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(54) **COMBINATION THERAPY FOR TREATING OBESITY OR MAINTAINING WEIGHT LOSS**

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(57) **ABSTRACT**

Combination therapies for treating obesity or related eating disorders and/or reducing food consumption are described herein which comprises administering a therapeutically effective amount of a cannabinoid-1 (CB-1) receptor antagonist and an intestinal-acting microsomal triglyceride transfer protein inhibitor (MTPi) to an animal in need of such treatment. The CB-1 receptor antagonist and intestinal-acting MTPi may be administered separately or together.

FIG. 1

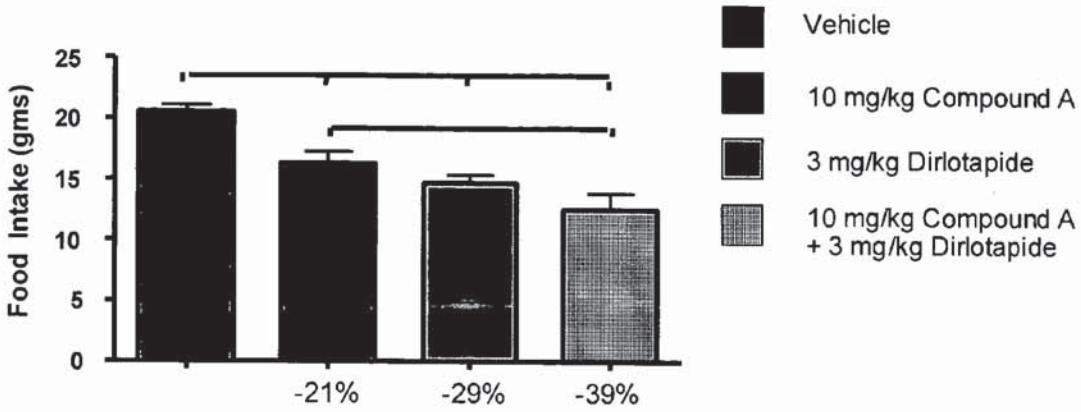


FIG. 2

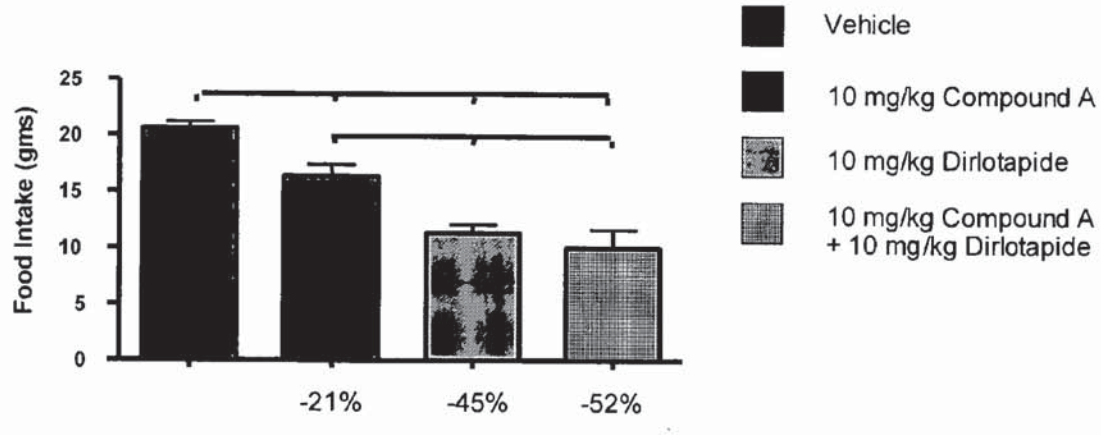


FIG. 3

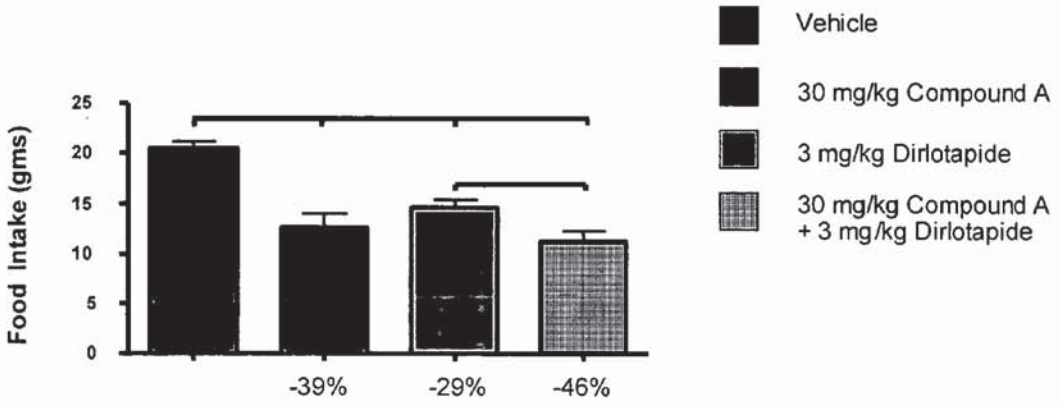
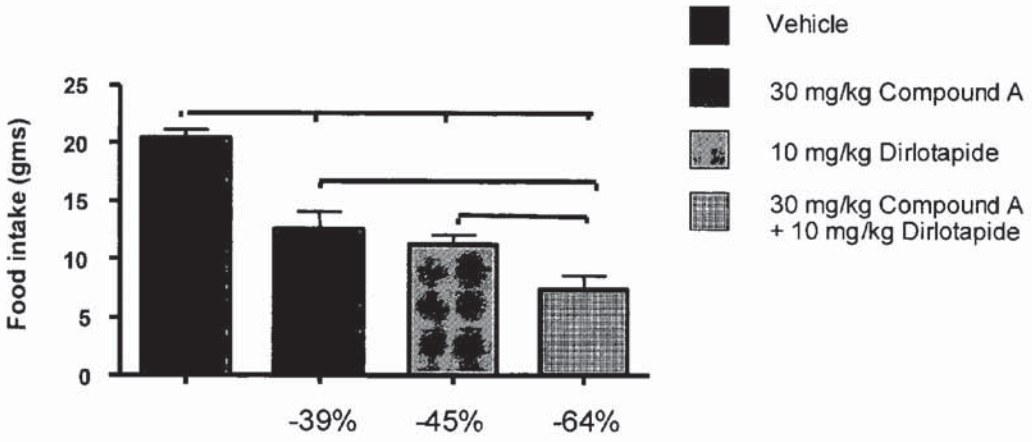


FIG. 4



COMBINATION THERAPY FOR TREATING OBESITY OR MAINTAINING WEIGHT LOSS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/685,752, filed on May 27, 2005, and 60/697,516, filed on Jul. 7, 2005, incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to combination therapies for treating obesity or related eating disorders and/or reducing food consumption by administering a cannabinoid receptor-1 (CB-1) antagonist in combination with an intestinal-acting microsomal triglyceride transfer protein inhibitor (MTPi).

BACKGROUND

[0003] Obesity is a major public health concern and is now recognized as a chronic disease that requires treatment to reduce its associated health risks. Although weight loss is an important treatment outcome, one of the main goals of obesity management is to improve cardiovascular and metabolic values to reduce obesity-related morbidity and mortality. It has been shown that 5-10% loss of body weight can substantially improve metabolic values, such as blood glucose, blood pressure, and lipid concentrations. Hence, it is believed that a 5-10% intentional reduction in body weight may reduce morbidity and mortality.

[0004] Currently available prescription drugs for managing obesity generally reduce weight by inducing satiety or decreasing dietary fat absorption. However, to date, the anti-obesity drugs available commercially provide only modest weight loss. The most successful drug regimens in humans have been combinations of phentermine and fenfluramine or of ephedrine, caffeine and/or aspirin. Each of these combinations have been discontinued due to safety concerns. Although investigations are on-going, there still exists a need for a more effective and safe therapeutic treatment for reducing or preventing weight-gain.

SUMMARY OF THE INVENTION

[0005] The present invention provides a method for treating obesity or related eating disorders (preferably, reducing weight and/or maintaining weight loss (or preventing weight gain)) comprising the step of administering a therapeutically effective amount of a combination of a cannabinoid-1 (CB-1) receptor antagonist and an intestinal-acting microsomal triglyceride transfer protein inhibitor (MTPi) to an animal in need of such treatment. The CB-1 receptor antagonist and intestinal-acting MTPi may be administered separately or together. Preferably, the combination therapy is administered in conjunction with exercise and a sensible diet.

[0006] In another embodiment of the present invention, a method for reducing food consumption (including the desire to consume food) is provided comprising the step of administering a therapeutically effective amount of a combination of a cannabinoid-1 (CB-1) receptor antagonist and an intestinal-acting microsomal triglyceride transfer protein inhibitor (MTPi) to an animal in need of such treatment. The CB-1 receptor antagonist and intestinal-acting MTPi may be administered separately or together. Preferably, the combination therapy is administered in conjunction with exercise

[0007] The combination therapies described above may be administered as (a) a single pharmaceutical composition which comprises the CB-1 antagonist, the intestinal-acting MTPi and a pharmaceutically acceptable excipient, diluent, or carrier; or (b) two separate pharmaceutical compositions comprising (i) a first composition comprising the CB-1 antagonist and a pharmaceutically acceptable excipient, diluent, or carrier, and (ii) a second composition comprising the intestinal-acting MTPi and a pharmaceutically acceptable excipient, diluent, or carrier. The pharmaceutical compositions may be administered simultaneously or sequentially and in any order.

[0008] In another embodiment of the present invention, a pharmaceutical composition is provided comprising (i) a CB-1 receptor antagonist; (ii) a intestinal-acting MTPi; and (iii) a pharmaceutically acceptable excipient, diluent, or carrier, wherein the amount of CB-1 receptor antagonist is from about 1.0 mg to about 100 mg (preferably from about 1.0 mg to about 50 mg, more preferably from about 2.0 mg to about 40 mg, most preferably from about 5.0 mg to about 25 mg) and the amount of intestinal-acting MTPi is typically from about 0.05 mg to about 50 mg (preferably from about 0.5 mg to about 30 mg, more preferably from about 0.5 mg to about 20 mg, most preferably from about 1.0 mg to about 15 mg.

[0009] In yet another aspect of the present invention, a pharmaceutical kit is provided for use by a consumer to treat obesity and related eating disorders. The kit comprises a) a suitable dosage form comprising a CB-1 antagonist and an intestinal-acting MTPi; and b) instructions describing a method of using the dosage form to treat obesity and/or related eating disorders and/or reducing food consumption.

[0010] In yet another embodiment of the present invention is a pharmaceutical kit comprising: a) a first dosage form comprising (i) a CB-1 antagonist and (ii) a pharmaceutically acceptable carrier, excipient or diluent; b) a second dosage form comprising (i) an intestinal-acting MTPi and (ii) a pharmaceutically acceptable carrier, excipient or diluent; and c) a container.

DEFINITIONS

[0011] As used herein, the phrase "therapeutically effective amount" means an amount of the combination of compounds of the present invention that (i) treats the particular disease (including conditions or disorders thereof), (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, or (iii) prevents or delays the onset of one or more symptoms of the particular disease described herein (e.g., reduces food intake or the desire to consume food). The terms "treating", "treat", or "treatment" also embraces preventative (i.e., weight maintenance) treatment.

[0012] The term "animal" refers to humans (male or female), companion animals (e.g., dogs, cats and horses), food-source animals, zoo animals, marine animals, birds and other similar animal species. "Edible animals" refers to food-source animals such as cows, pigs, sheep and poultry. Preferably, the animal is human or a companion animal (preferably, the companion animal is a dog), more preferably, the animal is human (man and/or woman).

[0013] The phrase "pharmaceutically acceptable" indi

chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0014] The term "antagonist" includes both full antagonists and partial antagonists, as well as inverse agonists.

[0015] The term "food" refers to food or drink for human or other animals' consumption.

BRIEF DESCRIPTION OF THE FIGURES

[0016] **FIG. 1** illustrates the decreased food intake observed for the combination of 10 mg/kg of Compound A and 3 mg/kg of Dirlotapide as compared to vehicle (no drug), 10 mg/kg of Compound A alone and 3 mg/kg of Dirlotapide alone.

[0017] **FIG. 2** illustrates the decreased food intake observed for the combination of 10 mg/kg of Compound A and 10 mg/kg of Dirlotapide as compared to vehicle (no drug), 10 mg/kg of Compound A alone and 10 mg/kg of Dirlotapide alone.

[0018] **FIG. 3** illustrates the decreased food intake observed for the combination of 30 mg/kg of Compound A and 3 mg/kg of Dirlotapide as compared to vehicle (no drug), 30 mg/kg of Compound A alone and 3 mg/kg of Dirlotapide alone.

[0019] **FIG. 4** illustrates the decreased food intake observed for the combination of 30 mg/kg of Compound A and 10 mg/kg of Dirlotapide as compared to vehicle (no drug), 30 mg/kg of Compound A alone and 10 mg/kg of Dirlotapide alone.

DETAILED DESCRIPTION

[0020] Applicants have discovered that significant reductions in food intake can be achieved by administering a CB-1 receptor antagonist in combination with an intestinal-acting MTP inhibitor. Preferably, the combination therapy is administered in conjunction with exercise and a sensible diet.

Cannabinoid-1 (CB-1) Receptor Antagonists:

[0021] As used herein, the term "CB-1 receptor" refers to a G-protein coupled type 1 cannabinoid receptor. Preferably, the CB-1 receptor antagonist is selective to the CB-1 receptor. "CB-1 receptor selective" means that the compound has little or no activity to antagonize the cannabinoid-2 receptor (CB-2). More preferably, the CB-1 antagonist is at least about 10 fold more selective for the CB-1 receptor in comparison to the CB-2 receptor. For example, the inhibitory concentration ($1C_{50}$) for antagonizing the CB-1 receptor is about 10 or more times lower than the $1C_{50}$ for antagonizing the CB-2 receptor. Bioassay systems for determining the CB-1 and CB-2 binding properties and pharmacological activity of cannabinoid receptor ligands are described by Roger G. Pertwee in "Pharmacology of Cannabinoid Receptor Ligands"*Current Medicinal Chemistry,* 6, 635-664 (1999) and in WO 92/02640 (U.S. application Ser. No. 07/564,075 filed Aug. 8, 1990, incorporated herein by reference).

[0022] Suitable CB-1 receptor antagonists include, com-

5,624,941; 5,747,524; 6,017,919; 6,028,084; 6,432,984; 6,476,060; 6,479,479; 6,518,264; and 6,566,356;

[0023] U.S. Patent Publication Nos. 2003/0114495; 2004/0077650; 2004/0092520; 2004/0122074; 2004/0157838; 2004/0157839; 2004/0214837; 2004/0214838; 2004/0214855; 2004/0214856; 2004/0058820: 2004/0235926; 2004/0248881; 2004/0259887; 2005/0080087; 2005/0026983 and 2005/0101592;

[0024] PCT Patent Publication Nos. WO 03/075660; WO 02/076949; WO 01/029007; WO 04/048317; WO 04/058145; WO 04/029204; WO 04/012671; WO 03/087037; WO 03/086288; WO 03/082191; WO 03/082190; WO 03/063781; WO 04/012671; WO 04/013120; WO 05/020988; WO 05/039550; WO 05/044785; WO 05/044822; WO 05/049615; WO 05/061504; WO 05/061505; WO 05/061506; WO 05/061507; and WO 05/103052: and

[0025] U.S. Provisional Application Ser. Nos. 60/673,535 filed on Apr. 20, 2005; and 60/673,546 filed on Apr. 20, 2005.

[0026] All of the above patents and patent applications are incorporated herein by reference.

[0027] Preferred CB-1 receptor antagonists for use in the methods of the present invention include: rimonabant (SR141716A also known under the tradename Acomplia™) is available from Sanofi-Synthelabo or can be prepared as described in U.S. Pat. No. 5,624,941; N-(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxamide (AM251) is available from Tocris™, Ellisville, Mo.; [5-(4-bromophenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-N-(1-piperidinyl)-**1**H-pyrazole-3-carboxamide] (SR147778) which can be prepared as described in U.S. Pat. No. 6,645,985; N-(piperidin-1-yl)-4,5-diphenyl-1-methylimidazole-2-carboxamide, N-(piperidin-1-yl)-4-(2,4-dichlorophenyl)-5-(4-chlorophenyl)-1-methylimidazole-2-carboxamide, N-(piperidin-1-yl)-4,5-di-(4-methylphenyl)-1-methylimidazole-2-carboxamide, N-cyclohexyl-4,5-di-(4-methylphenyl)-1-methylimidazole-2-carboxamide, N-(cyclohexyl)-4-(2,4-dichlorophenyl)-5-(4-chlorophenyl)-1-methylimidazole-2-carboxamide, and N-(phenyl)-4-(2,4-dichlorophenyl)-5-(4-chlorophenyl)-1-methylimidazole-2-carboxamide which can be prepared as described in PCT Patent Publication No. WO 03/075660; the hydrochloride, mesylate and besylate salt of 1-[9-(4-chloro-phenyl)-8-(2-chloro-phenyl)-9H-purin-6-yl]-4-ethylamino-piperidine-4-carboxylic acid amide which can be prepared as described in U.S. Patent Publication No. 2004/0092520; 1-[7-(2-chloro-phenyl)-8-(4-chloro-phenyl)-2-methyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylamino-azetidine-3-carboxylic acid amide and 1-[7-(2-chloro-phenyl)-8-(4-chloro-phenyl)-2-methyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-methylamino-azetidine-3-carboxylic acid amide which can be prepared as described in U.S. Patent Publication No. 2004/0157839; 3-(4-chloro-phenyl)-2-(2-chloro-phenyl)-6-(2,2-difluoro-propyl)-2,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one which can be prepared as described in U.S. Patent Publication No. 2004/0214855; 3-(4-chloro-phenyl)-2-(2-chloro-phenyl)-7-(2,2-difluoro-propyl)-6,7-dihydro-2H,5H-4-oxa-1,2,7-triaza-azulen-8-one which can be prepared as described in U.S. Patent Publication No. 2005/0101592;

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