Treatment Significantly Increases Conversion of Homocysteine to Methionine for Reducing Human Cardiovascular Disease (CVD) Risk and Use of Animal Feed Additives

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Technology description

This treatment method and pharmaceutical composition could be significantly more effective at lowering the risk of hyperhomocysteinemia-related cardiovascular disease than traditional betaine treatment. The treatment uses thetins, which are sulfonium analogs of betaine, to lower plasma homocysteine levels in humans and animals that have hyperhomocysteinemia, a condition that increases the risk of CVD. Thetins can confer a 700% faster methylation rate to the betaine-homocysteine methyltransferase catalyzed reaction when compared to equimolar concentrations of betaine. This method also might provide an effective alternative to methionine, choline, and betaine animal feed supplements, resulting in a lower cost feed that still maintains optimal animal performance.

DESCRIPTION/DETAILS

This technology provides a novel product for highly effective conversion of homocysteine to methionine, with two applications: treatment of human/animal CVD associated with hyperhomocysteinemia and replacement of existing animal feed supplements. CVD is a major cause of death in the United States. Of the almost 25% of Americans who will be diagnosed with the disease, 50% will die from it. The causes of CVD include hypertension, smoking, high blood cholesterol, genetic predisposition, and diet. Homocysteine is an amino acid synthesized naturally in the body, although more often it exists as a byproduct of metabolism of another amino acid, methionine, obtained from eating meat. Elevated levels of homocysteine in the blood (blood levels of homocysteine over 15M, a condition called hyperhomocysteinemia) may be linked to an elevated risk of CVD in a manner similar to blood cholesterol levels. Existing treatments for hyperhomocysteinemia include oral administration of pharmacological doses of a compound called betaine, either alone or with vitamin supplements. Betaine, a metabolite of choline oxidation, is a substrate for an enzyme called betaine-homocysteine methyltransferase, which adds a methyl group to homocysteine to create methionine. This treatment reduces plasma homocysteine by increasing the conversion of homocysteine to methionine; however it does not effectively lower plasma homocysteine to normal levels, still leaving considerable risk for CVD. Betaine treatment also yields increased plasma and urine concentrations of betaine and an inhibitor of

methionine production, dimethylglycine, a phenomenon which may explain the low efficacy of betaine.
In the animal feed industry, routine supplementation of feeds with various nutrients helps improve animal growth, gestation, or lactation.
Methionine often is added because it provides an essential amino acid, while addition of choline reduces the dietary requirements of the animals for methionine. Betaine is added to reduce both the dietary requirement for methionine and any choline requirement. This novel treatment relies on compounds called thetins to decrease or inhibit physiological homocysteine levels. Thetins are more effective plasma homocysteine-lowering agents than betaine because they produce a greater flux through the betaine-homocysteine methyltransferase reaction in vivo, resulting in greater reductions in plasma homocysteine. This treatment has a 700% faster methylation rate than equimolar concentrations of betaine. In addition, thetins have no toxicity and are completely oxidized in mammals. Administration of specific thetins, such as dimethylacetothetin or dimethylpropriothetin along with vitamin supplements and possibly betaine, might yield significantly lower CVD risk than previous methods.
For treatment of CVD, a thetin is administered at a dose from 1 mg/kg to about 50 mg/kg. For animal feed supplements, a dose of up to approximately 0.75% of the diet, on a dry-weight basis, is used. Use of thetins as human therapeutics or animal feed supplements has many advantages over existing, analogous treatments. Existing betaine treatments reduce plasma homocysteine in humans and animals that have hyperhomocysteinemia but not to normal levels. In vitro laboratory analyses indicate that thetins could increase homocysteine methylation up to 700% over equimolar betaine treatments, thus detoxifying homocysteine. Thetins (dimethylacetothetin and/or dimethylpropriothetin) also are more specific substrates for the betaine-homocysteine methyltransferase enzyme than betaine, and they produce byproducts with lower affinities for the enzyme.These properties are in contrast to the betaine-related production of dimethylglycine, a known inhibitor of methionine production.
Existing animal feed additives include expensive methionine, choline, and betaine to maximize animal performance. With its highly effective conversion of homocysteine to methionine, this treatment could eliminate the need for three expensive feed additives, thereby substantially lowering costs in maintaining optimal animal performance.

Application area

Clinical therapeutics: CVD pharmaceuticals Animal husbandry: Feed additives

Advantages

This new treatment might significantly reduce the risk of CVD. It also might reduce the costs of animal feed by replacing current additives while still promoting optimal animal health.
More effective at lowering plasma homocysteine: This alternative to betaine treatments could provide a significantly more effective method for reducing risks for CVD due to hyperhomocysteinemia. It increases the rate of methylation of homocysteine by 700% over that of equimolar betaine treatments.

Lower animal feed costs: By eliminating the need for supplementing animal feeds with costly methionine, choline, and betaine, this feed additive could lower the feed costs for animals while still maintaining their optimal performance.
Health care savings: This new treatment for hyperhomocysteinemia in humans could decrease morbidity and mortality rates from CVD and significantly lower health care costs.
No toxic effects: Thetins, the compounds comprising the pharmaceutical/nutritional component of the treatment, could replace betaine or dietary choline with no toxicity.

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