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(54) METHODS FOR TREATING DIABETES AND RELATED DISORDERS USING PDE10A INHIBITORS

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(57) **ABSTRACT**

The methods of the invention relate to the treatment of diabetes, including type 2 diabetes, and related disorders by administration of a PDE10A inhibitor. Such PDE10A inhibitors may be administered in conjunction with alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, hepatic glucose output lowering compounds, B-3 agonist, or insulin. Such PDE10A inhibitors may also be administered in conjunction with body weight reducing agents. Further methods of the invention relate to stimulating insulin release from pancreatic cells, for example, in response to an elevation in blood glucose concentration, by administration of a PDE10A inhibitor.

METHODS FOR TREATING DIABETES AND RELATED DISORDERS USING PDE10A INHIBITORS

[0001] This application claims benefit of U.S. Provisional Application Ser. No. 60/491,730, filed on Jul. 31, 2003, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The invention relates to methods of treating diabetes and related disorders by administering a compound that inhibits PDE10A. Such PDE10A inhibitors may be administered in combination with other pharmaceutical agents, for example, anti-diabetic agents or body weight reducing agents. Further methods of the invention relate to stimulating insulin release from pancreatic cells, for example, in response to an elevation in blood glucose concentration, by administration of a PDE10A inhibitor.

BACKGROUND

[0003] Diabetes is characterized by impaired glucose metabolism manifesting itself among other things by an elevated blood glucose level in the diabetic patient. Underlying defects lead to a classification of diabetes into two major groups: type 1 and type 2. Type 1 diabetes, or insulin dependent diabetes mellitus (IDDM), arises when patients lack insulin-producing β-cells in their pancreatic glands. Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), occurs in patients with impaired β-cell function and alterations in insulin action.

[0004] The current treatment for type 1 diabetic patients is the injection of insulin, while the majority of type 2 diabetic patients are treated with agents that stimulate β-cell function or with agents that enhance the tissue sensitivity of the patients towards insulin. The drugs presently used to treat type 2 diabetes include alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, metformin, and insulin.

[0005] Over time, more than one-third of all type 2 diabetic subjects lose their response to oral agents. Insulin treatment is instituted after diet, exercise, and oral medications have failed to adequately control blood glucose. The drawbacks of insulin treatment include, for example, the need for drug injection, the potential for hypoglycemia, and weight gain.

[0006] Another strategy for diabetes therapy is based on the cyclic adenosine monophosphate (cAMP) signaling mechanism and its effects on insulin secretion. Metabolism of glucose promotes the closure of ATP-dependent K^+ channels, which leads to cell depolarization and subsequent opening of Ca^{++} channels. This in turn results in the exocytosis of insulin granules. cAMP is a major regulator of glucose-stimulated insulin secretion. The effect of cAMP is, however, glucose-dependent, that is, cAMP has little if any effects on insulin secretion at low glucose concentrations (Weinhaus, et al., Diabetes 47:1426-1435, 1998). The effects of cAMP on insulin secretion are thought to be mediated by a protein kinase A pathway.

[0007] Endogenous secretagogues utilize the cAMP system to regulate insulin secretion in a glucose-dependent fashion (Kanatsu, et al., Diabetes 46:1028-1038, 1997). Pituitary adenylate cyclase activating peptide (PACAP), vasoactive intestinal polypeptide (VIP), and glucagon-like peptide-1 (GLP-1).

[0008] PACAP is a potent stimulator of glucose-dependent insulin secretion from pancreatic β-cells. Three different PACAP receptor types (R1, R2, and R3) have been described (Harmar, et al., Pharmacol. Rev. 50:265-270, 1998). The insulinotropic action of PACAP is mediated by the GTP binding protein Gs. Accumulation of intracellular cAMP in turn activates nonselective cation channels in β-cells increasing $[Ca^+]$, and promoting the exocytosis of insulin-containing secretory granules.

[0009] Vasoactive intestinal peptide (VIP) is a 28 amino acid peptide that was first isolated from hog upper small intestine (Said and Mutt, Science 169:1217-1218, 1970; U.S. Pat. No. 3,879,371). The biological effects of VIP are mediated by the activation of membrane-bound receptor proteins that are coupled to the intracellular cAMP signaling system.

[0010] GLP-1 is released from the intestinal L-cell after a meal and functions as an incretin hormone (i.e., it potentiates glucose-induced insulin release from the pancreatic β-cell). It is a 37-amino acid peptide that is differentially expressed by the glucagon gene, depending upon tissue type. The clinical data that support the beneficial effect of raising cAMP levels in β-cells have been demonstrated with GLP-1. Infusions of GLP-1 in poorly controlled type 2 diabetics normalized their fasting blood glucose levels (Gutniak, et al., New Eng. J. Med. 326:1316-1322, 1992) and with longer infusions improved the β-cell function as compared to normal subjects (Rachman, et al., Diabetes 45:1524-1530, 1996). A recent report has shown that GLP-1 improves the ability of β-cells to respond to glucose in subjects with impaired glucose tolerance (Byrne, et al., Diabetes 47:1259-1265, 1998).

[0011] The use of such endogenous secretagogues to treat type 2 diabetes also has some drawbacks. For instance, the peptidyl nature of these compounds requires that they be administered by injection. Additionally, the effects of the endogenous secretagogues are short-lived because of the short half-life of the peptides.

[0012] Because of the problems with current treatments, new therapies to treat type 2 diabetes are needed. In particular, new treatments to maintain normal (glucose-dependent) insulin secretion are needed. Such new drugs should have the following characteristics: 1) dependency on glucose for promoting insulin secretion, that is, compounds that stimulate insulin secretion only in the presence of elevated blood glucose and therefore, low probability for hypoglycemia; 2) low primary and secondary failure rates; and 3) preservation of islet cell function.

[0013] The present invention provides a novel treatment for diabetes and related disorders by focusing on regulation of the cAMP signaling system by inhibition of phosphodiesterase 10A PDE10A). Phosphodiesterases (PDEs) are a family of cAMP and/or cGMP-hydrolyzing enzymes that cleave 3',5'-cyclic nucleotide monophosphates to 5'-nucleotide monophosphates. PDEs are known to be involved in the regulation of the cAMP system. Specifically, PDE10A is a phosphodiesterase that hydrolyzes cAMP and cGMP with

Biol. Chem. 274 (26):18438-18445, 1999; Soderling, et al., PNAS 96:7071-7076, 1999; Loughney, et al., Gene 234:109-117, 1999). At least three splice variants of PDE10A have been described that are identical in their C-terminal catalytic domains, but differ in the size of the N-terminal portion of the molecule (Kotera, et al., Biochem. Biophy. Res. Comm. 261:551-557, 1999; Fujishige, et al., Eur. J. Biochem. 267:5943-5951, 2000).

[0014] Thus, by inhibiting PDE10A activity, intracellular levels of cAMP are increased thereby increasing the release of insulin-containing secretory granules and therefore, increasing insulin secretion. The present invention, therefore, provides a novel treatment for diabetes and related disorders, that is, the administration of a PDE10A inhibitor.

SUMMARY OF THE INVENTION

[0015] The present invention relates to methods of treating diabetes, including type 2 diabetes, in a mammal by administering an effective amount of a PDE10A inhibitor. Other methods of the invention relate to treatment of other disorders related to diabetes, such as Syndrome X, impaired glucose tolerance, and impaired fasting glucose, by administering a PDE10A inhibitor. In addition, the present invention relates to methods of treating type 1 diabetes, gestational diabetes, maturity-onset diabetes of the young (MODY), latent autoimmune diabetes adult (LADA), and associated diabetic dyslipidemia and other diabetic complications, as well as hyperglycemia, hyperinsulinemia, dyslipidemia, hypertriglyceridemia, and insulin resistance.

[0016] The invention further relates to methods of stimulating insulin release from pancreatic cells in a mammal by administering an effective amount of a PDE10A inhibitor. This method of insulin release may be in response to an elevation of the concentration of glucose in the blood of a mammal. In methods of the invention, the PDE10A inhibitor may also be administered in conjunction with other diabetes therapies, such as alpha-glucosidase inhibitors (e.g., acarbose), insulin sensitizers (e.g., thiazolidinediones), compounds that reduce hepatic glucose output (e.g., metformin), insulin secretagogues (e.g., sulfonylureas), β-3 agonists, and insulin. Furthermore, the PDE10A inhibitor may be administered in conjunction with one or more weight reduction agents, such as Xenical, Meridia, β-3 agonists, or a CB-1 antagonist. Finally, in another embodiment, methods of the invention provide for the administration of a PDE10A inhibitor in combination with an HMG-CoA reductase inhibitor, nicotinic acid, a bile acid sequestrant, a fibric acid derivative, or an antihypertensive drug.

[0017] In another aspect of the invention, a PDE10A inhibitor may be administered for the treatment of dementia or a urogenital tract disorder. Urogenital tract disorders include, but are not limited to, incontinence, stress incontinence, benign prostatic hyperplasia, erectile dysfunction, female sexual dysfunction, and hypertrophy of prostate. In further aspect of the invention, a PDE10A inhibitor may be administered for the treatment of a cardiovascular disorder, such as hypertension, ischemic heart disease, myocardial infarction, stable and unstable angina, peripheral occlusive disease, and ischemic stroke.

[0018] The present invention, therefore, provides methods for the treatment of diabetes by inhibition of PDE10A other aspects of the invention will be more apparent from the following description and claims.

DETAILED DESCRIPTION OF THE INVENTION

[0019] Methods of the invention provide for the treatment of diabetes and related disorders, particularly type 2 diabetes, and/or stimulation of insulin release from pancreatic cells, by the administration of a PDE10A inhibitor. Such methods provide for treatment of any condition in which glucose is elevated in the fasting or post-prandial state, by administration of a PDE10A inhibitor. PDE10A has been identified in islets of Langerhans. PDE10A hydrolyses cAMP to AMP and thereby decreases intracellular concentrations of cAMP. By inhibiting PDE10A activity, intracellular levels of cAMP are increased, thereby increasing the release of insulin-containing secretory granules and therefore, increasing insulin secretion. Also as described herein, a PDE10A inhibitor may be administered for the treatment of dementia, cardiovascular disease, or urogenital tract disorders.

Methods of Treatment

[0020] As used herein, various terms are defined below.

[0021] When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a,""an,""the," and "said" are intended to mean that there are one or more of the elements. The terms "comprising, ""including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[0022] The term "subject" as used herein includes mammals (e.g., humans and animals).

[0023] The term "treatment" includes any process, action, application, therapy, or the like, wherein a subject, including a human being, is provided medical aid with the object of improving the subject's condition, directly or indirectly, or slowing the progression of a condition or disorder in the subject.

[0024] The term "combination therapy" or "co-therapy" means the administration of two or more therapeutic agents to treat a diabetic condition and/or disorder. Such administration encompasses co-administration of two or more therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each inhibitor agent. In addition, such administration encompasses use of each type of therapeutic agent in a sequential manner.

[0025] The phrase "therapeutically effective" means the amount of each agent administered that will achieve the goal of improvement in a diabetic condition or disorder severity, while avoiding or minimizing adverse side effects associated with the given therapeutic treatment.

[0026] The term "pharmaceutically acceptable" means that the subject item is appropriate for use in a pharmaceutical product.

[0027] Methods of the invention may be used to treat diseases, such as diabetes, including both type 1 and type 2 diabetes. Such methods may also delay the onset of diabetes

that may be treated or prevented using methods of the invention include: Maturity-Onset Diabetes of the Young (MODY) (Herman, et al., Diabetes 43:40, 1994), Latent Autoimmune Diabetes Adult (LADA) (Zimmet, et al., Diabetes Med. 11:299, 1994), impaired glucose tolerance (IGT) (Expert Committee on Classification of Diabetes Mellitus, Diabetes Care 22 (Supp. 1):S5, 1999), impaired fasting glucose (IFG) (Charles, et al., Diabetes 40:796, 1991), gestational diabetes (Metzger, Diabetes, 40:197, 1991), and metabolic Syndrome X.

[0028] Methods of the invention may also be used to treat secondary causes of diabetes (Expert Committee on Classification of Diabetes Mellitus, Diabetes Care 22 (Supp. 1):S5, 1999). Such secondary causes include glucocorticoid excess, growth hormone excess, pheochromocytoma, and drug-induced diabetes. Drugs that may induce diabetes include, but are not limited to, pyriminil, nicotinic acid, glucocorticoids, phenytoin, thyroid hormone, β-adrenergic agents, α-interferon, and drugs used to treat HIV infection.

[0029] cAMP-mediated release of insulin is also dependent on the presence of stimulatory glucose concentrations. A method of the invention further relates to stimulating insulin release from islet cells by the administration of a PDE10A inhibitor. Glucose-dependent stimulation of insulin secretion with non-peptide compounds therefore, lowers blood glucose concentrations without causing hypoglycemia.

[0030] The methods of the present invention may be used alone or in combination with additional therapies and/or compounds known to those skilled in the art in the treatment of diabetes and related disorders. Alternatively, a PDE10A inhibitor may be used partially or completely, in combination therapy.

[0031] For example, a PDE10A inhibitor may be administered in combination with other known therapies for the treatment of diabetes, including PPAR ligands (e.g., agonists, antagonists), insulin secretagogues, for example, sulfonylurea drugs and non-sulfonylurea secretagogues, α-glucosidase inhibitors, insulin sensitizers, hepatic glucose output lowering compounds, insulin and insulin derivatives, and anti-obesity drugs. Such therapies may be administered prior to, concurrently with, or following administration of the compounds of the invention. Insulin and insulin derivatives include both long and short acting forms and formulations of insulin. PPAR ligands may include agonists and/or antagonists of any of the PPAR receptors or combinations thereof. For example, PPAR ligands may include ligands of PPAR-α, PPAR-γ, PPAR-δ or any combination of two or three of the receptors of PPAR. PPAR ligands include, for example, rosiglitazone, troglitazone, and pioglitazone. Sulfonylurea drugs include, for example, glyburide, glimepiride, chlorpropamide, tolbutamide, and glipizide. α-glucosidase inhibitors that may be useful in treating diabetes when administered with a compound of the invention include acarbose, miglitol, and voglibose. Insulin sensitizers that may be useful in treating diabetes include PPAR-γ agonists such as the glitazones (e.g., troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like) and other thiazolidinedione and non-thiazolidinedione compounds; biguanides such as metformin and phenformin; protein tyrosine phosphatase-1B (PTP-1B) inhibitors; dipeptidyl peptidase IV (DPP-IV) inhibitors. Hepatic glucose output lowering compounds that may be useful in treating diabetes when administered with a compound of the invention include, for example, glucagon anatgonists and metformin, such as Glucophage and Glucophage XR. Insulin secretagogues that may be useful in treating diabetes when administered with a compound of the invention include sulfonylurea and non-sulfonylurea drugs: GLP-1, GIP, PACAP, secretin, and derivatives thereof; nateglinide, meglitinide, repaglinide, glibenclamide, glimepiride, chlorpropamide, and glipizide. For example, GLP-1 includes derivatives of GLP-1 with longer half-lives than native GLP-1, such as, for example, fatty-acid derivatized GLP-1 and exendin.

[0032] A PDE10A inhibitor may also be administered in combination with anti-obesity drugs. Anti-obesity drugs include β-3 agonists; CB-1 antagonists; neuropeptide Y5 inhibitors; Ciliary Neurotrophic Factor and derivatives (e.g., Axokine); appetite suppressants, such as, for example, sibutramine (Meridia); and lipase inhibitors, such as, for example, orlistat (Xenical).

[0033] In addition, a PDE10A inhibitor may also be administered in combination with drugs commonly used to treat lipid disorders in diabetic patients. Such drugs include, but are not limited to, HMG-CoA reductase inhibitors, nicotinic acid, fatty acid lowering compounds (e.g., acipimox); lipid lowering drugs (e.g., stanol esters, sterol glycosides such as tiqueside, and azetidinones such as ezetimibe), ACAT inhibitors (such as avasimibe), bile acid sequestrants, bile acid reuptake inhibitors, microsomal triglyceride transport inhibitors, and fibric acid derivatives. HMG-CoA reductase inhibitors include, for example, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, cerivastatin, and ZD-4522. Fibric acid derivatives include, for example, clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate, etofibrate, and gemfibrozil. Sequestrants include, for example, cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran.

[0034] Furthermore, a PDE10A inhibitor may also be administered combination with anti-hypertensive drugs, such as, for example, β-blockers and ACE inhibitors. Examples of additional anti-hypertensive agents for use in combination with the compounds of the present invention include calcium channel blockers (L-type and T-type; e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e. g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan, neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

[0035] Such co-therapies may be administered in any combination of two or more drugs (e.g., a PDE10A inhibitor in combination with an insulin sensitizer and an anti-obesity drug). Such co-therapies may be administered in the form of

[0036] Other methods of the invention relate to administration of a PDE10A inhibitor for the treatment of dementia (Shimamoto, et al., Mech. Aging Dev. 5(4):241-250, 1976; Nicholson, et al., Trend Pharmacol. Sci. 12(1):19-27, 1991).

[0037] Still further methods of the invention relate to treatment of urogenital tract disorders by the administration of a PDE10A inhibitor. Such urogenital tract disorders include, but are not limited to, incontinence, stress incontinence, benign prostatic hyperplasia, erectile dysfunction, female sexual dysfunction (including female sexual arousal disorder), and hypertrophy of prostate (Ballard, et al., J. Urol. 159(6):2164-2171, 1998).

[0038] Other methods of the invention relate to administration of a PDE10A inhibitor to treat cardiovascular disorders, such as hypertension, ischemic heart disease, myocardial infarction, stable and unstable angina, peripheral occlusive disease, and ischemic stroke. Expression of PDE10 can be detected in the heart (Loughney, et al., Gene 234:109-117, 1999; Kotera, et al., Biochem. Biophy. Res. Comm. 261:551-557, 1999), and cGMP and cAMP are important second messengers that are involved in the regulation of vascular smooth muscle tone. The PDE10 family comprises enzymes that are responsible for the degradation of cAMP and cGMP in various tissues (Fujishige, et al., J. Biol. Chem. 274(26):18438-18445, 1999). The activation of soluble and membrane bound guanylate cyclases leads to increased intracellular cGMP levels and induces vasodilation. The stimulation of various G protein-coupled receptors (GPCRs) which are expressed in vascular smooth muscle cells (e.g., adrenomedullin and CGRP receptors) induces the activation of adenylate cyclases, generation of intracellular cAMP, and produces vasodilation. 3',5'-cyclic nucleotide phosphodiesterases (PDEs) catalyze the hydrolysis of 3',5'-cyclic nucleotides to their respective nucleoside 5'-monophosphates. Thus, PDE10A likely plays a role in the cardiovascular system.

Pharmaceutical Compositions

[0039] Based on well known assays used to determine the efficacy for treatment of conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of PDE10 inhibitor(s) can readily be determined for treatment of each desired indication. The amount of the active ingredient (e.g., PDE10 inhibitor) to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

[0040] PDE10A inhibitor(s) for use in methods of the invention may be administered as compound per se. Alternatively, PDE10A inhibitor(s) may be administered with an acceptable carrier in the form of a pharmaceutical composition. The pharmaceutically acceptable carrier must be compatible with the other ingredients of the composition and must not be intolerably deleterious to the recipient. The carrier can be a solid or a liquid, or both, and preferably is formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from about 0.05% to about 95% by weight of the active compound(s) based on active substances can also be present, including other compounds useful in the treatment of a diabetic condition.

[0041] PDE10A inhibitor(s) for use in methods of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a therapeutically effective dose for the treatment intended. The PDE10A inhibitor(s) may, for example, be administered orally, sublingually, nasally, pulmonary, mucosally, parenterally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically. Unit dose formulations, particularly orally administrable unit dose formulations such as tablets or capsules, generally contain, for example, from about 0.001 to about 500 mg, preferably from about 0.005 mg to about 100 mg, and more preferably from about 0.01 to about 50 mg, of the active ingredient. In the case of pharmaceutically acceptable salts, the weights indicated above for the active ingredient refer to the weight of the pharmaceutically active ion derived from the salt.

[0042] Of course, the specific initial and continuing dosage regimen to prevent, treat, give relief from, or ameliorate a diabetic condition or disorder, or to otherwise protect against or treat a diabetic condition for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific PDE10A inhibitor employed, the age of the patient, the diet of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular PDE10A inhibitor employed, whether a drug delivery system is utilized, and whether the PDE10A inhibitor is administered with other active ingredients, and the like. The desired mode of treatment and number of doses of a PDE10A inhibitor may be ascertained by those skilled in the art using conventional treatment tests.

[0043] The PDE10A inhibitor(s) may be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for a particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable carrier and a therapeutically effective amount of the PDE10A inhibitor(s). A pharmaceutically acceptable carrier is any carrier which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. The PDE10A inhibitor(s) may be administered with a pharmaceutically-acceptable carrier using any effective conventional dosage unit forms, including, for example, immediate and timed release preparations, orally, parenterally, topically, or the like.

[0044] For oral administration, the PDE10A inhibitor(s) may be formulated into solid or liquid preparations such as, for example, capsules, pills, tablets, troches, lozenges, melts, powders, solutions, pastes, syrups, suspensions, or emulsions, and may be prepared according to methods known to

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