

FATTY ANALOGUES FOR THE TREATMENT OF OBESITY, HYPERTENSION AND FATTY LIVER

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The present invention relates to novel fatty acid analogues which can be used for the treatment and/or prevention of obesity, fatty liver and hypertension. Further, the invention relates to a nutritional composition comprising such fatty acid analogues, and a method for reducing the total weight, or the amount of adipose tissue in an animal. The invention also relates to a method for improving the quality of product such as meat, milk and eggs.

BACKGROUND OF THE INVENTION

Hyperlipidemia and obesity afflict an increasing proportion of the population in Western societies and are associated with the development of serious conditions such as atherosclerosis, hypertension, fatty liver and insulin resistance. These conditions may eventually lead to the clinical manifestations of coronary heart diseases (CHD) and non-insulin dependent diabetes mellitus (NIDDM).

Treatment with modified fatty acids represent a new way to treat these diseases.

EP 345.038 describes the use of non- β -oxidizable fatty acid analogues for the treatment of hyperlipidaemic conditions and for reducing the concentration of cholesterol and triglycerides in the blood of mammals.

PCT/NO95/00195 describes alkyl-S—CH₂COOR and alkyl-Se—CH₂COOR for the inhibition of the oxidative modification OF ldl.

It has now been found that the analogues described in the prior art publication mentioned above, i.e. non- β -oxidizable fatty acids substituted with Sulphur or Selenium in the 3-position have broader area of applications.

Further, we have now synthesized and characterized novel fatty acid analogues which impose an effect on obesity, hypertension and fatty liver.

In feeding experiments with the fatty acid analogues in accordance with the present invention, the results show that these compounds lower the adipose tissue mass and body weight, and are thus potent drugs for the treatment of obesity and overweight.

Further, we have shown that the fatty acid analogues are potent antidiabetic compounds, with a profound effect on the levels of glucose and insulin.

Further, the compounds have been proved to have an favourable effect on restenosis, and exhibit good anti-oxidative properties.

Obesity

Obesity is a chronic disease that is highly prevalent in modern society and is associated not only with a social stigma, but also with decreased life span and numerous medical problems, including adverse psychological development, reproductive disorders such as polycystic ovarian disease, dermatological disorders such as infections, varicose veins, Acanthosis nigricans, and eczema, exercise intolerance, diabetes mellitus, insulin resistance, hypertension, hypercholesterolemia, cholelithiasis, osteoarthritis, orthopedic injury, thromboembolic disease, cancer, and coronary heart disease.

Existing therapies for obesity include standard diets and exercise, very low calorie diets, behavioral therapy, phar-

macotherapy involving appetite suppressants, thermogenic drugs, food absorption inhibitors, mechanical devices such as jaw wiring, waist cords and balloons, and surgery. Caloric restriction as a treatment for obesity causes catabolism of body protein stores and produces negative nitrogen balance.

Considering the high prevalence of obesity in our society and the serious consequences associated therewith as discussed above, any therapeutic drug potentially useful in reducing weight of obese persons could have a profound beneficial effect on their health. There is a need in the art for a drug that will reduce total body weight of obese subjects toward their ideal body weight without significant adverse side effects, and which also will help the obese subject to maintain the reduced weight level.

It is therefore an object of the present invention to provide a treatment regimen that is useful in returning the body weight of obese subjects toward a normal, ideal body weight.

It is another object to provide a therapy for obesity that results in maintenance of the lowered body weight for an extended period of time. Further, it is an object to reduce or inhibit the weight gain normally induced by fat rich diets.

It is yet another object to prevent obesity and, once treatment has begun, to arrest progression or prevent the onset of diseases that are the consequence of, or secondary to, the obesity, such as hypertension and fatty liver. These and other objects will be apparent to those of ordinary skill in the art.

The obesity herein may be due to any cause, whether genetic or environmental. Examples of disorders that may result in obesity or be the cause of obesity include overeating and bulimia, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, Type II diabetics, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity.

Hypertension

Increased blood pressure is a common condition in the developed countries of the world where, in very broad terms, the population eat too much and do not take sufficient exercise. Hypertension can have a variety of uncomfortable and dangerous side effects and it is seen as a major risk factor in relation to coronary heart disease. Hypertension can be associated with specific causes such as kidney disease or adrenal tumours but in most instances it is not. Obesity is regarded as a risk factor in relation to hypertension and a first line strategy in relation to obese hypertensive patients is to suggest weight reduction. It is therefore reasonable to anticipate that the present compounds, e.g. TTA and TSA which can have an effect on obesity, will reduce hypertension.

Specific ailments attributable to hypertension include heart failure, myocardial infarction, rupture or thrombus of the blood vessels in the brain, and kidney damage.

It is therefore an object of the present invention to provide a treatment regimen that is useful in lowering the blood pressure.

Fatty liver

The mechanism of production of fatty hepatosis is not entirely clear, but appears to be a combination of several factors, such as sparing action of ethanol oxidation on utilization of liver triacylglycerols, excessive mobilization of triacylglycerols from adipose tissue to the liver caused in