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# The Endocannabinoid System: Mechanisms Behind Metabolic Homeostasis and Imbalance

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**ABSTRACT**

Scientific interest in the endocannabinoid (EC) system developed as a result of the known effects of tetrahydrocannabinol, including an increased desire to consume food. Further investigation has led to the belief that the EC system plays a role in accumulation of intra-abdominal fat and worsening of cardiovascular disease (CVD) risk factors. The EC system has been identified as a neuromodulatory system that is normally inactive but can be overstimulated to cause and exacerbate numerous metabolic pathologies. EC agonists and receptors have been identified in the brain, liver, and peripheral adipose tissue, and the EC system is known to affect metabolism in these areas and others through neuromodulatory signals. Meal size, body weight, and numerous metabolic factors such as triglyceride and cholesterol levels, insulin resistance, and glucose intolerance can be affected via the EC system. Further research into the EC system is warranted to elucidate its role in metabolic homeostasis. 

**KEYWORDS:** Anandamide; 2–arachidonoylglycerol; Cardiometabolic risk; Lipogenesis; Obesity; Satiety

The modern history of endocannabinoid (EC) pharmacology began in 1964, when tetrahydrocannabinol (THC) was determined to be the active component in marijuana. In 1990, the cannabinoid-1 ($CB_1$) receptor was cloned,[1] and 2 years later, the first endogenous cannabinoid ligand, or EC, was discovered and named anandamide. The other well-studied EC is 2-arachidonoylglycerol (2-AG). All of the ECs known to date are long-chain polyunsaturated fatty acid derivatives of arachidonic acid. They display varying selectivity for 1 or both of 2 cannabinoid receptors ($CB_1$ or $CB_2$). The EC system is a natural endogenous physiologic system believed to play an important role in regulating coronary heart disease and cardiovascular disease (CVD) risk, in that increased activity in this system is thought to notably affect the accumulation of fat, especially intra-abdominal fat.

The EC system, particularly in the brain, is thought to be "turned off" or relatively silent under normal conditions and believed to become activated under certain circumstances of excess neuronal activity. In the "on" mode, this neuromodulatory system assists in enabling relaxation, reducing pain and anxiety, and initiating sedation or a slowing of metabolism. It affects both mental and physiologic processes. The EC system is physiologically multitiered, yet integrated through central and peripheral pathways to maintain metabolic homeostasis. What is important is that through chronic transient activation, the EC system appears to stimulate appetite, creating a metabolic imbalance and resulting in many pathologies. These conditions, in turn, create an increased risk for coronary disease and CVD through synergistic, multiple modalities, and these pathologic conditions can be ameliorated through treatment with $CB_1$ antagonists.[2-4]

## ENDOCANNABINOID RECEPTORS AND LIGANDS

The 2 known EC receptors, $CB_1$ and $CB_2$, are both G-protein–coupled, 7-transmembrane receptors. They differ structurally, however, and whereas $CB_2$ receptors populate the immune system, $CB_1$ receptors abundantly populate the central nervous system (CNS) as well as peripheral tissues and organs, and are of primary interest in modulating metabolism.[1,5]

The $CB_1$ receptor is the most abundant G-protein–coupled receptor in the brain, accounting for all of the well-known psychotropic effects of cannabinoid stimulation.

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$CB_1$ receptors have high concentrations in the basal ganglia, cerebellum, hippocampus, and cortex.[1] They also populate the hypothalamus, limbic structures, brainstem, gastrointestinal tract, adipocytes, and liver. In contrast to traditional neuronal systems, which form and store neurotransmitter in vesicles for use as needed, anandamide and 2-AG are produced from cell membranes when needed by activation of their synthetic enzymes. Derived from arachidonic acid, their synthesis involves phospholipid remodeling. They act as soon as they are secreted, mainly at cells in the immediate proximity of their release, and then are degraded rapidly by enzymes found in most cells; i.e., fatty acid amide hydrolase and monoacylglycerol (MAG) lipase.

The EC receptor system is structured and functions differently from traditionally studied neurotransmitter systems. In **Figure 1**, a neural circuit is depicted in which activity in one particular neuron leads to continued eating. Under normal circumstances, as a meal progresses, release of an inhibitory neurotransmitter onto this neuron eventually leads to satiety. In some situations, other factors might intervene. For example, if the food being eaten is particularly palatable, or if the social situation is particularly pleasing, a modulatory interneuron could become activated, leading in turn to activation of enzymes that synthesize ECs. An increase of EC activity at the presynaptic $CB_1$ receptors causes less neurotransmitter to be released, resulting in a prolonged meal in which more food is eaten. What is unique is that the ECs travel in a retrograde fashion across synapses to interact with $CB_1$ receptors on presynaptic cells. This overall process is known as retrograde suppression of neurotransmitter release. What is important about this example is that increased EC activity leads to increased energy intake.

## ENDOCANNABINOID SIGNALS

In influencing metabolic homeostasis, the key $CB_1$ receptors of primary interest are located in the brain, liver, and adipose tissue. Those in the brain play a role in control of appetite and the modulation of hypothalamic neuropeptides to maintain energy balance. Peripherally, $CB_1$ receptors modulate adipocyte cell function and hepatic function in the liver, as well as activity in the gastrointestinal and skeletal muscle systems.

Two major categories of signals arise in the periphery and regulate food intake in the brain. One comes from the gut, primarily through the vagus nerve to the brain, signaling satiety during meals; the other enters the brain via the circulation, signaling the amount of fat in the body (**Figure 2**).[6] Both types of signals are integrated in the hypothalamus to control the size of the meal and ultimately to regulate body fat content.[7,8]

### Satiety Signals Contribute to Control Meal Size

During consumption of a meal, partially digested food stimulates the gastrointestinal system to secrete a number of peptides and enzymes important in digestion. Some of these stimulate receptors on afferent vagus nerve fibers passing to the brain.[8] These satiety signals converge in the nucleus tractus solitarius (NTS), which integrates signals from the gastrointestinal tract and other abdominal viscera as well as from the mouth.[9] Other satiety signals, such as gastric stretch receptor signals, are integrated with the chemical signals in the NTS.[10] Neural input relating to energy metabolism in the liver, such as increased hepatic energy production, also contributes to these signals. Cholecystokinin (CCK) is the best-known satiety signal, and during meals its release occurs from neuroendocrine secretory cells that line the intestinal lumen.[11] Other peptides secreted from the gut that contribute to these signals include glucagon-like peptide–1, peptide YY, enterostatin, and glucagon. The combined action of all of the satiety signals in the NTS and in the hindbrain in general is sufficient to stop an ongoing meal in the absence of input from the hypothalamus and other forebrain areas.[12] Under normal conditions, the forebrain and hindbrain interact to control meal size, with adiposity signals such as leptin and insulin enhancing the satiating effect of CCK.[13,14]

An important point is that ECs directly inhibit the impact of these satiety signals, in large part because the same nerves that transport satiety signals to the brain express EC receptors. The system is reciprocal in that CCK release inhibits the expression of $CB_1$ receptors on afferent vagal neurons, whereas EC stimulation blunts the effects of satiety signals to reduce food intake.[15] The net effect is that EC stimulation enables the consumption of larger meals.

### Leptin, Insulin, and Adiposity Signaling

The first hormone implicated in CNS-mediated control of body fat was insulin. It enters the brain from the circulation by a receptor-mediated process that passes it through the blood-brain barrier, and it acts in the hypothalamus to reduce energy intake.[16,17] A second adiposity-signaling hormone, leptin, was subsequently identified through investigation of obese mice with defective leptin signaling.[18] Insulin (secreted from $\beta$-cells in the pancreas) and leptin (secreted from adipocytes) compose the best known adiposity-signaling molecules. Each is secreted in response to feeding and each circulates at levels directly proportional to body fat content.[19,20] Receptors for both leptin and insulin exist in brain neurons involved in energy intake, and both of these signaling molecules enter the CNS in proportion to circulating plasma levels.[16,21] Administration of leptin or insulin directly into the brain reduces food intake, whereas deficiency of either has the opposite effect, leading to obesity if prolonged.[17,18,22-25] Direct applicability of animal study findings to the human model cannot be made without reservation. Recent study has raised issues regarding the precise relevance of these findings to human studies.

## THE HYPOTHALAMIC ENDOCANNABINOID SYSTEM

The neural circuitry of the hypothalamus that controls energy homeostasis is organized into anabolic and catabolic