 3D pharmacophore for recognition of ligands initiating the hyperphagic response at benzodiazepine sites on the $GABA_A$ receptor complex. The result was a four-component 3D pharmacophore, consisting of two proton acceptor atoms, the centroid of an aromatic ring, and the centroid of a hydrophobic moiety in a common geometric arrangement. Filizola et al. (2000) suggest that their procedure may be a first step in the design of new molecules which will selectively initiate hyperphagia.

Although early proposals suggested that benzodiazepine-induced hyperphagia may be due to an anti-satiety effect (Margules and Stein, 1967), or to a hunger-inducing effect (Wise and Dawson, 1974), later work led to the hypothesis that benzodiazepine receptor agonists enhance food and taste palatability specifically (Berridge and Peciña, 1995; Cooper, 1989; Cooper and Estall, 1985). Considerable evidence bolsters this proposal, and, today, benzodiazepines provide a paradigmatic case for drug-induced enhancement of palatability-dependent appetite. Briefly, the evidence from animal studies consists of the following:

(i) benzodiazepine receptor agonists strongly enhance the consumption of highly palatable food (Cooper et al., 1985; Yerbury and Cooper, 1987, 1989);
(ii) they enhance consumption of preferred foods and taste stimuli (Cooper, 1987; Cooper and Green, 1993; Cooper and Greenwood, 1992);
(iii) in taste reactivity tests, benzodiazepines act selectively to enhance the positive hedonic reactions to taste stimuli (Berridge, 1988; Berridge and Treit, 1986; Gray and Cooper, 1995), and to ethanol consumption (Söderpalm and Hansen, 1998);
(iv) they enhance sucrose sham-feeding in the gastric-fistulated rat (Cooper et al., 1988a,b);
(v) they prolong bouts of licking for highly palatable solutions in microstructural analyses of rats' licking behaviour (Higgs and Cooper, 1997, 1998a);
(vi) they increase the incentive value of reinforcers of instrumental response in trained rats (Balleine et al., 1994).

Although a hypothalamic site of action was first considered for benzodiazepine-induced appetite (Anderson-Baker et al., 1979), recent evidence strongly indicates that the critical site lies in the brainstem near to the fourth ventricle. Thus, direct administration of benzodiazepines into the fourth ventricle elicits a hyperphagic response (Higgs and Cooper, 1996a) and an increase in taste palatability (Peciña and Berridge, 1996). The most pertinent structure near the ventricle is the parabrachial nucleus, since direct administration of midazolam into the nucleus elicits hyperphagia (Higgs and Cooper, 1996b), and an increase in taste palatability (Söderpalm and Berridge, 2000a). The parabrachial nucleus forms part of the taste projection which projects rostrally to the thalamus, gustatory cortex, and limbic

structures, including the amygdala and hypothalamus (Norgren, 1995; Sewards, 2004). It is likely, therefore, that benzodiazepines act at specific benzodiazepine receptors in the parabrachial nucleus to augment the responses to positively evaluated food-related taste stimuli, leading in turn to an elevated consumption of attractive foods.

There is evidence for a close functional link with dopaminergic pathways. Bilateral electrolytic lesions of the ventral tegmental area (location of dopaminergic cell bodies which project rostrally) reduce the consumption of a preferred sucrose solution, and 6-hydroxydopamine lesions of the ventral tegmental area blocked the effect of midazolam to increase sucrose consumption (Shimura et al., 2002). Moreover, the dopamine D2 receptor antagonist, raclopride, counteracted the palatability-enhancement effect of midazolam in a licking microstructure study (Higgs and Cooper, 2000). Recently it has been shown that oral stimulation during sucrose sham-feeding leads to an increase in dopamine release in the nucleus accumbens (Hajnal et al., 2004). Hence, benzodiazepines may initiate palatability changes in the parabrachial nucleus, one important consequence of which could be elevated dopamine release in the nucleus accumbens, leading in turn to increased food intake.

## 6. Opioids, food consumption and palatability

The first serious indication that endogenous opioids were involved in the control of feeding behaviour was the observation that opioid receptor antagonists, like naloxone and naltrexone, reduced food consumption (Holtzman, 1974; Brown and Holtzman, 1979). This coincided with the discovery of endogenous opioid peptides (Cooper et al., 1988a,b). Evidence rapidly accumulated to support the view that these neuropeptides played an important role in the control of ingestive responses, and that they may be involved in mediating food and taste palatability (Cooper and Kirkham, 1993).

The view that endogenous opioid peptides play some part in determining food and taste palatability derives from several sources of evidence:

(i) opioid receptor antagonists reduce the preference for palatable sweet or salty solutions (Cooper, 1983; Cooper and Gilbert, 1984; Siviy and Reid, 1983), while intracerebroventricular administration of opioid agonists increases the intake of sucrose, saccharin or salt solutions (Gosnell and Majchrazak, 1989, 1990; Gosnell et al., 1990; Ruegg et al., 1997);

(ii) direct stimulation of mu opioid receptors (MOR) in the nucleus accumbens using the selective agonist DAMGO {[D-Ala$^2$,*N*-Me-Phe$^4$,Gly$^5$-ol]-enkephalin} enhances feeding behaviour (Bakshi and Kelley, 1993), and, more significantly, selectively increases consumption of a palatable high-fat diet (Zhang et al., 1998, Zhang and Kelley, 2000), of sucrose drinking (Zhang and Kelley, 1997), and of saccharin, salt and ethanol solutions (Zhang and Kelley, 2002);

(iii) opioid receptor antagonists reduce sucrose sham-feeding in the gastric-fistulated rat (Kirkham and Cooper, 1988a,b; Leventhal et al., 1995);

(iv) microinjection of morphine into the nucleus accumbens shell not only elicits feeding responses (Söderpalm and Berridge, 2000b), but also selectively enhances positive responses in taste-reactivity test of taste hedonics or palatability (Peciña and Berridge, 2000);

(v) analyses of licking microstructure in rats licking for sucrose or Intralipid reveal opioid modulation of palatability (Higgs and Cooper, 1998b).

Neuroanatomically, endogenous opioid mechanisms appear to be involved in the control of feeding responses at a number of interrelated structures distributed within the central nervous system, including the nucleus accumbens, ventral tegmental area and lateral parabrachial nucleus. Evidence reviewed above strongly implicates opioid mechanisms in the nucleus accumbens in the hedonic evaluation of foodstuffs (Kelley et al., 2002). In addition, however, microinjection of the mu opioid receptor agonist, DAMGO, in the ventral tegmental area produces increases in food consumption (Macdonald et al., 2003), which may depend upon increased dopamine activity in the nucleus accumbens. Furthermore, infusion of DAMGO into the lateral parabrachial nucleus produces a hyperphagic effect (Wilson et al., 2003), and may interact there with neuropeptide FF which exerts both pro- and anti-opioid actions within the parabrachial nucleus (Nicklous and Simansky, 2003).

There is long-standing evidence that benzodiazepine-induced hyperphagia is opioid-dependent (e.g. Jackson and Sewell, 1985), including the finding that the palatability-enhancing effect of benzodiazepines determined in a licking microstructure test is opioid-dependent (Higgs and Cooper, 1997). Since evidence strongly suggests that benzodiazepine-induced hyperphagia and increased hedonic evaluation of taste stimuli depends on actions in the parabrachial nucleus (Higgs and Cooper, 1996b; Söderpalm and Berridge, 2000a), it would be particularly interesting to investigate possible benzodiazepine-opioid interrelations in this region.

## 7. Cannabinoids and appetite: behavioural and pharmacological mechanisms, and neural sites of action

At present, there are relatively few behavioural data with which to characterize the effects of cannabinoids on appetite and food intake, and it would be premature to draw firm conclusions at this stage. Observational analysis of pre-satiated rats, administered either $\Delta^9$-THC (0.5–2.00 mg/kg, p.o.) or anandamide (1.0–10.0 mg/kg, s.c.), revealed that both drugs markedly reduced the latency to initiate feeding

in an open-field (Williams and Kirkham, 2002a). Associated with small increases in food intake, there were increases in the total duration of eating, and increases in the number of eating bouts, following the drug treatments. Importantly, no stereotyped or other aberrant behaviour was induced by either drug. In an explicit test of the possible effects on taste palatability, Higgs et al. (2003) used a licking microstructure test in rats ingesting a palatable sucrose solution. Over a 30-min test, animals treated with either $\Delta^9$-THC (0.5–3.0 mg/kg, i.p.) or anandamide (0.5–3.0 mg/kg, i.p.) showed increases in the total number of licks emitted, and in the overall duration of licking. There was evidence of increases in the mean duration of bouts of licking (but significant only in the case of 3 mg/kg $\Delta^9$-THC), and increases in the number of bouts of licking. In contrast, the cannabinoid receptor antagonist SR141716 significantly reduced the total number of licks emitted during the test period (Higgs et al., 2003). These data, as they stand, while suggestive, are not conclusive on the point of cannabinoid involvement in palatability-dependent appetite. More sources of behavioural evidence are required to determine if this is an appropriate interpretation of cannabinoid-induced hyperphagia (see Sections 5 and 6).

Similarly, at this relatively early stage, there are a number of possible candidates for sites of action of cannabinoids, underpinning their hyperphagic effect: the hypothalamus, nucleus accumbens and lower brainstem are currently under consideration, although relevant data are sparse. Jamshidi and Taylor (2001) briefly reported that direct infusion of anandamide into the ventromedial hypothalamus of rats produced a small increase in the intake of food pellets. Di Marzo et al. (2001) reported that a single injection of recombinant mouse leptin led to significant reductions in hypothalamic levels of anandamide and 2-arachidonoyl glycerol (2-AG) in Sprague–Dawley rats. They hypothesized a link between hypothalamic endocannabinoids and leptin influences on the control of food intake. However, in dietary-obese rats, Harrold et al. (2002) found no change in cannabinoid $CB_1$ receptor density in the hypothalamus, although there was evidence for receptor down-regulation in hippocampus, cortex, nucleus accumbens and entopeduncular nucleus. These authors suggested that extrahypothalamic sites may be more relevant to palatable food consumption and dietary-induced obesity. Variations in endogenous cannabinoid levels have been detected in the hypothalamus and "limbic forebrain", when the feeding status of rats were manipulated (Kirkham et al., 2002). During food deprivation, the level of 2-AG in the hypothalamus was elevated, while levels of both anandamide and 2-AG were raised in limbic forebrain areas. Such changes may be more relevant to hunger-related food consumption, as distinct from palatability-dependent appetite.

Kirkham et al. (2002) also observed a robust hyperphagic response, following administration of 2-AG into the nucleus accumbens shell. The response was blocked by subcutaneous administration of SR141716. We noted above that the nucleus accumbens shell appears to be closely involved in the enhanced hedonic responses elicited by mu opioid receptor agonists. Possible interactions between endocannabinoids and endogenous opioid peptides in the ventral striatum would be worth investigating, especially in view of the evidence for cannabinoid-opioid interactions in relation to food intake (Chen et al., 2004; Gallate et al., 2003; Kirkham and Williams, 2001b; Rowland et al., 2001; Williams and Kirkham, 2002b). In a recent study, Miller et al. (2004) report that the cannabinoid receptor agonist, CP55,940{[1*a*,2-(*R*)-5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]-phenol}, microinjected into the fourth ventricle, increased consumption of sweetened condensed milk. Importantly, the drug was considerably less potent when injected into the forebrain lateral ventricles. These authors suggest, therefore, that CP55,940 may act in the hindbrain to enhance food consumption. Since, as we have seen, both benzodiazepines and opioids can promote food consumption when administered directly into the parabrachial nucleus, adjacent to the fourth ventricle, it would be particularly interesting to test whether endogenous cannabinoids would increase food ingestion through actions in the same hindbrain nucleus.

In summary, the behavioural bases of the hyperphagic effects of cannbinoids are not yet well understood, and it is too early to conclude that endogenous cannabinoids directly affect palatability-dependent appetite leading to increased food intake. The role of endocannabinoids in the hypothalamus is at best ambiguous, and, in any event, may not have an immediate bearing on palatability-dependent appetite. Two brain regions that warrant closer scrutiny at this stage are the nucleus accumbens shell in the forebrain, and the lateral parabrachial nucleus in the hindbrain. There is strong evidence that these two regions are intimately involved in the enhancement of food and taste palatability produced by opiates and by benzodiazepines, respectively. Perhaps one, or conceivably both, may link endocannabinoids more closely to palatability-dependent appetite.

## 8. Concluding remarks

The discovery of the endocannabinoid system, its components, and its roles in a wide variety of behavioural and neurophysiological functions has been of great importance. Particularly interestingly, it has been established as a major retrograde signalling system, involved in synaptic plasticity and homeostasis, and operating throughout the central nervous system. It is not, therefore, simply another neurotransmission system in the brain, and is likely to exhibit interesting and, perhaps, unsuspected novel features. In the specific context of the pharmacology of appetite and ingestive behaviour, the endocannabinoid system features as the first example of a ubiquitous retrograde signalling

system having considerable influence on the controls of food and fluid consumption.

When considering the central taste projection system (Norgren, 1995), we are apt to think of the ascending system from the first central relay, in the nucleus of the solitary tract, forward to the lateral parabrachial nucleus, projecting rostrally to thalamus, gustatory cortex, amygdala and hypothalamus. Hedonic evaluation (assignment of palatability) may be conducted at several stages, including the parabrachial nucleus (Berridge, 2003; Sewards, 2004). However, there is considerable evidence now for descending, recurrent projections from gustatory cortex, central nucleus of the amygdala and hypothalamus (Lundy and Norgren, 2001, 2004). Such feedback loops allow for dynamic control of hedonic evaluation, and can draw in a range of modulatory appraisals based in previous experience and higher cognitive processes, amongst other factors. One can speculate that endogenous cannabinoids may be effective in a number of ways within this open, recurrent system, and future research will no doubt reveal how this may be achieved.

Much of the experimental work reviewed here has been conducted using rats and mice. However, innovative new research has revealed features of the hedonic evaluation or palatability system in primates and in humans. Rolls et al. (1990), for example, recorded single neurones in the macaque orbitofrontal cortex and showed that they respond to taste stimuli, to olfactory stimuli (Critchley and Rolls, 1996), to fat stimuli in the mouth (Rolls et al., 1999), and to viscosity, grittiness, and capsaicin (Rolls et al., 2003). The primate orbitofrontal cortex, therefore, is in receipt of a wide variety of sensory inputs, which when integrated and evaluated, places it in a position to mediate the reward or pleasure of ingested foodstuffs and liquids (Rolls, 1999). Few of these sensory factors have been evaluated in the context of the pharmacology of appetite and food consumption.

Human brain imaging has revolutionised the study of human perception, cognition and affective processes. A number of studies have established activations in human orbitofrontal cortex and amygdala in response to pleasant and aversive taste stimuli (e.g. O'Doherty et al., 2001; Zald et al., 2002). Recent work indicates that the viscosity of oral stimuli is represented in the primary taste cortex, and that oral delivery of fatty vegetable oil activates the primary taste cortex, cingulate cortex, and hypothalamus (de Araujo and Rolls, 2004). This is the first indication of the brain mechanisms which represent the sensory properties of foods which renders them palatable, and attractive to eat. Functional neuroimaging studies may help not only to determine neural bases for palatability of foods, but also may contribute importantly to understanding obesity and eating disorders (Tataranni and Del Parigi, 2003).

The discovery of the endocannabinoid system may lead to material benefits in the treatments of human obesity and eating disorders (Cota et al., 2003; Kirkham and Williams, 2004). Currently available evidence implies a key role for the system in the control of appetite and food consumption; future research should address the issue of its involvement in palatability-induced appetite in both animal experiments and in human functional studies of food pleasure.

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