USE OF A PPAR-DELTA AGONIST IN THE TREATMENT OF FATTY ACID OXIDATION DISORDERS (FAOD)

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/800,995 filed on February 4, 2019, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are methods of using a peroxisome proliferator-activated receptor delta (PPAR-delta) agonist in the treatment or prevention of fatty acid oxidation disorders (FAOD).

BACKGROUND OF THE INVENTION

[0003] Healthy mitochondria are vital to normal cellular activities. Mitochondrial dysfunction drives the pathogenesis of a wide variety of medical disorders, including acute conditions and chronic diseases. Distinct aspects of mitochondrial function, for example, bioenergetics, dynamics, and cellular signaling are well described and impairments in these activities likely contribute to disease pathogenesis. Impairments of mitochondrial function result in a family of disorders termed fatty acid oxidation disorders. PPAR-delta, a member of the nuclear regulatory superfamily of ligand-activating transcriptional regulators, is expressed throughout the body. PPAR-delta agonists induce genes related to fatty acid oxidation and mitochondrial biogenesis. PPAR-delta also has anti-inflammatory properties.

SUMMARY OF THE DISCLOSURE

[0004] In one example, described herein are methods for treating a fatty acid oxidation disorders (FAOD) in a mammal comprising administering to the mammal with a fatty acid oxidation disorder (FAOD) a peroxisome proliferator-activated receptor delta (PPARδ) agonist compound.

[0005] In another example, described herein is a method for improving whole-body fatty acid oxidation in a mammal with a fatty acid oxidation disorder (FAOD) comprising administering to the mammal with a fatty acid oxidation disorder (FAOD) a peroxisome proliferator-activated receptor delta (PPARδ) agonist compound.

[0006] In another example, described herein is a method of modulating peroxisome proliferator-activated receptor delta (PPARδ) activity in a mammal with a fatty acid oxidation disorder (FAOD) comprising administering to the mammal with the fatty acid oxidation disorder (FAOD) a proliferator-activated receptor delta (PPARδ) agonist compound.

[0007] In some examples, modulating peroxisome proliferator-activated receptor delta (PPARδ) activity comprises activating peroxisome proliferator-activated receptor delta (PPARδ).

[0008] In some examples, modulating peroxisome proliferator-activated receptor delta (PPARδ) activity comprises increasing peroxisome proliferator-activated receptor delta (PPARδ) activity.

[0009] In yet another example, described herein is a method for increasing fatty acid oxidation (FAO) in a mammal with a fatty acid oxidation disorder (FAOD) comprising administering to the mammal with the fatty acid oxidation disorder (FAOD) a proliferator-activated receptor delta (PPARδ) agonist compound.

[0010] In some examples, the peroxisome proliferator-activated receptor delta (PPARδ) agonist compound is administered to the mammal in an amount sufficient for normalizing FAO capacities in the mammal, up-regulating gene expression of any one of the enzymes or proteins involved in FAO, or a combination thereof.

[0011] In some examples, normalizing FAO capacities in the mammal comprises increasing FAO capacities to sufficient levels for ameliorating or reducing the severity of any one of symptoms of any one of the fatty acid oxidation disorders described herein.

[0012] In one example, described herein is a method for treating a fatty acid oxidation disorder (FAOD) in a mammal comprising administering to the mammal with a FAOD a peroxisome proliferator-activated receptor delta (PPARδ) agonist compound.

[0013] In some examples, treating FAOD comprises improving whole-body fatty acid oxidation (FAO) in the mammal, improving the mammal's exercise tolerance, decreasing pain, decreasing fatigue, or a combination thereof.

[0014] In some examples, improving the mammal's exercise tolerance comprises increasing the distance walked in about a 12-minute walk test. In some examples, the distance walked in such a 12 minute walk test increases by at least about 1 meter, at least about 5 meters, at least about 10 meters, at least about 20 meters, at least about 30 meters, at least about 40 meters, at least about 50 meter, at least about 60 meters, at least about 70 meters, at least about 80 meters, at least about 90 meters, at least about 100 meters, or more than about 100 meters.

[0015] As used herein the term "about" means within ± 10% of the value.

[0016] In some examples, improving the mammal's exercise tolerance comprises decreases in heart rate during the about 12-minute walk test. In some examples, heart rate decreases by 1 heart beat per minute, by 2 heart beats per minute, by 3 heart beats per minute, by 4 heart beats per minute, by 5 heart beats per minute, by at least about 10 heart beats per minute, or by at least about 20 heart beats per minute.

[0017] In some examples, improving the mammal's exercise tolerance comprises decreases in measured respiratory exchange ratios (RER).

[0018] In some examples, improving whole-body fatty acid oxidation in the mammal comprises increasing fatty acid oxidation (FAO) in the mammal. In some examples, increasing fatty acid oxidation (FAO) in the mammal comprises increases in the amount of exhaled $^{13}CO_2$ from the mammal after consuming a meal comprising ^{13}C-enriched fatty acids. In some examples, the amount of exhaled $^{13}CO_2$ increases by at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%,about 90%, or more than about 90% as compared to a mammal who is fed a meal comprising ^{13}C-enriched fatty acids and not administered a PPARδ agonist compound. In some examples, the amount of exhaled $^{13}CO_2$ increases by at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%,about 90%, or more than about 90% as compared to a mammal who is not fed a meal comprising ^{13}C-enriched fatty acids. In some examples, the amount of exhaled $^{13}CO_2$ increases by at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%,about 90%, or more than about 90% as compared to a mammal who is not fed a meal comprising ^{13}C-enriched fatty acids and not administered a PPARδ agonist compound.

[0019] In some examples, administration of the PPARδ agonist compound to the mammal normalizes FAO capacities in the mammal, up-regulates gene expression of any one of the enzymes or proteins involved in FAO, increases the activity of an enzyme or protein involved in FAO, or a combination thereof.

[0020] In some examples, the peroxisome proliferator-activated receptor delta (PPARδ) agonist compound is administered to the mammal in an amount sufficient for increasing the activity of mutated enzymes or proteins involved in FAO. In some examples, the peroxisome proliferator-activated receptor delta (PPARδ) agonist compound is administered to the mammal in an amount sufficient for increasing the activity of mutated but catalytically active enzymes or proteins involved in FAO.

[0021] In some examples, the fatty acid oxidation disorder comprises defects in the enzymes or proteins involved in the entry of long-chain fatty acids into mitochondria, intramitochondrial β-oxidation defects of long-chain fatty acids affecting membrane bound enzymes, β-oxidation defects of short- and medium-chain fatty acids affecting enzymes of the mitochondrial matrix, defects in the enzymes or proteins involved with electron transfer to the respiratory chain from mitochondrial β-oxidation, or a combination thereof.

[0022] In some examples, the fatty acid oxidation disorder (FAOD) comprises carnitine transporter deficiency, carnitine/acylcarnitine translocase deficiency, carnitine palmitoyl transferase deficiency Type 1, carnitine palmitoyl transferase deficiency Type 2, glutaric acidemia Type 2, long-chain 3-hydroxyacyl CoA dehydrogenase deficiency, medium-chain acyl CoA dehydrogenase deficiency, short-chain acyl CoA dehydrogenase deficiency, short-chain 3-hydroxyacyl CoA dehydrogenase deficiency, trifunctional protein deficiency, or very long-chain acyl CoA dehydrogenase deficiency, or a combination thereof.

[0023] In some examples, the fatty acid oxidation disorder comprises carnitine palmitoyltransferase II (CPT2) deficiency, very long-chain Acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, Trifunctional Protein (TFP) Deficiency; or a combination thereof.

[0024] In another example, described herein is a method of increasing activity of an enzyme or protein of the mitochondrial fatty acid beta-oxidation pathway in a mammal comprising administering a PPARδ agonist compound to a mammal with a mutation or deficiency in an enzyme or protein of the mitochondrial fatty acid beta-oxidation pathway.

[0025] In yet another example, described herein is a method of increasing activity of an enzyme or protein of the mitochondrial fatty acid beta-oxidation pathway in a mammal comprising administering a PPARδ agonist compound to a mammal with a deficiency in the activity of an enzyme or protein of the mitochondrial fatty acid beta-oxidation pathway.

[0026] In some examples, the deficiency in the activity of the enzyme or protein of the mitochondrial fatty acid beta-oxidation pathway results from a mutation in any one of the enzyme or protein of the mitochondrial fatty acid beta-oxidation pathway.

[0027] In some examples, the enzyme or protein of the mitochondrial fatty acid beta-oxidation pathway is short-chain acyl-CoA dehydrogenase (SCAD), medium-chain acyl-CoA dehydrogenase (MCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), very long-chain acyl-CoA dehydrogenase (VLCAD), mitochondrial trifunctional protein (TFP), carnitine transporter (CT), Carnitine palmitoyltransferase I (CPT I), carnitine-acylcarnitine translocase (CACT), carnitine palmitoyltransferase II (CPT II), isolated long-chain L3-hydroxyl-CoA dehydrogenase, medium-chain L3-hydroxyl-CoA dehydrogenase, short-chain L3-hydroxyl-CoA dehydrogenase, medium-chain 3-ketoacylCoA thiolase, or long-chain 3-ketoacylCoA thiolase (LCKAT).

[0028] In some examples, the mutation is K304E of MCAD; L540P, V174M, E609K, or combination thereof, of VLCAD; E510Q of TFP-alpha subunit (HADHA); R247C of TFP-beta subunit (HADHB); or a combination thereof.

[0029] In some examples, the mutation is a nucleotide mutation in the gene encoding VLCAD. In some examples, the mutation is 842C>A,848T>C, 865G>A, 869G>A, 881G>A, 897G>T, 898A>G, 950T>C, 956C>A, 1054A>G, 1096C>T, 1097G>A, 1117A>T, 1001 T>G, 1066A>G, 1076C>T,1153C>T, 1213G>C, 1146G>C, 1310T>C, 1322G>A, 1358G>A, 1360G>A, 1372T>C, 1258A>C, 1388G>A, 1405C>T, 1406G>A, 1430G>A, 1349G>A, 1505T>C, 1396G>T, 1613G>C, 1600G>A, 1367G>A, 1375C>T, 1376G>A, 1532G>A, 1619T>C, 1804C>A, 1844G>A, 1825G>A, 1844G>A, 1837C>G, or a combination thereof.

[0030] In some examples, the mammal has one or more symptoms typically associated with a fatty acid oxidation disorder. In some examples, symptoms typically associated with a fatty acid oxidation disorder include, but are not limited to: elevated creatine kinase (CPK) levels, hepatic dysfunction, cardiomyopathy, hypoglycemia, rhabdomyolysis, acidosis, decreased muscle tone (hypotonia), muscle weakness, exercise intolerance, or combinations thereof.

[0031] In some examples, the PPARδ agonist binds to and activates the cellular PPARδ and does not substantially activate the cellular peroxisome proliferator activated receptors - alpha (PPARα) and - gamma (PPARγ). In some examples, the PPARδ agonist compound is a phenoxyalkylcarboxylic acid compound. In some examples, the PPARδ agonist compound is a phenoxyethanoic acid compound, phenoxypropanoic acid compound, phenoxybutanoic acid compound, phenoxypentanoic acid compound, phenoxyhexanoic acid compound, phenoxyoctanoic acid compound, phenoxynonanoic acid compound, or phenoxydecanoic acid compound.

[0032] In some examples, the PPARδ agonist compound is a phenoxyethanoic acid compound or a phenoxyhexanoic acid compound. In some examples, the PPARδ agonist compound is an allyloxyphenoxyethanoic acid acid compound.

[0033] In some examples, the PPARδ agonist is a compound selected from the group consisting of *(Z)*-[2-Methyl-4-[3-(4-methylphenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-phenoxy]acetic acid; *(E)*-[2-Methyl-4-[3-[4-[3-(pyrazol-1-yl)prop-1-ynyl]phenyl]-3-(4-trifluoromethylphenyl)-allyloxy]phenoxy]acetic acid; *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid; *(E)*-[2-Methyl-4-[3-[4-[3-(morpholin-4-yl)propynyl]phenyl]-3-(4-trifluoromethylphenyl)allyloxy]-phenoxy]acetic acid; *(E)*-[4-[3-(4-Chlorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid; (*E*)-[4-[3-(4-Chlorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methylphenyl]-propionic acid; {4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-2-methyl-phenoxy}-acetic acid; or a pharmaceutically acceptable salt thereof.

[0034] In some examples, the PPARδ agonist is a compound selected from the group consisting of *(Z)*-[2-Methyl-4-[3-(4-methylphenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-phenoxy]acetic acid; *(E)*-[2-Methyl-4-[3-[4-[3-(pyrazol-1-yl)prop-1-ynyl]phenyl]-3-(4-trifluoromethylphenyl)-allyloxy]phenoxy]acetic acid; *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid; *(E)*-[2-Methyl-4-[3-[4-[3-(morpholin-4-yl)propynyl]phenyl]-3-(4-trifluoromethylphenyl)allyloxy]-phenoxy]acetic acid; *(E)*-[4-[3-(4-Chlorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid; (*E*)-[4-[3-(4-Chlorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methylphenyl]-propionic acid; {4-[3-Isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid; {4-[3-Isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-phenylsulfanyl]-2-methyl-phenoxy}-acetic acid; {4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-2-methyl-phenoxy}-acetic acid; 2-[2-methyl-4-[[3-methyl-4-[[4-(trifluoromethyl)phenyl]methoxy]phenyl]thio]phenoxy]-acetic acid; (S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)piperazine-1-sulfonyl]-indan-2-carboxylic acid or a tosylate salt thereof (KD-3010); 4-butoxy-a-ethyl-3-[[[2-fluoro-4-(trifluoromethyl)benzoyl]amino]methyl]-benzenepropanoic acid (TIPP-204); 2-[2-methyl-4-[[[4-methyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]methyl]thio]phenoxy]-acetic acid (GW-501516); 2-[2,6 dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl]phenoxyl]-2-methylpropanoic acid (GFT-505); {2-methyl-4-[5-methyl-2-(4-trifluoromethyl-phenyl)-2H-[1,2,3]triazol-4-ylmethylsylfanyl]-phenoxy}-acetic acid; (R)-3-methyl-6-(2-((5-methyl-2-(4-(trifluoromethyl)phenyl)-1H-imidazol-1-yl)methyl)phenoxy)hexanoic acid; (R)-3-methyl-6-(2-((5-methyl-2-(6-(trifluoromethyl)pyridin-3-yl)-1H-imidazol-1-yl)methyl)phenoxy)hexanoic acid; 2-(2-methyl-4-(((2-(4-(trifluoromethyl)phenyl)-2H-1,2,3-triazol-4-yl)methyl)thio)phenoxy)acetic acid; and (R)-2-(4-((2-ethoxy-3-(4-(trifluoromethyl)phenoxy)propyl)thio)phenoxy)acetic acid; or a pharmaceutically acceptable salt thereof.

[0035] In some examples, the PPARδ agonist is a compound selected from the group consisting of PPARδ agonist is a compound selected from the group consisting of: *(Z)*-[2-Methyl-4-[3-(4-methylphenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-phenoxy]acetic acid; *(E)*-[2-Methyl-4-[3-[4-[3-(pyrazol-1-yl)prop-1-ynyl]phenyl]-3-(4-trifluoromethylphenyl)-allyloxy]phenoxy]acetic acid; *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid; *(E)*-[2-Methyl-4-[3-[4-[3-(morpholin-4-yl)propynyl]phenyl]-3-(4-trifluoromethylphenyl)allyloxy]-phenoxy]acetic acid; *(E)*-[4-[3-(4-Chlorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid; (*E*)-[4-[3-(4-Chlorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methylphenyl]-propionic acid; {4-[3-Isobutoxy-5-(3-morpholin-

4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid; {4-[3-Isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-phenylsulfanyl]-2-methyl-phenoxy}-acetic acid; and {4-[3,3-Bis-(4-bromo-phenyl)-allyloxy]-2-methyl-phenoxy}-acetic acid; or a pharmaceutically acceptable salt thereof.

[0036] In some examples, the PPARδ agonist is *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid (Compound I) or a pharmaceutically acceptable salt thereof.

[0037] In some examples, *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, is administered to the mammal at a dose of about 10mg to about 500mg, about 50mg to about 200mg, or about 75mg to about 125mg.

[0038] In some examples, the PPARδ agonist is *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, and is administered to the mammal at a dose of about 10mg to about 500mg. In some examples, the PPARδ agonist is *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, and is administered to the mammal at a dose of about 50mg to about 200mg. In some examples, the PPARδ agonist is *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid (Compound I) or a pharmaceutically acceptable salt thereof, and is administered to the mammal at a dose of about 75mg to about 125mg.

[0039] In some examples, a PPARδ agonist (e.g. Compound 1, or a pharmaceutically acceptable salt thereof), is systemically administered to the mammal with a fatty acid oxidation disorder (FAOD). In some examples, the PPARδ agonist is administered to the mammal orally, by injection or intravenously. In some examples, the PPARδ agonist is administered to the mammal in the form of an oral solution, oral suspension, powder, pill, tablet or capsule.

[0040] In one example, described herein is a pharmaceutical composition comprising PPARδ agonist and at least one pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration. In some examples, the pharmaceutical composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, or oral administration. In some examples, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some examples, the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, a

suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion. In some examples, the pharmaceutical composition is in the form of a tablet, a pill, or a capsule.

[0041] In one example, described herein is a method of treatment or prevention of any one of the fatty acid oxidation disorders (FAOD) described herein comprising administering a therapeutically effective amount of a PPARδ agonist to a mammal in need thereof.

[0042] In any of the aforementioned examples are further examples in which the effective amount of the PPARδ agonist (e.g. Compound 1, or a pharmaceutically acceptable salt thereof), is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered non-systemically or locally to the mammal.

[0043] In any of the aforementioned examples are further examples comprising single administrations of the effective amount of the PPARδ agonist (e.g. Compound 1, or a pharmaceutically acceptable salt thereof), including further examples in which the PPARδ agonist (e.g. Compound 1, or a pharmaceutically acceptable salt thereof), is administered once daily to the mammal or is administered to the mammal multiple times over the span of one day. In some examples, the PPARδ agonist (e.g. Compound 1, or a pharmaceutically acceptable salt thereof), is administered on a continuous dosing schedule. In some examples, the PPARδ agonist is administered on a continuous daily dosing schedule.

[0044] In any of the aforementioned examples involving the treatment of a disease or condition are further examples comprising administering at least one additional agent in addition to the administration of a PPARδ agonist (e.g. Compound 1, or a pharmaceutically acceptable salt thereof). In various examples, each agent is administered in any order, including simultaneously.

[0045] In some examples, the at least one additional therapeutic is ubiquinol, ubiquinone, niacin, riboflavin, creatine , L-carnitine, acetyl-L-carnitine, biotin, thiamine, pantothenic acid, pyridoxine, alpha-lipoic acid, n-heptanoic acid, CoQ10, vitamin E, vitamin C, methylcobalamin, folinic acid, N-acetyl-L-cysteine (NAC), zinc, folinic acid/leucovorin calcium, resveratrol, or a combination thereof. In some examples, the at least one additional therapeutic is an odd-chain fatty acid, odd-chain fatty ketone, L-carnitine, or combinations thereof. In some examples, the at least one additional therapeutic is triheptanoin, n-heptanoic acid, a triglyceride, or a salt or thereof, or combinations thereof.

[0046] In any of the examples disclosed herein, the mammal is a human.

[0047] In some examples, the PPARδ agonist (e.g. Compound 1, or a pharmaceutically acceptable salt thereof), is administered to a human. In some examples, the PPARδ agonist (e.g. Compound 1, or a pharmaceutically acceptable salt thereof), is orally administered.

[0048] Articles of manufacture, which include packaging material, a compound described herein, or a pharmaceutically acceptable salt thereof, within the packaging material, and a label that indicates that a PPARδ agonist (e.g. Compound 1, or a pharmaceutically acceptable salt thereof), is used for modulating the activity of PPARδ, or for the treatment, prevention or amelioration of one or more symptoms of a fatty acid oxidation disorder (FAOD) that would benefit from modulation of PPARδ activity, are provided.

[0048a] In one aspect, provided herein is a use of a peroxisome proliferator-activated receptor delta (PPARδ) agonist compound in the manufacture of a medicament for the treatment of a fatty acid oxidation disorder (FAOD) in a mammal, wherein the PPARδ agonist compound is *(E)*-[4-[3-(4-fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid, or a pharmaceutically acceptable salt thereof, and wherein the mammal is a human.

[0048b] In one aspect, provided herein is a method for measuring whole-body fatty acid oxidation in a human with a fatty acid oxidation disorder (FAOD) comprising: feeding the human with a fatty acid oxidation disorder (FAOD) a meal comprising ^{13}C-enriched fatty acids and measuring the amount of exhaled $^{13}CO_2$ from the human, wherein the human with a fatty acid oxidation disorder (FAOD) is undergoing treatment with a PPARδ agonist compound.

[0048c] In one aspect, provided herein is a method for measuring changes in whole-body fatty acid oxidation in a human with a fatty acid oxidation disorder (FAOD) comprising the steps of: 1) providing a meal enriched with a ^{13}C labeled fatty acid; 2) administering to the human a PPARδ agonist compound, or a pharmaceutically acceptable salt thereof; and 3) collecting breath samples from the human at regular intervals and measuring for the content of $^{13}CO_2$ in the breath samples.

[0048d] In one aspect, provided herein is a use of *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a fatty acid oxidation disorder (FAOD) in a mammal; wherein the fatty acid oxidation disorder comprises

carnitine palmitoyltransferase II (CPT2) deficiency, very long-chain Acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, Trifunctional Protein (TFP) Deficiency; or a combination thereof; wherein *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, is to be administered to the mammal at a dose of about 50 mg to about 200 mg; and wherein the mammal is a human.

[0049] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0050] **Figure 1** shows the effect of Compound 1 (50 mg once a day for 12 weeks) on the 12-minute walk test in patients with genetically diagnosed long chain FAOD with symptoms of myopathy.

DETAILED DESCRIPTION

[0051] Mitochondria are the main site for the oxidation of fatty acids and triglycerides through a series of four enzyme reactions called β-oxidation. The β-oxidation pathway is a cyclic process in which two carboxy-terminal carbon atoms are released from fatty acids as acetyl-CoA units each time a cycle is fully completed. The acetyl-CoA can enter the citric acid cycle and the electron carriers deliver the electrons to the electron transport chain. Fatty acid oxidation (FAO) both produces acetyl-CoA to fuel the tricarboxylic acid (TCA) cycle and ketogenesis, and reduces flavin adenine dinucleotide (to FADH2) and nicotinamide adenine dinucleotide (to NADH); these reduced products directly feed into the respiratory chain. As the acyl-CoA gets shorter, its physicochemical properties change. To be able to fully degrade fatty acids, the β-oxidation machinery harbors different chain length–specific enzymes. Inherited defects for most

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a peroxisome proliferator-activated receptor delta (PPARδ) agonist compound in the manufacture of a medicament for the treatment of a fatty acid oxidation disorder (FAOD) in a mammal, wherein the PPARδ agonist compound is *(E)*-[4-[3-(4-fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid, or a pharmaceutically acceptable salt thereof, and wherein the mammal is a human.

2. The use of claim 1, wherein:
treatment of the FAOD comprises improving whole-body fatty acid oxidation (FAO) in the mammal, improving the mammal's exercise tolerance, decreasing pain, decreasing fatigue, or a combination thereof.

3. The use of claim 2, wherein:
administration of the PPARδ agonist compound to the mammal increases FAO capacities in the mammal, normalizes FAO capacities in the mammal, up-regulates gene expression of any one of the enzymes or proteins involved in FAO, increases the activity of an enzyme or protein involved in FAO, or a combination thereof.

4. The use of any one of claims 1-3, wherein:
the fatty acid oxidation disorder comprises one or more defects in one or more of the enzymes or proteins involved in the entry of long-chain fatty acids into mitochondria, intramitochondrial β-oxidation defects of long-chain fatty acids affecting membrane bound enzymes, β-oxidation defects of short- and medium-chain fatty acids affecting enzymes of the mitochondrial matrix, defects in the enzymes or proteins involved with electron transfer to the respiratory chain from mitochondrial β-oxidation, or a combination thereof.

5. The use of any one of claims 1-4, wherein:
the fatty acid oxidation disorder (FAOD) comprises carnitine transporter deficiency, carnitine/acylcarnitine translocase deficiency, carnitine palmitoyl transferase deficiency Type 1, carnitine palmitoyl transferase deficiency Type 2, glutaric acidemia Type 2, long-chain 3-hydroxyacyl CoA dehydrogenase deficiency, medium-chain acyl CoA dehydrogenase deficiency, short-chain acyl CoA dehydrogenase deficiency, short-chain 3-hydroxyacyl CoA dehydrogenase deficiency, trifunctional protein deficiency, or very long-chain acyl CoA dehydrogenase deficiency, or a combination thereof.

6. The use of any one of claims 1-5, wherein:

the fatty acid oxidation disorder comprises carnitine palmitoyltransferase II (CPT2) deficiency, very long-chain Acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, Trifunctional Protein (TFP) Deficiency; or a combination thereof.

7. The use of any one of claims 1-4, wherein:
the mammal has one or more mutations in one or more of the enzymes or proteins of the mitochondrial fatty acid beta-oxidation pathway.

8. The use of claim 7, wherein:
the one or more enzymes or proteins of the mitochondrial fatty acid beta-oxidation pathway are selected from the group consisting of short-chain acyl-CoA dehydrogenase (SCAD), medium-chain acyl-CoA dehydrogenase (MCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), very long-chain acyl-CoA dehydrogenase (VLCAD), mitochondrial trifunctional protein (TFP), carnitine transporter (CT), Carnitine palmitoyltransferase I (CPT I), carnitine-acylcarnitine translocase (CACT), carnitine palmitoyltransferase II (CPT II), isolated long-chain L3-hydroxyl-CoA dehydrogenase, medium-chain L3-hydroxyl-CoA dehydrogenase, short-chain L3-hydroxyl-CoA dehydrogenase, medium-chain 3-ketoacylCoA thiolase, and long-chain 3-ketoacylCoA thiolase (LCKAT).

9. The use of any one of claims 1-8, wherein:
the mammal has elevated creatine kinase (CPK) levels, hepatic dysfunction, cardiomyopathy, hypoglycemia, rhabdomyolysis, acidosis, decreased muscle tone (hypotonia), muscle weakness, exercise intolerance, or combinations thereof.

10. The use of any one of claims 1-9, wherein:
the PPARδ agonist compound is *(E)*-[4-[3-(4-fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid, or a pharmaceutically acceptable salt thereof, and is to be administered to the mammal at a dose of about 10mg to about 500mg.

11. The use of any one of claims 1-9, wherein:
the PPARδ agonist compound is *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, and is to be administered to the mammal at a dose of about 50mg to about 200mg.

12. The use of any one of claims 1-9, wherein:

the PPARδ agonist compound is *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, and is to be administered to the mammal at a dose of about 50mg.

13. The use of any one of claims 1-9, wherein:
the PPARδ agonist compound is *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, and is to be administered to the mammal at a dose of about 100mg.

14. The use of any one of claims 1-13, wherein:
the PPARδ agonist compound is to be systemically administered to the mammal in the form of an oral solution, oral suspension, powder, pill, tablet or capsule; and the PPARδ agonist compound is to be administered to the mammal once daily.

15. The use of any one of claims 1-14, wherein at least one additional therapeutic is to be further administered to the mammal, wherein:
the at least one additional therapeutic is ubiquinol, ubiquinone, niacin, riboflavin, creatine , L-carnitine, acetyl-L-carnitine, biotin, thiamine, pantothenic acid, pyridoxine, alpha-lipoic acid, n-heptanoic acid, CoQ10, vitamin E, vitamin C, methylcobalamin, folinic acid, resveratrol, N-acetyl-L-cysteine (NAC), zinc, folinic acid/leucovorin calcium, or a combination thereof;
or the at least one additional therapeutic is an odd-chain fatty acid, odd-chain fatty ketone, L-carnitine, or combinations thereof;
or the at least one additional therapeutic is an odd-chain fatty acid, odd-chain fatty ketone, L-carnitine, or combinations thereof;
or the at least one additional therapeutic is triheptanoin, n-heptanoic acid, a triglyceride, or a salt or thereof, or combinations thereof;
or the at least one additional therapeutic is an antioxidant;
or the at least one additional therapeutic is bezafibrate.

16. A method for measuring whole-body fatty acid oxidation in a human with a fatty acid oxidation disorder (FAOD) comprising: feeding the human with a fatty acid oxidation disorder (FAOD) a meal comprising ^{13}C-enriched fatty acids and measuring the amount of exhaled $^{13}CO_2$ from the human, wherein the human with a fatty acid oxidation disorder (FAOD) is undergoing treatment with a PPARδ agonist compound.

17. A method for measuring changes in whole-body fatty acid oxidation in a human with a fatty acid oxidation disorder (FAOD) comprising the steps of:
1) providing a meal enriched with a ^{13}C labeled fatty acid;

2) administering to the human a PPARδ agonist compound, or a pharmaceutically acceptable salt thereof; and

3) collecting breath samples from the human at regular intervals and measuring for the content of $^{13}CO_2$ in the breath samples.

18. The method of claim 16 or claim 17, wherein:

the PPARδ agonist binds to and activates the cellular PPARδ and does not substantially activate the cellular peroxisome proliferator activated receptors - alpha (PPARα) and - gamma (PPARγ).

19. The method of any one of claims 16-18, wherein:

the PPARδ agonist compound is a phenoxyalkylcarboxylic acid compound; or a pharmaceutically acceptable salt thereof.

20. The method of any one of claims 16-19, wherein the PPARδ agonist compound is: *(E)*-[4-[3-(4-fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid; or a pharmaceutically acceptable salt thereof.

21. Use of *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a fatty acid oxidation disorder (FAOD) in a mammal;

wherein the fatty acid oxidation disorder comprises carnitine palmitoyltransferase II (CPT2) deficiency, very long-chain Acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, Trifunctional Protein (TFP) Deficiency; or a combination thereof;

wherein *(E)*-[4-[3-(4-Fluorophenyl)-3-[4-[3-(morpholin-4-yl)propynyl]phenyl]allyloxy]-2-methyl-phenoxy]acetic acid or a pharmaceutically acceptable salt thereof, is to be administered to the mammal at a dose of about 50 mg to about 200 mg; and

wherein the mammal is a human.

22. The use of claim 21, wherein treatment of the FAOD comprises improving whole-body fatty acid oxidation (FAO) in the mammal, improving the mammal's exercise tolerance, decreasing pain, decreasing fatigue, or a combination thereof.