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(57) Abstract: The present invention relates to the use of inhibitors of microsomal triglyceride transfer protein (MTP) for increasing plasma levels of the satiety hormones such as GLP-1, PYY and CCK

WO 2008/090198 A1

USE OF MTP INHIBITORS FOR INCREASING LEVELS OF SATIETY HORMONES

[0001] The present invention relates to the use of inhibitors of microsomal triglyceride transfer protein (MTP) for increasing plasma levels of the satiety hormones such as GLP-1, PYY and CCK.

[0002] Microsomal triglyceride transfer protein (hereinafter referred to as MTP) is known to catalyze the transport of triglyceride, cholesteryl ester and phospholipids such as phosphatidylcholine. This indicates that MTP is required for the synthesis of Apo B-containing lipoproteins such as chylomicrons and VLDL, the precursor to LDL. It therefore follows that an MTP inhibitor would inhibit the synthesis of VLDL and chylomicrons, thereby lowering levels of VLDL, LDL, cholesterol and triglyceride in humans. Compounds capable of inhibiting MTP are believed to be useful in the treatment of disorders such as obesity, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, class II diabetes, atherosclerosis and for the reduction of postprandial serum triglyceride plasma levels.

[0003] Satiety hormones are hormones released from the gastrointestinal tract in response to changes in the nutritional state. These hormones influence central mechanisms involved in the regulation of energy balance, through a range of bloodborne and neural pathways.

[0004] Glucagon-like peptide 1 (GLP-1) is an intestinal hormone which generally stimulates insulin secretion during hyperglycemia, suppresses glucagon secretion, stimulates (pro) insulin biosynthesis and decelerates gastric emptying and acid secretion. GLP-1 is secreted from L cells in the small and large bowel following the ingestion of fat and proteins. GLP-1 has been implicated as a possible therapeutic agent for the management of type 2 non-insulin-dependent diabetes mellitus as well as related metabolic disorders, such as obesity.

[0005] Pancreatic polypeptide ("PP") was discovered as a contaminant of insulin extracts and was named by its organ of origin rather than functional importance. A related peptide was subsequently discovered in extracts of intestine and named Peptide YY ("PYY") because of the N- and C-terminated tyrosines (Tatemoto, Proc. Natl. Acad. Sci. USA, 79 : 2514 –2518 (1982)). PYY is secreted from the endocrine L cells of the small and large bowel, with high concentration at the terminal ileum, colon and maximum concentration in the rectum. Plasma PYY levels are suppressed in the

fasted state and increase within 30 minutes of nutrients reaching the gut. PYY release is stimulated by nutrient intake in proportion to energy content. It is particularly stimulated by fat intake, compared to carbohydrate and protein meals with a similar calorie content. Recent studies suggest that PYY can induce appetite reduction.

[0006] Cholecystokinin is structurally related to gastrin and exists in several molecular forms with differing numbers of amino acids – examples include CCK-8, CCK-33, CCk-39 and CCK-54. CCK is an endogenous gut hormone found mainly within the duodenum and jejunum and is released following the consumption of food. Release of CCK has been shown to be a satiety signal in humans. When food is consumed, CCK releasing protein (CCKRP) is released in the small intestine. CCKRP stimulates CCK release from the intestinal cells. It has been shown that CCK release results in appetite reduction so that the person will stop eating.

[0007] The ability of CCK to reduce appetite appears to make it a useful agent in the treatment of obesity. An increase in the level of the satiety hormone CCK would result in less food consumed and reduction of hunger cravings between meals. These effects would enable an overweight individual to better comply with a diet that has a reduced caloric intake.

[0008] An increase in the level of the satiety hormone CCK extends the feeling of satiety, resulting in a decrease of food intake which over time results in a decrease in body weight while providing better regulation of glucose and insulin levels following consumption of a meal. The release of CCK also causes a delay in stomach emptying which blunts the post-prandial rise in glucose and insulin. Most persons with Type II diabetes are obese and have an inability to respond normally to insulin. An increase in CCK levels may permit Type II diabetics to be satiated with a lower caloric intake and may offer a better degree of glycemic control.

[0009] Bulimia is an eating disorder characterised by an inability to become satiated by food. As a result bulimics tend to binge on food and regurgitate it to prevent weight gain. Studies have shown that bulimics have a defect in their normal satiety mechanism. Hence an increase of the satiety hormones would permit bulimics to feel satiated.

[0010] Unexpectedly it has now been observed that when inhibitors of microsomal triglyceride transfer protein (MTP) are administered to a mammalian subject, the plasma levels of the satiety hormones such as GLP-1, PYY and CCK are increased.

[0011] The present invention provides the use of a MTP inhibiting compound for the manufacture of a medicament for increasing the levels of satiety hormones, such as the GLP-1, PYY and CCK hormones. Also provided is the use of a pharmaceutical composition comprising a MTP inhibiting compound for the manufacture of a medicament for increasing the levels of satiety hormones, such as the GLP-1, PYY and CCK hormones.

[0012] Further, the present invention provides a method for increasing the levels of satiety hormones, in particular GLP-1, PYY and CCK, in a mammalian subject, which method comprises administering to a mammal a therapeutically effective amount of an MTP inhibiting compound or a pharmaceutical composition comprising a MTP inhibiting compound.

[0013] The use of MTP inhibiting compound for increasing the levels of satiety hormones, in particular the GLP-1, PYY and CCK hormones, also has a lowering effect on the level of glucose in blood plasma and increases insulin sensitivity. Insulin resistance is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevates free fatty acids in the blood plasma. Insulin resistance in muscle reduces glucose uptake whereas insulin resistance in liver reduces glucose storage, with both effects serving to elevate blood glucose. High plasma levels of insulin and glucose due to insulin resistance often leads to the metabolic syndrome and type 2 diabetes.

[0014] Studies in dogs with an induced dilated cardiomyopathy have shown that a 48 hour of GLP-1 infusion improved the left ventricular function, and reduced systemic vascular resistance compared with saline-treated control animals (Nikolaidis LA et al., Circulation 2004;110:955-961). Accordingly the present invention also relates to the use of MTP inhibiting compounds for increasing the levels of the satiety hormone GLP-1 for the treatment of cardiomyopathy.

[0015] Studies in rats with pyridoxine induced peripheral sensory neuropathy suggest neuroprotection mediated by agonism at the GLP-1 receptor (Perry T. et al, Experimental Neurology 2007:203, 293 – 301). Accordingly the present invention also relates to the use of MTP inhibiting compounds for increasing the levels of the satiety hormone GLP-1 for the treatment of peripheral neuropathies.

[0016] MTP inhibiting compounds have been disclosed in, e.g., Janssen Pharmaceutica : WO-96/13499, WO-02/20501, WO-02/42271, WO-02/081460, WO-2005/058824, and WO-2005/085226; Bristol-Myers-Squibb : EP-0,584,446, EP-0,643,057, WO-96/26205, WO-97/26240, WO-91/43255, WO-97/43257, WO-98/27979, and WO-99/21564; GSK : WO-98/16526, WO-98/47877, WO-98/56790, WO-00/32582, WO-01/92241, WO-01/96327, and WO-03/048121; Japan Tobacco : WO-99/31085, WO-03/072532, and WO-2006/008962; Meji Seika Kaisho : WO-98/54135; Novartis : WO-01/77077 and WO-2000/005201; Pfizer : WO-96/40640, and WO-98/23593.

[0017] Particular MTP inhibiting compounds are, e.g., dirlotapide or (S)-N-{2-[benzyl(methyl)amino]-2-oxo-1-phenylethyl}-1-methyl-5-[4'-(trifluoromethyl)[1,1'-biphenyl]-2-carboxamido]-1H-indole-2-carboxamide; BMS201038 or N-(2,2,2-trifluoroethyl)-9-[4-[4-[[(4'-trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl]amino)-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide (EP-0,643,057); mitratapide or (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (WO-96/13499); (+)-phenyl-(4-{4-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-phenyl}-piperidin-1-yl)-acetic acid methyl ester (WO-02/20501); JTT-130 or diethyl ester[[[[3-[(dimethylamino)carbonyl]-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]phenyl]acetyl]oxy]methyl]phenyl propanedioic acid (WO-2006/008962); SLx 4090 from Surface Logix; NA-2003 from Meiji Seika Kaisha; [(2R)-2,3-dihydro-5-[[[6-methyl-4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-inden-2-yl]-carbamic acid methyl ester (WO-2000/005201); T-0126 or N-[2-[2-(1H-Pyrazol-1-yl)acetyl]-2,3-dihydro-1H-isoindol-5-yl]-2-[5-(trifluoromethyl)pyridin-2-yl]benzamide from Tanabe Seiyaku (WO-2002/014276).

[0018] As used herein, "mammal" or “mammalian subject” refers to human and non-human patients.

[0019] As used herein, a "therapeutically effective amount" of a MTP inhibiting compound, is the quantity of a compound which, when administered to a mammalian subject, results in a sufficiently high level of that MTP inhibiting compound in the mammalian to cause a discernible increase of the blood plasma levels of the satiety

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