

METHOD OF TREATING A VERTEBRATE ANIMAL TO REDUCE PLASMA TRIGLYCERIDES AND CHOLESTEROL LEVELS AND TO ALLEVIATE AND PREVENT ATHEROSCLEROSIS

FIELD OF THE INVENTION

This invention relates to a method for the treatment of conditions associated with atherosclerosis in vertebrate animals, particularly man. Plasma cholesterol and triglyceride levels are lowered, and blood vessel plaques in vertebrate animals are reduced by administering to the animal a prolactin-inhibiting compound.

BACKGROUND OF THE INVENTION

Over the last several years there has been an increasing interest in the role of plasma cholesterol and lipoproteins in the causation of coronary artery disease. Studies regarding the concentrations of plasma cholesterol and triglyceride have received a great deal of publicity regarding their roles in the initiation of atherosclerosis. At high concentrations, these lipids tend to cross arterial cell wall membranes. The cumulative deposition leads to the formation of lipid plaques in the arterial wall which is indicative of an atherosclerotic condition.

Prolactin has recently been shown to have an important role in stimulating the synthesis of lipids in the liver. Suppression of prolactin secretion can block hepatic lipogenesis, and prolactin replacement has fully restored lipogenesis because some of the lipid in the blood is produced in the liver. We believed therefore, that there was a possibility that inhibition of prolactin secretion might also reduce plasma lipids.

Ergot-related prolactin-inhibiting compounds are known and have been administered to vertebrate animals. In U.S. Pat. No. 3,752,814 and U.S. Pat. No. 3,752,888, e.g., 2-bromo-alpha-ergocryptine and certain of its pharmaceutically acceptable acid addition salts and methods for their preparation are described in detail. It is recognized that these compounds are useful in inhibiting lactation, and they exhibit antifertility effects.

In accordance with U.S. Pat. No. 4,659,715 ergot-related prolactin-inhibiting compounds, e.g., 2-bromo-alpha-ergocryptine, are administered to vertebrate animals to decrease body fat stores without concomitant decrease in body weight, and in accordance with U.S. Pat. No. 4,747,709 these compounds are administered to decrease body fat stores, with concomitant loss in body weight.

Despite the considerable usage of the ergot-related prolactin-inhibiting compounds in having been administered in the past to vertebrates for one purpose or another, insofar as known, these compounds have never been viewed as possibly useful for the treatment of atherosclerosis. Various other compounds, or drugs, however, have been employed generally for such purpose; albeit none, insofar as known, have proven entirely satisfactory. One drug of this type is colestipal hydrochloride (Colestid) described in Chapter 21, at Page 224, under "Antilipemics" of "Nurses Guide to Drugs."

There exists a great need, and a tremendous interest by the scientific and medical communities, to develop pharmacological methods for treating vertebrate animals, especially humans, to suppress or to reverse, or both suppress and reverse, the formation of arterial lipid

plaques in subjects, or victims to the atherosclerotic condition.

OBJECTS

It is, accordingly, the primary object of this invention to satisfy this need, and others.

In particular, it is an object of this invention to provide a pharmacological method for the treatment of a vertebrate animal, particularly a human, to decrease the total plasma cholesterol and total triglyceride levels in animals exhibiting, or diagnosed as having, undesirably high levels of these lipids and to reduce lipid plaques on the walls of the arteries and blood vessels of atherosclerotic subjects.

A further, and more specific objective is to provide a pharmacological method for decreasing the total plasma cholesterol and total triglyceride levels to suppress atherosclerosis and reduce arterial lipid plaques with minimal adverse side effects, if any.

THE INVENTION

These objects and others are achieved by administering to a vertebrate animal, or human, diagnosed as having an atherosclerotic condition, or the risk factors associated with the atherosclerotic condition (viz., high plasma cholesterol, or high plasma triglycerides, or both), a prolactin-inhibiting compound sufficient to decrease the total plasma cholesterol and total triglyceride levels in the blood, and over a period of time sufficient to reduce arterial lipid plaques in the walls of the blood vessels of said animal, or human. Thus, it has been found that a prolactin-inhibiting compound, notably an ergot-related prolactin-inhibiting compound, can be administered to a subject exhibiting the atherosclerotic condition, or diagnosed as having an atherosclerotic condition, to suppress the total cholesterol and total triglyceride levels in the blood, or plasma, of the subject. Such treatments will suppress the formation of arterial lipid plaques in the walls of the blood vessels, and continued over a sufficient period of time will reduce the arterial lipid plaques in the walls of the blood vessels of atherosclerotic subjects.

Studies, principally epidemiologic studies, have shown a direct relationship between coronary atherosclerotic disease and elevated cholesterol in the blood of humans. Whereas medical scientists, and practitioners, have not determined a precise total plasma cholesterol at which medical intervention is necessary in treating the disease, there are levels at which majority expert opinion would favor treatment of a subject. In general, when the total plasma cholesterol of a human subject exceeds about 200 mg/dl (milligrams/deciliter) the subject is diagnosed as having an atherosclerotic condition; and for purposes of this invention this level can be regarded as indicative of the atherosclerotic condition, or level at which a human subject would be diagnosed as having an atherosclerotic condition. The formation of lipid plaques in the arterial wall, at any level, is regarded as an atherosclerotic condition. In vertebrate animals other than human, the levels of total plasma cholesterol defining the atherosclerotic condition will differ and may be independently determined for each species. Total plasma cholesterol levels defining the atherosclerotic condition for Syrian hamsters should not exceed about 100 mg/dl, for pigs should not exceed about 100 mg/dl, Swiss Webster white mice should not exceed about 100 mg/dl, and for Zucker rats should not exceed about 100 mg/dl. The formation of lipid plaques