Possible Role of Adipose Tissue and the Endocannabinoid System in Coronavirus Disease 2019 Pathogenesis: Can Rimonabant Return?

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"Obesity is an Independent Risk Factor for Severe COVID-19"

This is the main conclusion of a recent study describing a strong relationship between the degree of obesity and the severity of coronavirus disease 2019 (COVID-19) infection (1). Obesity has various negative consequences relative to the course of COVID-19, including adverse effects on lung physiologic processes, and it induces comorbidities such as type 2 diabetes or hypertension. However, additional mechanisms involving the low-grade inflammatory state accompanying obesity can also be suggested (1).

Obesity Involves an Inflammatory State of Adipose Tissue

A main medical problem raised by COVID-19 is the hyperinflammation accompanying the most severe forms of disease, characterized by acute respiratory distress syndrome and multiorgan failure in the general context of a life-threatening cytokine storm (2). In obesity, adipose tissue expansion is accompanied by infiltration of macrophages producing inflammatory cytokines, such as tumor necrosis factor α, interleukin-1β, and interleukin-6. There is a significant correlation between BMI and the number of macrophages present in adipose tissue, with macrophages representing as much as 25% of adipocyte cell numbers (3). Although inflammation accompanying obesity appears as a low-grade chronic inflammatory state, one can question whether the huge numbers of immune cells present in adipose tissue of patients with obesity might not represent a kind of time bomb contributing to the cytokine storm observed in COVID-19. Despite perturbing data suggesting a paradoxical protection of obesity against bacterial sepsis (4), the opposite has been observed for influenza, pneumonia (4), and COVID-19 (1).

Endocannabinoid Tone Plays a Key Role in the Development of Obesity

Considering these data, we put forward the hypothesis that reducing the inflammatory potential of adipose tissue in patients with obesity might decrease the risk of developing severe complications of COVID-19. This goal could be achieved by weight loss (3), but this does not correspond to the urgency of the situation, which might better benefit from an appropriate pharmacological intervention. Adipose tissue development is under the control of the endocannabinoid system, which involves at least two receptors (cannabinoid receptor type 1 [CB1] and cannabinoid receptor type 2 [CB2]), endocannabinoid ligands (mainly anandamide and 2-arachidonoyl glycerol), and various proteins involved in endocannabinoid metabolism (5). CB1 is particularly abundant in the brain, where it is responsible for the psychotropic effects of (−)-*trans*-Δ^9-tetrahydrocannabinol, whereas CB2 is mainly present in immune cells (5). CB1 is also expressed in peripheral tissues such as the liver, skeletal muscle, pancreatic islets, and adipose tissue, where it regulates energy metabolism (5). In brief, obesity is accompanied by elevated endocannabinoid tone, in which stimulation of central CB1 promotes increased food uptake, whereas peripheral CB1 induces lipogenesis and fat accumulation in adipose tissue (5). This led to the development of CB1 antagonists aimed at reducing obesity by decreasing endocannabinoid tone. One of them (SR141716 or rimonabant, an inverse agonist of CB1 acting on both central and peripheral CB1) was effective at reducing body weight (6). However, the central action of rimonabant also induced serious mood disorders, which led to the withdrawal of the marketing authorization of rimonabant in the European Union (6).

Rimonabant is Efficient at Reducing Inflammation in Adipose Tissue from Rodents with Diet-induced Obesity

The first clinical trials on rimonabant were essentially focused on cardiovascular risk factors typical of obesity. However, several preclinical studies have been developed in the past 15 years, with one of the latest describing the molecular mechanisms underlying the inhibition by rimonabant of inflammation accompanying diet-induced obesity in mice (7). In addition, in a rat model of bacterial sepsis, rimonabant was shown to reduce mortality and to correct vascular hyperreactivity (8), which might be relevant in the context of the worse clinical outcomes associated with COVID-19 (2).

Rimonabant as a CB1 Antagonist Currently Available for Rapid Clinical Trials

Second- and third-generation CB1 antagonists unable to cross the blood-brain barrier were developed to avoid side effects related to

inhibition of central CB1, and they have been shown to display similar antiobesity and anti-inflammatory effects (9). However, despite a few preliminary clinical trials, none of these drugs reached the level of clinical translation, making it difficult to emphasize their use in the emergency context of the COVID-19 outbreak (9). Thus, rimonabant appears as the only drug immediately available for clinical trials, together with taranabant, which also reached phase 3 clinical trials with similar secondary effects (10).

Advocacy for Clinical Trials Aimed at Exploring the Capacity of Rimonabant to Modify the Prognosis of Severe Forms of COVID-19

In view of the dramatic consequences of COVID-19, the time required to obtain vaccines or to reach herd immunity has concentrated hope on drug repositioning, including repositioning of antiviral and anticytokine drugs as well as drug-combination therapy. We suggest rimonabant as an interesting avenue to reduce the infection severity occurring in patients with visceral obesity. Indeed, the weight loss–independent increase of adiponectinemia induced by rimonabant suggests a direct effect of the drug on adipocytes from abdominal tissue (6). The interaction of rimonabant with CB1 adipocytes is thus expected to decrease the inflammatory state of abdominal tissue, in a manner similar to the specific invalidation of CB1 in adipocytes (11). In addition, CB1 blockade was shown to reduce pulmonary inflammation in at least two different preclinical models (12,13). This might be particularly relevant in the context of COVID-19, although the opposite was observed in mice infected with respiratory syncytial virus (14). However, three concerns must be considered. First, the adverse psychiatric effects evoked by rimonabant might not be an intractable difficulty, as long as its administration can be restricted to the acute phase of infection in intensive care units, where patients are sedated and strictly monitored, thus preventing the risk of anxiety, depression, and suicide at this stage. However, for patients treated with rimonabant, subacute and chronic psychiatric complications should be carefully monitored, as survivors of critical illness are at risk of persistent psychiatric impairment. Moreover, although the chronic neuropsychiatric sequelae are still unknown for severe acute respiratory syndrome coronavirus 2, depressed mood, anxiety, and traumatic memories have been associated with previous coronavirus infections in the long term (15). Therefore, psychiatric surveillance should be initiated for patients after discharge from the intensive care unit and reinforced in cases of rimonabant administration. Second, rimonabant

was associated with upper-respiratory-tract infections in adverse-event reporting, which is unexplained but should not be a fatal flaw in exploring its use in the context of COVID-19 (16). A last concern relates to using any anti-inflammatory drug as part of antiviral therapy, as reducing inflammation could promote virus spreading by decreasing the level of immune defense. The same dilemma faced anticytokine treatments. We suggest that rimonabant be considered for appropriate clinical trials for patients with COVID-19.**O**

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