The Endocannabinoid System (ECS) in regulation of **Energy Balance, Obesity, Leaky Gut & Inflammation**

"Obesity is a hormonal, not a caloric imbalance" -Dr. Jason Fung
The Obesity Code: Unlocking the Secrets of Weight Loss

“Energy balance is controlled by centers of the brain which receive important inputs from the gastrointestinal tract, liver, pancreas, adipose tissue and skeletal muscle, mediated by many different signaling molecules. **Obesity occurs when control of energy intake is not matched by the degree of energy expenditure. Obesity is not only a state of disordered energy balance it is also characterized by systemic inflammation. Systemic inflammation is triggered by the leakage of bacterial lipopolysaccharide through changes in intestinal permeability. The endocannabinoid system, consisting of the cannabinoid receptors, endogenous cannabinoid ligands and their biosynthetic and degradative enzymes, plays vital roles in the control of energy balance, the control of intestinal permeability and immunity.** In this review we will discuss how the endocannabinoid system, intestinal microbiota and the brain-gut axis are involved in the regulation of energy balance and the development of obesity-associated systemic inflammation. **Through direct and indirect actions throughout the body, the endocannabinoid system controls the development of obesity and its inflammatory complications**.”

Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary, Calgary, Alberta, Canada.
http://www.ncbi.nlm.nih.gov/pubmed/22269477

“Grains and legumes typically contain very high levels of a substance called phytic acid. Phytic acid actively binds minerals and eliminates them from the body, which results with increased grain consumption, widespread deficiencies of minerals, including calcium, iron, magnesium, and zinc. Legumes typically contain 60 percent starch and only relatively small amounts of incomplete protein, and they also contain potent protease inhibitors, which can damage one’s ability to properly digest and use dietary protein and can potentially damage the pancreas over time, when one is overly dependent on them as a source of calories.”

- Nora T. Gedgaudas, CNS, CNT

"Obesity also has a strong inflammatory component that can be driven by diet-induced increases in arachidonic acid [omega-6]."

-Inflammation Research Foundation, Marblehead, MA 01945, USA
-Diabetes Research Institute, University of Miami, Miami, FL 33316, USA
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952901/

“Obesity is characterized by chronic low-grade, systemic inflammation, altered gut microbiota, and gut barrier disruption. Additionally, obesity is associated with increased activity of the endocannabinoid system (eCB). However, the clear connection between gut microbiota and the eCB system in the regulation of energy homeostasis and adipose tissue inflammation and metabolism, remains to be established.”

https://www.ncbi.nlm.nih.gov/pubmed/29142285

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Gut Healing

“Mammalian cells have machinery, the socalled Endocannabinoid system (ECS), to produce and metabolize their own cannabinoids in order to control homeostasis of the gut in a rapidly adapting manner.”
Division of Gastroenterology, Department of Medicine, University of Calgary

http://www.ncbi.nlm.nih.gov/pubmed/22111567

The Dietary Intake of Wheat and other Cereal Grains and Their Role in Inflammation

"Wheat is one of the most consumed cereal grains worldwide and makes up a substantial part of the human diet. Although government-supported dietary guidelines in Europe and the U.S.A advise individuals to eat adequate amounts of (whole) grain products per day, cereal grains contain “anti-nutrients,” such as wheat gluten and wheat lectin, that in humans can elicit dysfunction and disease. In this review we discuss evidence from in vitro, in vivo and human intervention studies that describe how the consumption of wheat, but also other cereal grains, can contribute to the manifestation of chronic inflammation and autoimmune diseases by increasing intestinal permeability and initiating a pro-inflammatory immune response."

-University of Girona
-University of Graz

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3705319/

“Caloric restriction (CR), in the absence of malnutrition, delays aging and prevents aging-related diseases through multiple mechanisms. A reduction in chronic inflammation is widely observed in experimental models of caloric restriction.The low inflammation status may contribute to the reduced incidence of osteoporosis, Alzheimer’s disease, cardiovascular diseases and cancer in the aging subjects. The association of caloric restriction with low

inflammation suggests a role of energy accumulation in the origin of the chronic inflammation. This point is enforced by recent advances in obesity research. Abundant literature on obesity suggests that chronic inflammation is a consequence of energy accumulation in the body."

Pennington Biomedical Research Center, Louisiana State University System,
https://www.ncbi.nlm.nih.gov/pubmed/20606248

Systemic low-grade inflammation is related to both circulating and adipose tissue TNFalpha, leptin and IL-6 levels in obese women.
https://www.ncbi.nlm.nih.gov/pubmed/15211360

The "Perfect Storm" for Type 1 Diabetes

"In the case of type 1 diabetes, evidence for a synergism between aberrant intestinal microbiota, a "leaky" intestinal

mucosal barrier, and altered mucosal immunity contributing
to the disorders pathogenesis has begun to evolve.”

- Laboratory for Immunobiology, Department of Viral Diseases and Immunology, National Public Health Institute
- Department of Clinical and Experimental Medicine, Division of Pediatrics and Diabetes Research Center
- Department of Pathology, University of Florida College of Medicine
- Department of Pediatrics, University of Florida College of Medicine

https://www.ncbi.nlm.nih.gov/pubmed/18820210

Dietary Strategies to Reduce Inflammation

“Reducing the incidence of coronary heart disease with diet is possible. The main dietary strategies include adequate omega-3 fatty acids intake, reduction of saturated and transfats, and consumption of a diet high in fruits, vegetables, nuts, and whole grains and low in refined grains. Each of these strategies may be associated with lower generation of inflammation. This review examines the epidemiologic and clinical evidence concerning diet and inflammation. Dietary patterns high in refined starches, sugar, and saturated and Trans fatty acids, poor in natural antioxidants and fiber from fruits, vegetables, and whole grains, and poor in omega3 fatty acids may cause an activation of the innate immune system, most likely by an excessive production of proinflammatory cytokines associated

with a reduced production of antiinflammatory cytokines. The whole diet approach seems particularly promising to reduce the inflammation associated with the metabolic syndrome. The choice of healthy sources of carbohydrate, fat, and protein, associated with regular physical activity and avoidance of smoking, is critical to fighting the war against chronic disease. Western dietary patterns warm up inflammation, while prudent dietary patterns

cool it down."

Division of Metabolic Diseases, Center of Excellence for Cardiovascular Diseases,
University of Naples

https://www.ncbi.nlm.nih.gov/pubmed/16904534

Endocannabinoids in the Gut

"Cannabis has been used medicinally for centuries to treat a variety of disorders, including those associated with the gastrointestinal tract. The discovery of our bodies' own "cannabis-like molecules" and associated receptors and metabolic machinery – collectively called the endocannabinoid system – enabled investigations into the physiological relevance for the system, and provided the field with evidence of a critical function for this endogenous signaling pathway in health and disease. Recent investigations yield insight into a significant participation for the endocannabinoid system in the normal physiology of gastrointestinal function, and its possible dysfunction in gastrointestinal pathology. Many

gaps, however, remain in our understanding of the precise neural and molecular mechanisms across tissue departments that are under the regulatory control of the endocannabinoid system. This review highlights research that reveals an important – and at times surprising – role for the endocannabinoid system in the control of a variety of gastrointestinal functions, including motility, gut-brain mediated fat intake and hunger signaling, inflammation and gut permeability, and dynamic interactions with gut microbiota."

Division of Biomedical Sciences, School of Medicine, University of California

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4940133/

Crosstalk between the gut microbiota and the endocannabinoid system: impact on the gut barrier function and the adipose tissue.

Obesity is associated with type 2 diabetes, insulin resistance and low grade inflammation. The gut microbiota is now considered as one of the most important environmental factors impacting on host physiology and metabolism. We have recently pointed out the role of this 'organ' on the onset of insulin resistance and the low grade inflammatory tone characterizing obesity. Among the mechanisms, we have introduced the novel concept of metabolic endotoxemia as factor triggering low grade inflammation and associated disorders. More recently, two novel mechanisms involved in the development of gut permeability and adipose tissue plasticity have been identified. Specific attention has been paid to the role of the glucagon-like peptide 2 and the endocannabinoid system. This review briefly discusses the role of prebiotics as a key tool to modulate the gut microbiota, the gut barrier function, inflammation and the insulin resistance associated with obesity.

Louvain Drug Research Institute, Metabolism and Nutrition Research Group, Université Catholique de Louvain, Brussels, Belgium.

https://www.ncbi.nlm.nih.gov/pubmed/22647050

ECS and the GUT

"Anatomical, physiological and pharmacological studies have shown that the endocannabinoid system [ECS] is widely distributed throughout the gut, with regional variation and organ specific actions. It is involved in the regulation of food intake, nausea and emesis, gastric secretion and gastroprotection, GI motility, ion transport, visceral sensation, intestinal inflammation and cell proliferation in the gut."

- Department of Experimental Pharmacology, University of Naples Federico II
- The Endocannabinoid Research Group, Naples Italy

http://www.ncbi.nlm.nih.gov/pubmed/20117132

"22 immune diseases diagnosed at hospitalization correlated with obesity"
PMID: 21284531

“It is becoming more evident that inflammation plays an important role in the metabolic consequences of obesity, as well as other chronic degenerative conditions.”

- Inflammation Research Foundation, Marblehead, MA 01945, USA
- Diabetes Research Institute, University of Miami, Miami, FL 33316, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952901/

An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity

“A diet high in the omega-6/omega-3 ratio causes an increase in the endocannabinoid signaling and related mediators, which lead to an increased inflammatory state, energy homeostasis, and mood. In animal experiments a high omega-6 acid intake leads to decreased insulin sensitivity in muscle and promotes fat accumulation in adipose tissue. Nutritional approaches with dietary omega-3 fatty acids reverse the

dysregulation of this system, improve insulin sensitivity and control body fat.

Endocannabinoids are lipids, derived from the omega-6 AA. Their concentrations are regulated by (1) dietary intake of omega-6 and omega-3 fatty acids; and (2) by the activity of biosynthetic and catabolic enzymes involved in the endocannabinoid pathway, which is an important player in regulation of appetite and metabolism [81,104]. The endocannabinoid system is involved in regulation of energy balance and sustained hyperactivity of the endocannabinoid system contributes to obesity [81,82]. AA is the precursor of 2-arachidonoylglycerol (2-AG) and anandamide (AEA). Increasing the precursor pool of AA causes excessive endocannabinoid signaling leading to weight gain and a metabolic profile associated with obesity. Endocannabinoids activate endogenous cannabinoid CB1 and CB2 receptors in the brain, liver, adipose tissue, and the gastrointestinal tract [105]. Activation of CB1 receptors in the hypothalamus leads to increased appetite and food intake [82]. In mouse experiments endocannabinoids selectively enhance sweet taste, which in the current highly palatable food supply stimulate food intake [106]. The endocannabinoid system functions in concert with other systems regulating food intake and energy balance, and is regulated by leptin, insulin, ghrelin, cholecystokinin, and other signals. Targeting the endocannabinoid system has been a strategy for weight loss. Randomized controlled clinical trials in overweight or obese humans showed that CB1 receptor antagonists such as rimonabant led to significant weight loss after one year of treatment [107]. However the drug was withdrawn from the market due to severe side effects that led to increased risk of anxiety, depression, and suicide [108].”
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808858/

“For many years, the brain has been the primary focus for research on eating behavior. More recently, the discovery of the endocannabinoids (EC) and the endocannabinoid system (ECS), as well as the characterization of its actions on appetite and metabolism, has provided greater insight on the brain and food intake. The purpose of this review is to explain the actions of

EC in the brain and other organs as well as their precursor polyunsaturated fatty acids (PUFA) that are converted to these endogenous ligands. The binding of the EC to the cannabinoid receptors in the brain stimulates food intake, and the ECS participates in systemic macronutrient metabolism where the gastrointestinal system, liver, muscle, and adipose are involved. The EC are biosynthesized from two distinct families of dietary PUFA, namely the n-6 and n-3. Based on their biochemistry, these PUFA are well known to exert considerable physiological and health-promoting actions. However, little is known about how these different families of PUFA compete as precursor ligands of cannabinoid receptors to stimulate appetite or perhaps down-regulate the ECS to amend food intake and prevent or control obesity. The goal of this review is to assess the current available research on ECS and food intake, suggest research that may improve the complications associated with obesity and diabetes by dietary PUFA intervention, and further reveal mechanisms to elucidate the relationships between substrate for EC synthesis, ligand actions on receptors, and the physiological consequences of the ECS. Dietary PUFA are lifestyle factors that could potentially curb eating behavior, which may translate to changes in macronutrient metabolism, systemically and in muscle, benefiting health overall."
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4285050/

Acute Activation of Cannabinoid Receptors by Anandamide Reduces Gastrointestinal Motility and Improves Postprandial Glycemia in Mice
http://diabetes.diabetesjournals.org/content/64/3/808

"Insulin resistance is defined as a reduced response of target tissues such as skeletal muscle, liver, and adipocytes to insulin [1]. Adipose tissue plays an important role in maintaining glucose homeostasis, however obesity

results in an inflammatory state that contributes to insulin resistance [2]. With obesity rates on the rise around the world [3], it is important to understand how diet impacts the risk of developing insulin resistance as this condition increases the likelihood that other metabolic abnormalities will also be present, such as elevated plasma glucose, endothelial dysfunction, dyslipidemia, and increased inflammation.”..
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5579679/

"It is now well established that the ECS is involved in many biological functions, including the regulation of energy balance and the pathogenesis of obesity. Obesity is associated with central ECS overactivation, and since activation of CB1R in the brain stimulates food intake, ECS appears to be located at the center of a vicious circle inducing weight gain and related disorders (4,5). However, even if the CB1R-dependent stimulation of food intake may be the main initial cause of various metabolic deregulations associated with obesity, several data collected from animal and human studies using the specific CB1R antagonist SR141716 (rimonabant) suggested that peripheral ECS might also directly regulate energy metabolism (6–8). It was recently reported that activation of peripheral CB1R signaling in key tissues

relevant to insulin action is associated with alteration of glucose homeostasis and contributes to diet-induced insulin resistance in mice (9–11)."
https://diabetes.diabetesjournals.org/content/64/3/808