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Système endocannabinoïde et physiopathologie de l'obésité : rôle des CB1R (périphériques) du tissu adipeux et du foie

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Résumé

Le système endocannabinoïde (SEC) est impliqué dans plusieurs fonctions biologiques dont la régulation du métabolisme énergétique. Ces dernières années, de nombreuses études ont montré que l'obésité était associée à une suractivation du SEC et en particulier des récepteurs CB1 (CB1R) centraux. Ainsi, l'inactivation des CB1R par des antagonistes spécifiques comme le rimonabant (SR141716) conduit à une amélioration des paramètres métaboliques chez le sujet obèse. L'inactivation des CB1R périphériques pourrait également contribuer à l'amélioration de ces paramètres, et c'est cette dernière notion que nous avons cherché à approfondir. Pour cela, nous avons testé les effets du SR141716, sur des souris obèses afin d'établir des relations entre l'activité du SEC et le statut lipidique en étudiant plus particulièrement la régulation du métabolisme dans deux tissus clés, le foie et le tissu adipeux (TA). Des souris préalablement rendues obèses via un régime alimentaire enrichi en sucre et en graisse ont été traitées six semaines par SR141716. Le traitement a conduit à une perte de poids associée à une normalisation des paramètres plasmatiques, ainsi qu'à une résorption de la stéatose hépatique. Cette étude a également permis de démontrer que la réversion de la stéatose est associée à un effet bénéfique du traitement sur le métabolisme du TA viscéral suggérant ainsi l'existence d'effets directs du SR141716 sur les tissus périphériques. Par conséquent, les effets de l'antagonisme des CB1R périphériques sur le métabolisme lipidique ont ensuite été étudiés in vitro. Pour cela, nous avons tout d'abord développé un modèle d'explants de foie en culture traités avec SR141716. Dans ce modèle, le blocage des CB1R hépatiques est associé à une diminution de leur expression génique et dans certaines conditions à une augmentation des capacités β-oxydatives. En conclusion, ces travaux associés à ceux de la littérature démontrent que les CB1R périphériques constituent une cible thérapeutique très prometteuse pour le traitement de l'obésité et des désordres associés.

Mots clés

Système endocannabinoïde Endocannabinoïde SR141716 Anandamide Stéatose Adiponectine CB1R CB2R Foie Tissu adipeux Métabolisme glucidolipidique

The endocannabinoïd system (ECS)

Abstract

The endocannabinoïd system (ECS) is involved in many biological functions such as the regulation of energy metabolism. Recently, several studies have shown an association between obesity and ECS overactivity. In addition, specific CB1R antagonists such as rimonabant (SR141716) improved metabolic parameters in obese patients essentially through the inactivation of central CB1R. However, peripheral CB1R inactivation could also contribute to the improvement of these parameters. To further investigate this notion, we tested the effects of SR141716 on obese mice in order to establish relationships between the ECS activity and lipid metabolism by looking more specifically to its regulation in two key tissues, the liver and the adipose tissue (AT). Obese mice previously fed with a high-sucrose, high-fat diet were treated six weeks with SR141716, and this treatment induced weight loss associated with a normalization of plasma parameters and a reduction of hepatic steatosis. The major hypothesis of this study is that steatosis reversion was associated with a beneficial effect of treatment on visceral AT metabolism and that SR141716 would have direct effects on peripheral tissues. Therefore, these effects of CB1R antagonist on peripheral lipid metabolism have been studied in vitro. In this way, we first developed a model of liver explants in culture treated with SR141716. In this model, CB1R antagonism in the liver was associated with a decrease in CB1 gene expression and in certain conditions with an increase in β-oxidative capacity. In conclusion, this work showed that peripheral CB1R is a very promising therapeutic target for treating obesity and related disorders.

Keywords

Endocannabinoïd system Endocannabinoïd SR141716 Anandamide Steatosis Adiponectin CB1R CB2R Liver Adipose tissue Carbohydrate and lipid metabolism

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