An emerging body of evidence implicates peripheral and central endocannabinoid pathways in the regulation of feeding behavior and body weight. A report in this issue of the JCI demonstrates the presence of a common endocannabinoid-regulated molecular pathway for peripheral lipogenic and central appetitive regulation (see the related article beginning on page 1298). This pathway involves the activation of the transcription factor SREBP-1c and its associated enzymes, acetyl-CoA carboxylase-1 and fatty acid synthase, in the liver and hypothalamus. Activation of cannabinoid receptor 1 (CB₁) in liver plays a key role in increased serum lipid production, fatty liver, and possibly diet-induced obesity. Conversely, stimulation of these receptors in the hypothalamus may lead to an increase in food consumption. Thus, targeting both of these pathways with CB₁ antagonists could promote sustained weight loss and favorable serum lipid profiles in obese patients.

Cannabis has been used since antiquity for the treatment of many ailments, including pain, rheumatoid arthritis, epilepsy, and eating disorders. William O’Shaughnessy played a leading role in introducing this substance to Western medicine in the middle of the eighteenth century. One of the many pharmacological properties of cannabis he described was the induction of a “remarkable increase of appetite” (1). Over 120 years later, Gaoni and Mechoulam identified the structure Δ⁹-tetrahydrocannabinol (Δ⁹-THC) as the primary psychoactive constituent of cannabis (2). A considerable amount of preclinical research validated these early reports of the effects of cannabis on feeding by demonstrating that low-to-moderate doses of Δ⁹-THC and other cannabinoid receptor agonists increase feeding or food-motivated behavior (3). Importantly, administration of oral Δ⁹-THC (Marinol) was found to have some efficacy in treating the AIDS wasting syndrome by enhancing appetite and preventing weight loss (4).

Δ⁹-THC, along with other naturally occurring and synthetic cannabinoids, binds to 2 separate G protein–coupled receptors: cannabinoid receptor 1 (CB₁), which is located in both the CNS and periphery (5), and CB₂, which is found primarily on cells of the immune system (6). These receptors and their endogenous ligands, which include the fatty acid amide N-arachidonoyl ethanolamine (anandamide) and the monoacylglycerol 2-arachidonoylglycerol (2-AG) (7, 8), together constitute an endogenous cannabinoid (endocannabinoid) system. This system has been proposed to modulate several physiological functions, including pain (9, 10), cognition (11, 12), drug dependence (13), excitotoxicity (14), and feeding (15).

Endocannabinoid regulation of feeding and lipogenesis
A common experimental strategy to investigate whether the endocannabinoid system tonically modulates a physiological system is to disrupt CB₁ signaling using either the CB₁ antagonist SR141716 (Rimonabant) (16) or CB₁−/− mice (13, 17). SR141716 administration has been shown to have an anorexic action in a variety of rodent models of feeding (3). In rats, it caused a dose-dependent decrease in consumption of either sucrose pellets or sucrose solution, but had limited effects on the intake of standard chow or water (18), which suggests that the endocannabinoid system plays a role in the increased consumption of palatable substances. Similarly, Di Marzo and colleagues (15) reported that SR141716-treated mice and CB₁−/− mice ate significantly less than did control mice following 18 hours of food deprivation. They also found that ob/ob and db/db mice and Zucker rats, genetic rodent models of obesity, possessed elevated levels of endocannabinoids in the hypothalamus compared with those in nonobese control mice, while no differences were found in other brain regions (e.g., the cerebellum). The observation that SR141716 decreases food intake in obese animals suggests that endocannabinoids in the hypothalamus may play a role in hyperphagic responses. Other evidence indicates that endocannabinoids are involved in the neural circuitry of feeding regulated by leptin, a hormone that plays a key role in modulating food intake and body fat. Whereas leptin-deficient mice become obese and exhibit increased levels of endogenous cannabinoids in the hypothalamus, administration of leptin leads to a decrease in feeding and a concomitant reduction of anandamide and 2-AG expression in the hypothalamus (15). Conversely, CB₁−/− mice possess significantly decreased plasma levels of leptin and have reduced body fat, but exhibit enhanced sensitivity to exogenously administered leptin compared with that in wild-type mice (19, 20).

Cota and colleagues proposed that the endocannabinoid system plays a dual role in regulating body weight through a central orexigenic effect and in the regulation of peripheral lipogenesis (19). While stimulation of the endocannabinoid system can lead to increases in caloric consumption depending on the type of food available and whether the animal has been fasted, the number of calories consumed does not account for body weight differences found between SR141716-treated or CB₁−/− animals and controls. Instead, several lines of evidence suggest a peripheral role for endocannabinoids in the regulation of lipogenesis and body weight in adult animals. SR141716 consistently alters hormone and serum lipid levels associated with animal models of obesity (21, 22). In addition, the cannabinoid receptor agonist WIN-55,212-2...
stimulates lipogenesis in primary adipocyte cell cultures (19). The presence of CB₁ mRNA in fat tissue from wild-type mice is consistent with a direct role of endocannabinoids in the regulation of lipogenesis.

**CB₁ activation of SREBP-1c in liver and hypothalamus**

In this issue of the *JCI*, Osei-Hyiaman and colleagues identify the liver as a primary site responsible for endocannabinoid-mediated modulation of lipogenesis (23). Moreover, they present compelling evidence supporting a common molecular pathway for peripheral lipogenic and central appetitive processes in liver and hypothalamus. In liver (left), a high-fat diet leads to increased CB₁ levels as well as increased levels of anandamide, the latter of which results from decreased activity of FAAH, the primary enzyme responsible for this endocannabinoid’s catabolism. CB₁ stimulation increases expression of the transcription factor SREBP-1c and its associated enzymes, ACC1 and FAS. Stimulation of this pathway leads to a functional increase in the rate of de novo fatty acid synthesis in liver and the increased occurrence of fatty liver and obesity. Through either direct or indirect mechanisms, this pathway also regulates plasma levels of hormones associated with metabolism and feeding, including insulin, leptin, and adiponectin. These altered levels of hormones may negatively affect feeding behavior and metabolism. For example, exogenous administration of leptin leads to decreased levels of anandamide and 2-AG in the hypothalamus and consequently inhibits feeding behavior. Conversely, stimulation of CB₁ in the hypothalamus (right) activates SREBP-1c and FAS, which leads to a hyperphagic response to a high-carbohydrate meal following a fast. Disruption of CB₁ signaling through the use of CB₁⁻/⁻ mice or SR141716 (Rimonabant) administration blocks both pathways, leading to a net effect of decreased fatty acid production and prevention of hyperphagia.

**Figure 1**

Proposed model for the dual role of the endocannabinoid-mediated pathway in regulation of peripheral metabolic and central appetitive processes in liver and hypothalamus. In liver (left), a high-fat diet leads to increased CB₁ levels as well as increased levels of anandamide, the latter of which result from decreased activity of FAAH, the primary enzyme responsible for this endocannabinoid’s catabolism. CB₁ stimulation increases expression of the transcription factor SREBP-1c and its associated enzymes, ACC1 and FAS. Stimulation of this pathway leads to a functional increase in the rate of de novo fatty acid synthesis in liver and the increased occurrence of fatty liver and obesity. Through either direct or indirect mechanisms, this pathway also regulates plasma levels of hormones associated with metabolism and feeding, including insulin, leptin, and adiponectin. These altered levels of hormones may negatively affect feeding behavior and metabolism. For example, exogenous administration of leptin leads to decreased levels of anandamide and 2-AG in the hypothalamus and consequently inhibits feeding behavior. Conversely, stimulation of CB₁ in the hypothalamus (right) activates SREBP-1c and FAS, which leads to a hyperphagic response to a high-carbohydrate meal following a fast. Disruption of CB₁ signaling through the use of CB₁⁻/⁻ mice or SR141716 (Rimonabant) administration blocks both pathways, leading to a net effect of decreased fatty acid production and prevention of hyperphagia.
diet, supports the assertion that increased cannabinoid-mediated lipogenesis plays a more dominant role in diet-induced obesity than does hyperphagia. In addition to calo-
rie intake and lipogenesis, other factors such as resting metabolic rate, total energy expen-
diture, and dietary-induced thermogenesis play a critical role in regulating body weight. 

Presently, the relationship between endocan-
nabinoids and methods of energy expendi-
ture is largely unknown, and the possibility
that endocannabinoids may modulate these
processes cannot be negated.

A particularly provocative implication of
the work by Osei-Hyiaman et al. (23) is that
endocannabinoid-mediated modulation of
lipogenesis in the liver may contribute to
the development of fatty liver and obesity.
Wild-type mice maintained on a high-fat
diet gained significant amounts of weight,
mostly in the form of adipose tissue, and had
altered levels of enzymes associated with
metabolism, including insulin, leptin, and
adiponectin. Additionally, these mice had an
increased rate of hepatic fatty acid synthesis,
showed increased levels of triglycerides, and
developed fatty liver. In contrast, CB1/– mice
maintained on a high-fat diet did not exhibit
an increase in fatty acid synthesis, exhibited
serum hormone and lipid profiles similar to
wild-type mice fed regular chow, and did
not develop fatty liver. Similarly, SR141716
administration significantly attenuated the
elevation in hepatic fatty acid synthesis
in wild-type mice fed a high-fat diet. These
findings are corroborated in other reports
(25, 26), in which chronic SR141716 treat-
ment of mice maintained on high-fat diets
was found to have similar beneficial effects
with respect to serum lipids, leptin, and body
weight as those observed in CB1/– mice.

Another important finding reported by
Osei-Hyiaman et al. is that the endogenous
 cannabinoid system in the liver undergoes
adaptive changes in response to diet (23). 
Wild-type mice maintained on a high-fat
diet developed fatty liver associated with
significant increases in hepatic levels of
CB1 and anandamide. Hepatic 2-AG levels
were unaffected by diet, which suggests that
anandamide is the predominant endocan-
nabinoid signaling molecule in this liver
pathway. The elevated levels of hepatic
anandamide appear to be due to a decrease
in activity of fatty acid amide hydrolase
(FAAH), the primary enzyme responsible for
anandamide catabolism in vivo (27). Curi-
ously, the level of FAAH protein in liver was
unaffected by diet, suggesting that the high-
fat diet led to a decrease in anandamide deg-
radation, possibly the result of the elevated
levels of fatty acids and other endogenous
factors competing for FAAH. In contrast,
N-acyltransferase, an enzyme regulating
anandamide synthesis (28), was unaffected.

Collectively, Osei-Hyiaman and col-
leagues have demonstrated that stimulation
of CB1 in liver with HU210 leads to an
increased rate of hepatic fatty acid synthesis
through a mechanism involving increases
in SREBP-1c and its target enzymes, ACC1
and FAS (23). Similarly, they report intriguing
evidence that anandamide activation of
CB1 in liver is necessary for increased fatty
acid synthesis following consumption of a
high-fat diet. According to this model, con-
sumption of a diet high in fats would lead to
increases in fatty acid synthesis through the
upregulation of endocannabinoid-mediated
SREBP-1c in liver. Future work will need to
address the issue of whether conditions that
elevate hepatic anandamide levels are suffi-
cient to stimulate SREBP-1c, ACC1, and FAS.
Increasing the storage of fat could conceiv-
able be an adaptive advantage in situations
in which food is scarce, but could contribute
to obesity, along with decreases in energy
expenditure, when high-fat diets are con-
sumed on a regular basis. A similar pathway
involving endocannabinoid modulation of
SREBP-1c in the hypothalamus may account
for increased feeding behavior following
periods of food deprivation. Both pathways
are likely to contribute to the purported
therapeutic efficacy of CB1 antagonists for
the treatment of obesity and hyperlipidemia.
Nonetheless, the devastating impact that the
disruption of CB1 signaling has on feeding
behavior and growth in young mice (19, 29) necessi-
tates that caution should be applied for
the use of this approach in pregnant women
and nursing mothers. Conversely, stimulation
of hepatic and hypothalamic endocannabinoid
pathways may account for the efficacy of
Δ9-THC in the treatment of wasting syn-
dromes associated with AIDS and cancer.

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Angiogenesis may be an important factor in the development of fibrotic lung disease. Prior studies have strongly suggested a role for angiogenic vascular remodeling in pulmonary fibrosis, and emerging evidence indicates that new vessel formation is critical in airway fibrosis. Bronchiolitis obliterans syndrome is a fibrotic occlusion of distal airways that is largely responsible for the morbidity and mortality of patients after lung transplantation. In this issue, Belperio et al. demonstrate a role for CXC chemokine receptor 2 in the regulation of angiogenesis-mediated airway fibroproliferation (see the related article beginning on page 1150). By integrating an understanding of neovascularization into the study of events that occur between inflammation and fibrosis, it becomes increasingly possible to rationally design therapies that can halt conditions of maladaptive fibrosis.

Neovascularization is an important component of fibrotic responses (1). In this issue of the JCI, Belperio and colleagues extend this relationship to the development of chronic lung transplant rejection (2). Using bronchoalveolar lavage fluid from patients with pending or established bronchiolitis obliterans syndrome (BOS) and tracheal allograft tissue from a mouse model of obliterative airway disease, the authors make a convincing case for the central role of CXC chemokine receptor 2 (CXCR2) regulation of angiogenesis-mediated airway fibroproliferation.

Airway inflammation and fibrosis in the evolution of BOS

Chronic allograft rejection is the chief factor limiting long-term survival following lung transplantation. BOS is the pathological correlate of chronic rejection and primarily affects the respiratory and terminal bronchioles, which culminates in a fibrotic occlusion of the distal airways (3). The cumulative incidence of BOS at 5 years after lung transplant is between 50% and 80%, and 5-year survival after BOS onset is only 30–50%. The International Society of Heart and Lung Transplantation Registry has noted that the development of BOS within the first year after transplantation is the single most important factor influencing 5-year mortality among patients undergoing lung transplantation (3). As a fibrotic disease, BOS is poorly responsive to standard immunosuppression employed by transplant physicians. Similarly, pulmonary fibrosis, which affects the lung interstitium rather than the conducting airways, responds poorly to immunotherapy and has long been associated with pathologic angiogenesis (4).

It is a generally recognized phenomenon that inflammation is an initiating event that precedes the progression to fibrosis in several lung diseases, including BOS and idiopathic pulmonary fibrosis. While fibrosis may be a frequent sequela of an acute or subacute inflammatory event, it is also clear that inflammation does not always result in fibrosis. The long-term effect of interstitial or airway fibrosis is irreversible lung architectural remodeling. Key questions regarding the mechanisms of airway remodeling are: (a) What are the specific inflammatory initiators? and (b) What is the sequence of events that culminates in fibroproliferation? In lung transplantation, the answer to the first question most certainly involves the response to alloantigen triggering of innate and adaptive immune responses. The answer to the second question is probably less well understood but is perhaps of greater importance in the development of therapies that reach beyond immunosuppression. Lung transplant clinicians well appreciate that acute rejection treated early may respond excellently to immunosuppressive therapies but that late intervention is rarely successful. Unfortunately, it is not always possible to intervene early, and occasionally even apparently early intervention with high-dose steroids or T cell–depleting strategies cannot halt the decline in lung function once fibroproliferation is initiated.

The potential role of CXC chemokines in angiogenicfibroproliferative BOS

The study by Belperio and colleagues (2) firmly establishes that neovascularization is an important contributor to the process of fibroproliferation in airway fibrosis. The investigators present a cohesive and clearly argued interpretation of experimental data from human BOS patients and a well-characterized murine model of tracheal transplant rejection. Their findings make a convincing case for the central role of CXCR2-dependent Glu-Leu-Arg–positive (ELR+ ) chemokine regulation of angiogenesis-mediated BOS fibroproliferation. The study extends their previ-