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Short communication

Role of cannabinoid CB_2 receptors in glucose homeostasis in rats

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Abstract

Here we show that the activation of cannabinoid CB_2 receptors improved glucose tolerance after a glucose load. Blockade of cannabinoid CB_2 receptors counteracted this effect, leading to glucose intolerance. Since blockade of cannabinoid CB_1 receptors mimics the actions of cannabinoid CB_2 receptor agonists, we propose that the endocannabinoid system modulates glucose homeostasis through the coordinated actions of cannabinoid CB_1 and CB_2 receptors. We also describe the presence of both cannabinoid CB_1 and CB_2 receptor immunoreactivity in rat pancreatic β- and non-β-cells, adding the endocrine pancreas to adipose tissue and the liver as potential sites for endocannabinoid regulation of glucose homeostasis.

Keywords: Endocannabinoid; Cannabinoid receptor; Glucose intolerance; Diabetes; Pancreatic islet

1. Introduction

Endocannabinoids are lipid mediators that counteract satiety signals at the gastrointestinal and hypothalamic levels, promoting overfeeding and lipid biosynthesis and storage (Cota et al., 2003; Gomez et al., 2002). A role for cannabinoid CB_1 receptors has been established for these actions (Di Marzo and Matias, 2005). As confirmation, a clinical trial involving obese patients treated with Rimonabant, a cannabinoid CB_1 receptor antagonist, resulted in a relevant reduction in body weight, waist circumference and insulin resistance (Van Gaal et al., 2005). Recent reports have established that in rats cannabinoid CB_1 receptors modulate glucose homeostasis after a glucose load (Bermudez-Silva et al., 2006), and that glucose levels modulate anandamide and 2-arachidonoyl glycerol production by the pancreatic beta-cell line RIN-m5F (Matias et al., 2006). Additionally, a recent report suggest that there is overactivation of the endocannabinoid system in obese humans and in humans with eating disorders (Engeli et al., 2005; Monteleone et al., 2005). The effects of natural and endogenous cannabinoids on lipid and glucose metabolism might be mediated by cannabinoid CB_1 receptors located in insulin-sensitive tissues such as adipose tissue (Cota et al., 2003) and the liver (Osei-Hyiaman et al., 2005). The endocrine pancreas is an additional potential target for exogenously administered cannabinoids since there are cannabinoid CB_1 receptors in pancreatic islets (Juan-Pico et al., 2006) and in rat insulinoma β-cell line RIN-m5F (Matias et al., 2006). Besides cannabinoid CB_1 receptors, we have described that cannabinoid CB_2 receptors modulate calcium oscillations and insulin secretion in mouse pancreatic islets *in vitro* (Juan-Pico et al., 2006). However, we do not know whether cannabinoid CB_2 receptors modulate glucose homeostasis *in vivo*, a question addressed in this study. To this end we analyzed whether cannabinoid CB_2 receptor-acting drugs modulate glucose homeostasis in rats receiving an i.p. glucose load. We compared these actions with those described for cannabinoid CB_1 receptor antagonists and analyzed the presence of cannabinoid CB_1 and CB_2 receptors in rat pancreatic islets.

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2. Materials and methods

2.1. Animals

We carried out the experiments with male Wistar rats (250 g), in strict compliance with the European Communities directive 86/609/EEC regulating animal research. Animals were housed in groups of four in a room with controlled temperature (20±2 °C) and humidity (55±5%) with free access to water and standard food pellets. Food was withdrawn in the early morning (4 h before the procedure of glucose tolerance test).

2.2. Glucose tolerance test

This was carried out by injecting an intraperitoneal glucose load of 2 g/kg body wt. Tail blood samples were collected before (0 min) and 5, 10, 15, 30, 60 and 120 min after glucose administration. Glucose was determined using a standard glucose oxidase method as described previously (Bermudez-Silva et al., 2006).

2.3. Drugs and treatments

Awake rats ($n=8$ per group) were injected i.p. with either vehicle (5% Tween 80 in saline), the mixed cannabinoid CB_1/CB_2 receptor agonists 2-arachidonoylglycerol (2-AG, 4 mg/kg) and (*R*)-(+)-(2,3-dihydro-5-methyl-3-[(morphoninyl)-methyl]-pyrrolo-[1,2,3-de]-1,4-benzoxazinyl)-(1-napthalenyl) methanone mesylate (WIN 33,212-2, 5 mg/kg), the cannabinoid CB_2 receptor agonist 3-(1′,1′-dimethylbutyl)-1-deoxy-delta8-THC, JWH 133 (0.1; 1 and 2 μg/kg, Huffman et al., 1999), the selective cannabinoid CB_2 receptor antagonist 6-iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-yl](4-methoxyphemyl) methanone (AM630, 0.001, 0.01 and 0.05 mg/kg, Ross et al.,

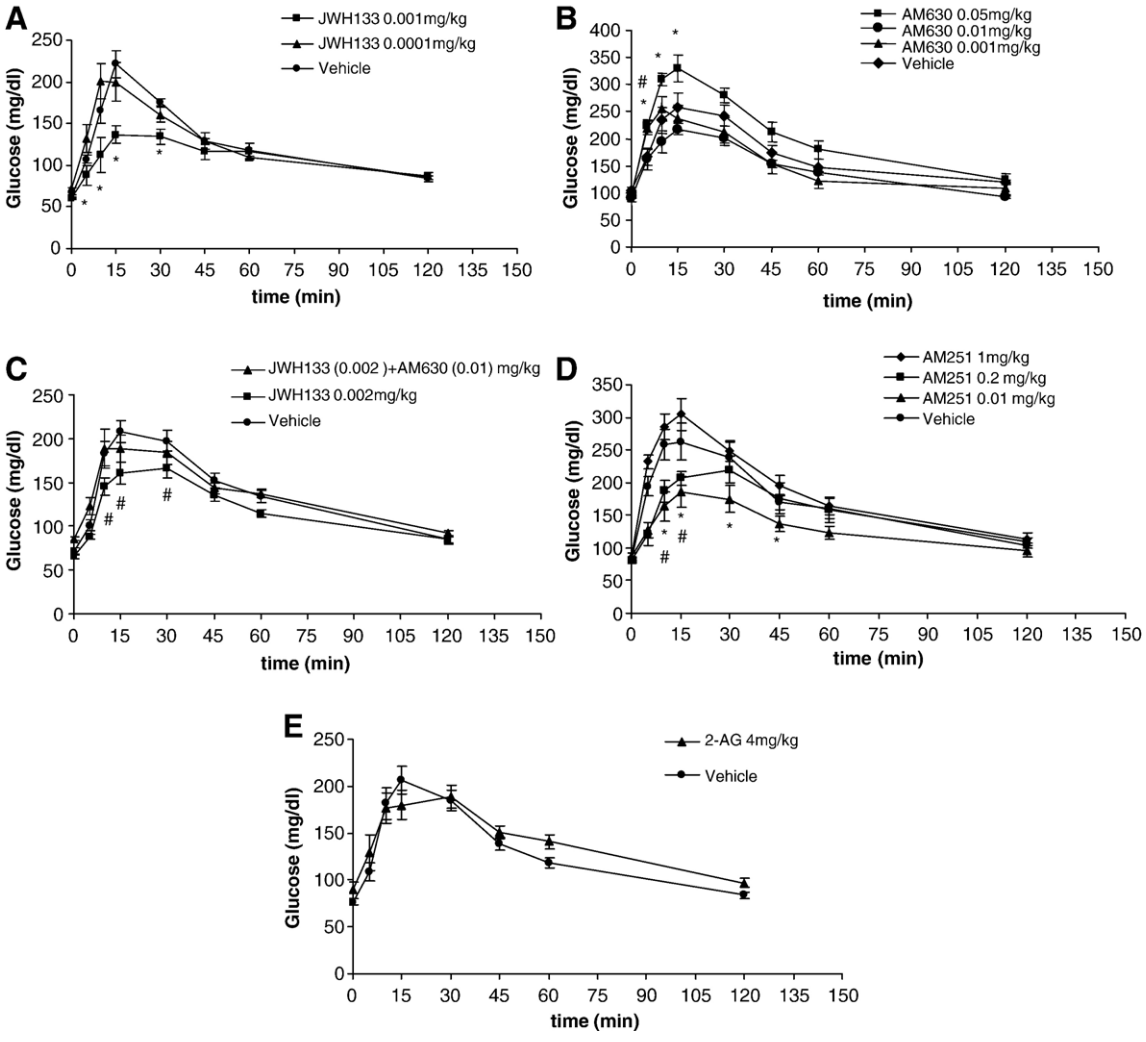

Fig. 1. Administration of the cannabinoid CB_2 receptor agonist JWH 133 improved glucose homeostasis after a glucose load (A). The opposite effect was observed when a cannabinoid CB_2 receptor antagonist, AM630, was administered before glucose (B). Pretreatment with AM630 antagonized the effects of JWH 133, confirming the role of cannabinoid CB_2 receptors on the effects of JWH 133 (C). The effects of administration of a cannabinoid CB_1 receptor antagonist, AM251, resembled the effects of JWH 133, at doses selective for CB_1 receptors, but not at the highest dose tested (1 mg/kg) that targets both cannabinoid CB_1 and CB_2 receptors (D). Administration of 2-arachidonoylglycerol, a full agonist at both cannabinoid CB_1 and CB_2 receptors, did not modify glucose homeostasis (E). Data are means±S.E.M. of 8–10 determinations per group. (*, # and &) $P<0.01$ different doses *versus* vehicle-treated animals, Newman–Keul's.