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Mini-review

The endogenous cannabinoid system: a new player in the brain-gut-adipose axis

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Abstract

The 'endocannabinoid (CB) receptor (ECBR) system', consists of specific receptors and several endogenous ligands. The ECBR system is involved in many physiological functions including immunity, inflammation, neurotoxicity and neurotrauma, epilepsy, depression and stress, appetite, food intake and energy homeostasis, cardiovascular regulation, reproduction, and bone remodeling. The brain and gastrointestinal system interact bidirectionally in the regulation of digestive processes, food ingestion and energy balance (hence the 'brain-gut axis'). Emotional stress and and the 'reward' center in the brain modulate the brain-gut axis. ECBR presence in brain, gastrointestinal as well as adipose (fat) tissue as well as its involvement in stress and emotional processing, provide it with a major role in food intake, digestion and the regulation of adipose tissue mass and adipocyte endocrine function. With cannabinoid receptors and endocannabinoids present from the early embryonic stages and in maternal milk, the ECBR system seems of critical value for newborn milk ingestion.

It is concluded that (i) the ECBR system is a major mediator between the brain and the digestive system, (ii) the role of the ECBR system in adult regulation of food processing is a remnant of its critical role for the initiation of feeding in the newborn, and (iii) the pervasive influence of the ECBR system in alimentary control, make it a highly suitable target for therapeutic developments for conditions such as inflammatory bowel disease, irritable bowel syndrome, gastric ulcers, nausea, obesity, anorexia and failure-to-thrive.

Key words: CB_1, CB_2, development, feeding, appetite, gastrointestinal tract, adipose tissue

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Introduction: the "alimentary control system"

Appetite, hunger and satiety are regulated by a number of hormonal signals emanating from the central nervous system (CNS) and gastrointestinal (GI) tract [1, 2]. It is impossible to separate the appetite-hunger-satiety signals which regulate food intake, from the digestive processes in the GI tract and secretions from adipose (fat) tissue such as the hormone leptin. Therefore in this review, regulation of food intake, appetite and the brain-gut-adipose system will be considered as one system regulating ingestion and digestion, and will be denoted the "alimentary control system".

The rich bidirectional interactions between the brain and the local neuronal network (the enteric nervous system - ENS) in the intestinal system (the 'brain-gut axis'), have been extensively studied. Thus, for example, psychological stress has been shown to affect gut activities such as secretion and motility [3]. Conversely, using brain imaging techniques such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), it has been demonstrated that visceral sensation resulting from stimulation of the oesophagus, stomach or rectum, resulted in activation of higher brain centers including the somatosensory cortex, thalamus and prefrontal cortex [3].

Ingestion and digestion are controlled by a large number of hormones which originate from the brain, GI tract and adipose tissue and which act in as a signaling network of mutual influence. The major hormones

include leptin (from adipose tissue), cholecystokinin (CCK), peptide tyrosine (PYY) and orexin A and B [2, 4-6].

Emotional stress and reward

Interestingly, the major hormones (such as corticotrophic releasing hormone (CRH)) and brain structures involved in modulating emotional and stress responses (such as the hypothalamus and the amygdala) are also important modulators of gastrointestinal tract activity such as GI motility and gastric emptying [1]. Conversely, hormones associated with gastrointestinal functioning such as the gastrin-releasing peptide (GRP), and ghrelin, affect emotional processes [7, 8].

It also appears that the same neuropeptides and transmitters (including opioids and dopamine) which are known to control appetite and satiety [9], also mediate "reward" processes in the brain (for example, the satisfaction following natural rewarding stimuli such as food, sexual activity or artificial rewarding stimuli such as recreational drugs). Thus, the common basis for food intake and the feeling of reward/satisfaction probably explains the rewarding qualities of food ingestion.

The ECBR (endocannabinoid CB receptor) system and alimentary control

The ECBR system, consisting of the cannabinoid (CB_1 and CB_2) receptors and their endogenous activating ligands, the 'endocannabinoids' (mainly anandamide and 2-arachidonoyl glycerol, 2AG) and their synthesizing and degrading enzymes and putative reuptake transporters [4, 10, 11], is fully functional in the nervous system, in the GI system as well as in fat cells [12, 13].

Nervous system

Components of the ECBR system are present in most structures throughout the brain [4, 14], including one of the dopamine-carrying neural pathways, the 'mesolimbic system' [10]. As mentioned above, the incentive, pleasurable value of food is apparently controlled by this "reward" system. Not surprisingly then, the endocannabinoid 2AG directly administered to this system, induced the intake of exaggerated amounts of food (hyperphagia) [15]. These and similar findings strongly suggest a role for the ECBR system in regulating food intake through the incentive value of food [10].

A role for the ECBR system in the ability to cope with stress has been studied using behavioral and biochemical [16-18] techniques. As outlined above, stress strongly influences both feeding and digestion. Therefore, the ECBR system may be expected to exert part of its influence on alimentary control through its influence on the stress-regulating physiological systems.

In addition to the influence of the ECBR system on feeding, appetite and digestion through the reward- and the stress-regulating systems, the cannabinoids influence feeding and digestion by interacting with a number of additional alimentary control hormones, including the appetite-inducing (orexigenic) ghrelin hormone [19] and the appetite reducing hormone leptin [20].

In the lower parts of the brain (the hindbrain), a number of small structures (the 'area postrema', 'nucleus of the solitary tract' and 'dorsal motor nucleus of the vagus') form the dorsal vagal complex, from where nausea and vomiting as well as muscle control of the oesophagus, is controlled. The presence of CB_1 and recently, CB_2 receptors in the dorsal vagal complex, have been demonstrated; functionally, they have been shown to regulate nausea and vomiting [21-23], inhibition of gastric motility [24] and gastric acid secretion [21]. Thus it is clear now, how cannabinoids including the plant-derived THC (dronabinol) or synthetic nabilone, exert their antiemetic effects, as seen in their administration to patients undergoing chemotherapy.

CB_1 receptors are also present in the peripheral vagus nerve, on the afferent nerve endings in the gut. There, when activated, they influence the brain's perception of intestinal activity [21, 22], thus participating in the feedback loop from the gut to the brain.

Interestingly, activating CB_1 and CB_2 receptors which are found in the saliva of rats, reduced saliva secretion [25]. Thus it seems that that CB receptors play a role in alimentory control starting with the initial stage of the digestive process.

Gastrointestinal tract

CB_1 receptors are located in the lower sphincter muscle of the oesophageal (LOS) [21]. Cannabinoid receptor activating ligands (Δ^9-THC, WIN 55,212-2) inhibited the relaxation of this muscle in ferrets and dogs, thereby counteracting gastroesophageal acid reflux [22, 26], suggesting that cannabinoid-based drugs may be useful therapeutics in the condition of gastroesophageal acid reflux.

CB_1 are present throught the gastrointestinal tract [27, 28]. However in the colon (upper large intestine) and the stomach the densities are the highest. [29, 30]. Some of the CB_1 receptors were found in the same neuronal cells as those containing the appetite and digestion-regulating hormones 'vasointestinal peptide and 'neuropetide Y' (VIP and NPY) [31], thus suggesting that the endocannabinoid cooperate with these hormones in controlling the gastrointestinal tract.

Thus the ubiquitous presence of the ECBR system in the GI system is supportive of the suggestion that the endocannabinoids and their receptors play a highly influential role in numerous key aspects of digestion. Indeed experiments have shown an effect of the ECBR system on secretory activity and motility of the gut [27]; it promotes inhibition of gastric emptying [32] and intestinal motility and food transit through the intestines [33-35]. Additional experiments have demonstrated a protective role for the ECBR system against inflammation of the GI system, for instance, in a mouse model for colitis [36].

A role for CB_2 receptors in gastrointestinal activity was only recently fully accepted. An earlier report on CB_2-mediated effects (by the CB_2-selective agonist HU-308) on defecation in mice [37], was followed by many negative reports on a role for CB_2 receptors in GI functions [27, 28, 38]. However, CB_2 receptors have now been demonstrated in the stomach [30] and in the intestines [39]. Although the issue needs further clarification, the accompanying commentary to the report by Mathison and colleagues was aptly entitled "Cannabinoids and intestinal motility: welcome to CB_2 receptor" [38].

Experiments have demonstrated that the endocannabinoids, as well as the degrading enzymes and uptake transporters [33, 40, 41] are present in the GI tract; the endocannabinoids at several-fold higher concentrations than in the brain [33, 42] and are physiologically active [40]. Anandamide-induced inhibition of defecation in mice was the first report that endocannabinoids influence intestinal function [43]. Thus the ECBR system appears to be highly important in the GI tract, probably playing a major role in digestion.

Adipose tissue

Di Marzo, Kunos and colleagues showed for the first time a link between leptin, the hormone originating in fat tissue which enters the brain to attenuate food intake, and the ECBR system [44]. Thus leptin injection to rats reduced the concentrations of the endocannabinoids anandamide and 2AG [20]; anandamide and 2AG in turn, stimulate appetite and food intake. Conversely, specific mutations of mice and rats which are obese due to inherent deficiencies of the leptin system, displayed elevated levels of endocannabinoids [20] thus explaining their exaggerated food intake. Importantly, leptin was found to enhance the activity of the endocannabinoid degrading enzyme FAAH (fatty acid amide hydroxylase), by up-regulating the expression of the FAAH gene at the promotor level [45], thereby explaining the underlying mechanism of the leptin-endocannabioid negative balance reported earlier [20]. CB_1 receptors have also been detected in animal adipose (fat) tissue [46-48], while the full set of ECBR system components (CB_1 and CB_2 receptors, anandamide and 2AG, synthesizing and degrading enzymes) has recently also been described in human adipose cells [13, 49]. Importantly, CB_1 receptors are dysregulated in human abdominal obesity [47].

Concluding this section, it is clear that every level of the alimentary system is affected by the ECBR system. In addition to the organ systems discussed here, and beyond the scope of the present review, organs such as the liver [50] and the pancreas [51] may also be involved in this intricate network. Strikingly, ECBR influence on ingestion, digestion and emesis is always, at the organismic level, in harmony (see also Table 1). Thus (endo)cannabinoids reduce intestinal and gastric motility, gastric acid secretion, emesis and nausea, are anti-diarrheal and enhance appetite. Conversely, CB1 receptor blocking agents (antagonists) cause emesis, anorexia and enhanced motility. This unified activity makes the ECBR system exquisitely suitable for multi-leveled treatment of digestive and appetite-related syndromes such as irritable bowel syndrome and cachexia/anorexia, using ECBR-activating agents [21] or obesity/metabolic syndrome, using ECBR-inhibitors [52].

Table 1: Levels of alimentary control by the ECBR system

Location	Effect	Selected references
CNS-forebrain including hypothalamus	Rewarding/Stress effect on food intake and digestion; Orexigenic effect	[10, 15, 19]
CNS-hindbrain	Gastric secretion and Intestinal motility/secretion reduced; Antiemetic effect	[21, 23, 24, 34, 65, 66, 80]
Mouth	Salivation decreased	[25]
Lower oesophageal sphincter muscle	Relaxation	[21, 22, 26]
Stomach	Decreased gastric secretion and motility	[21, 24]
Intestinal tract	Decreased intestinal motility and secretion	[33-35, 53]
Adipose tissue (adipocytes)	Enhanced lipogenesis	[51]

The ECBR system in pathophysiological and psychosomatic conditions of ingestion and digestion

The ECBR system, as described above, is strongly represented in brain, GI tract and adipose tissue. Especially its involvement in emotional processing makes the ECBR system an excellent candidate as an underlying factor in the pathology of psychosomatic problems of the digestive system as well as a target for new therapeutic approaches.

Irritable bowel syndrome (IBS). Solid evidence exists for an (endo)cannabinoid-regulated reduction of intestinal motility [40, 43, 53, 54] through CB_1 [33] and CB_2 [39, 43, 55] receptors. This property of the ECBR system has been proposed to be beneficial for IBS which is often characterized by enhanced intestinal motility and contractility [40, 41].

Inflammatory bowel disease (IBD). Inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, result from inflammatory processes in the intestine and are characterized by ulcers, rectal bleeding diarrhea, nausea and lack of appetite [41]. As stated above, the importance of CB_1 receptors in pro-

tecting the organism against inflammation of the GI system was demonstrated in an animal study for experimentally-induced colitis [36]. In an animal model for Crohn's disease, a beneficial, slowing effect of endocannabinoids on intestinal motility has been demonstrated [33, 34]. This effect was apparently mediated by CB receptors in the gut (and not via the brain). Therefore cannabinoid-based treatment is promising when psychological approaches are not likely to be helpful.

Gastroesophageal reflux disease (GORD). This disorder results from a weak lower oesophagal sphincter muscle causing gastric content to flow upward, hence symptoms including heartburn and acid regurgitation appear [41, 56]. The influence of psychological stress, anxiety and depression on this condition has been shown [56-58]. Cannabinoid-based therapies may be developed, acting through cannabinoid receptors in the brain or through peripheral neural control. Indeed, cannabinoid CB_1 receptor agonists have been shown to relax the oesophageal sphincter in dogs and ferrets; this effects was mediated by cannabinoid receptors on the vagus nerve at peripheral as well as central sites [22, 26, 27].

Secretory diarrhea. Fluid-induced increase in stool volume, that is, secretory diarrhea, is caused by abnormal and/or absorption of water and electrolytes as well as dysregulated intestinal motility [59, 60]. Psychological stress may precipitate secretory diarrhea. This occurs probably when stress induces the activation of receptors for corticotrophin releasing hormone (CRH1) [60]. Several studies have demonstrated the role of the ECBR system in this process. Thus, stimulation of the ECBR system reduced intestinal fluid accumulation; conversely, the blocking CB_1 receptors with the antagonist rimonabant increased fluid accumulation [27]. These observations suggest that the endocannabinoids exert a tonic regulation of intestinal secretory activity which can be up-or down-regulated according to the (psycho)physiological environment. Further, since cannabinoid CB_1 receptor activation resulted in decreased fluid accumulation in the small intestine of the rat, cannabinoid-based treatment may be beneficial for diarrhea [61].

Gastric ulcer. The formation of gastric ulcers is known to be stimulated by psychological stress. The ability of cannabinoids to reduce gastric secretions and ulcer formation has been observed many years ago. Interestingly, cannabinoids reduced ulcers which had been caused by stress [62]. This effect may have been achieved by direct activation of cannabinoid receptors in the stomach or by reducing the stress reponse [30] in the central nervous system [63], or by both mechanisms.

Emesis. Antiemetic effects of (endo)cannabinoids have been extensively demonstrated as described above and several Δ^9-THC (dronabinol) or THC-like cannabinoid drugs (the synthetic nabilone) are selectively available for oral clinical use [27, 41, 64, 65]. The antiemetic effects are mediated by CB_1 and CB_2 receptors located on gastric vagal nerves or via lower brain structures of the dorsal vagal complex [27, 66]. Taken together, it is widely agreed that CB-based drugs, especially those which do not have central side effects, should be developed as antiemetic drugs for cancer and AIDS patients who receive chemotherapeutic treatment. Cannabinoids may be especially effective in combating anticipatory nausea and vomiting [67]. Since the area postrema has receptors located outside the brain, CB_1 receptor-specific cannabinoids which are not active within the CNS, should be particularly suitable [68, 69].

Neonatal milk intake

Although perhaps one of the major physiological systems (see also Table 1), the ECBR system does not seem critical for survival. Thus for example, the majority of mice which genetically lack CB_1 and/or CB_2 receptors, survive into adulthood, albeit with reduced body weights [70-72]. Similarly, very long term treatment (4 months) with the CB_1 receptor antagonist rimonabant did not cause mortality or (overt) detrimental effects, except for a robust reduction in body weight [73]. In contrast, we have shown that a single injection with rimonabant administered to newborn mice within 24 h of birth, interferes with milk ingestion; this in turn resulted in growth failure and death in many cases. Further investigation into the sequelae of neonatal rimonabant-treatment suggested that CB_1 receptor activation in neonates is required for oral-motor development required for sucking [74]. Since the behavioral and physiological deficiencies of CB_1 receptor-blocked mouse pups resemble infants suffering from "non-organic failure-to-thrive" (NOFTT), we have suggested that CB_1 receptor-blocked neonates may be used as a model for NOFTT and form the basis for the development of cannabinoid-based treatments.

Conclusions and future directions

Three major conclusions emanate from the material reviewed here: (i) the ECBR system is a of major mediating system between the brain, the alimentary system and the adipose tissue, (ii) it is speculated that the role of the ECBR system in adult regulation of digestion and ingestion may be a remnant of their critical role for the initiation of feeding and survival in the newborn, and (iii) the pervasive influence of the ECBR system in alimentary control, make it a highly suitable target for therapeutic developments aimed at alleviating pathophysiological conditions such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), gastric ulcers, nausea, anorexia and obesity.

The CB_1 receptor, rather than the CB_2 receptor, seems to be the major mediator of ECBR control of the gastrointestinal tract and food intake, and should therefore be the main target of therapeutic cannabinoid-based drugs. However CB_1 receptor agonists often have un-

desirable psychoactive effects such as confusion and anxiety. We have recently demonstrated that several (+)cannabidiol derivates [such as (+)cannabidiol-demethyl heptyl and (+)carboxy-cannabidiol-demethyl heptyl], displayed CB_1-receptor mediated inhibition of intestinal motility in the absence of psychoactive effects [68, 69]. Further, upregulating the ECBR system by the inhibition of enzymatic breakdown or reuptake inhibition, is expected to yield more selective therapeutic effects, since the manipulation of ECBR function would be restricted to the anatomical sites which are activated at that moment. Preventing endocannabinoid degradation with oleamide, a fatty acid amide which is considered by most [75-78] not to bind CB_1 receptors, resulted in psychoactive effects similar to those of anandamide itself [75]. On the other hand, URB597, the highly selective inhibitor of the FAAH enzyme responsible for endocannabinoid breakdown, is thought to have anxiolytic and antidepressant potential without sedative and addictive properties [79]. Thus this or similar FAAH inhibitors may also be useful for the treatment of digestive and ingestive dysfunctions without undesirable psychoactive side effects.

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