METHOD FOR OPENING THE BLOOD-BRAIN BARRIER

Oral administration of sugar opens the blood-brain barrier and permits a co-administered chemical compound to enter the central nervous system in a higher amount than occurs without co-administration of the sugar. The increased amount that enters the central nervous system results in an increased biologic effect of the chemical compound.
METHOD FOR OPENING THE BLOOD-BRAIN BARRIER

FIELD OF THE INVENTION

The present invention relates to the field of delivering therapeutic substances into the body. More particularly, the invention relates to eliciting a therapeutic effect by administering a substance that permits a compound to enter the brain from the bloodstream.

BACKGROUND OF THE INVENTION

The blood-brain barrier that exists in all vertebrate brains was discovered in the latter part of the 19th century and the first half of the 20th century. Researchers discovered that dyes injected intravenously into the bloodstream stained all internal organs except the brain and that dyes injected into the cerebrospinal fluid stained cells of the brain but did not enter the bloodstream to stain other internal organs. It was later discovered that the blood-brain barrier was due to the structure of the capillary walls of the brain.

In organs other than the brain, fluid leaks out of capillaries and enters tissues through pores formed at the junction of adjacent endothelial cells. In the brain, however, endothelial cells of capillaries are intimately fused by intercellular tight junctions. The tight junctions prevent the paracellular leakage of fluid from the capillaries, leaving transcellular flow from the capillary to the brain as the only means for fluid, and solutes, to enter the brain from the bloodstream.

Among the means of transcellular fluid flow available to other organs of the body, pinocytosis is virtually nonexistent in brain capillaries. Consequently, solutes may enter the brain in one of two ways. In facilitated transport, a specialized carrier or receptor catalyst molecule transports a particular molecule through the endothelial cell wall into the
brain. In lipid-mediated transport, small lipid soluble molecules dissolve in and diffuse through the endothelial cell membrane.

While these mechanisms permit the entry into the brain of essential nutrients, the existence of the blood-brain barrier effectively prevents other substances, such as hormones, proteins, certain ions, and drugs, from entering the brain. Although it is normally beneficial to protect the brain from exposure to these substances, the blood-brain barrier also serves to prevent therapeutic or diagnostic agents from reaching the substance of the brain or the cerebrospinal fluid, rendering it difficult to treat or diagnose certain diseases.

Consequently, methods of penetrating the blood-brain barrier so as to permit entry of therapeutic or diagnostic substances have long been sought. Kozarich et al., U.S. Patent No. 5,686,416, incorporated herein by reference, discloses that intravenous injection of certain peptide analogues of bradykinin increase the permeability of the blood-brain barrier to co-administered therapeutic or diagnostic agents. The peptides function by attaching to certain receptors on the surface of brain-blood barrier endothelial cells. As disclosed in Kozarich, only peptides having a particular amino acid sequence adopt the proper conformation to interact with the receptors and increase the permeability of the blood-brain barrier. Kozarich states that the peptides may be administered by several routes, including intravascular, subcutaneous, and intramuscular injection, and by oral, transdermal, intranasal, and inhalation administration. However, in all eleven examples of in vivo treatment with the peptides disclosed in Kozarich, only intravascular injections were shown to be effective.

In contrast to Kozarich, U.S. Patent No. 4,866,042 (Neuwelt) and U.S. Patent No. 5,059,415 (Neuwelt) disclose the opening of the blood-brain barrier
by an osmotic disruption of the blood-brain barrier. According to Neuwelt, the blood-brain barrier is temporarily opened to permit the entry of genetic material and diagnostic imaging agents into the brain by the intraarterial injection of a hyperosmotic sugar, such as mannitol, arabinose, and glucose. The resultant hypertonicity of the blood adjacent to the cells of the blood-brain barrier causes these cells to shrink, leaving gaps between the cells. Compounds within the bloodstream can then enter the brain through these gaps. Neuwelt reports that, in contrast to the normal state in which the blood brain barrier excludes molecules having a molecular weight larger than 180 Daltons, when the blood-brain barrier is opened by osmotic disruption, molecules having a molecular weight of 1,000,000 Daltons can pass. These two Neuwelt patents are incorporated herein by reference.

A. Naito, in European Patent No. 652012A1; Canadian Patent No. 2,103,339, Japanese Patent Application No. 01-186086, and U.S. Patent Application No. 08/554,410, each of which is incorporated herein by reference, discloses that certain pure sugars in combination with certain amino acids, when administered orally or intravenously in sufficient quantities, have the ability to transport other materials across the blood-brain barrier. The disclosure of Naito represents an advance over that of Kozarich in that no particular amino acid sequence is necessary. In fact, amino acids as found in protein containing foods, and even free amino acids, were found to be effective. The disclosure of Naito represents an advance over that of Neuwelt in that intraarterial administration is unnecessary. The method disclosed by Naito requires the presence of both a sugar and amino acid to be essential.
BRIEF SUMMARY OF THE INVENTION

The inventor has discovered that oral administration of a sugar, even without an accompanying amino acid as described as essential in the Naito European, Canadian, and Japanese patents, can cause the elicitation of a biologic response, or can increase the response, to a co-administered chemical compound. The biologic response may be for a therapeutic, diagnostic, or experimental purpose. It is believed that the effect of the sugar to increase the biologic response of the chemical compound is due to the ability of the sugar to open the blood-brain barrier, thus permitting the co-administered chemical compound to enter the brain. It is further believed that the opening of the blood-brain barrier following sugar administration is due to the temporary formation of a hyperosmotic environment in the blood adjacent to the endothelial cells of the capillaries of the brain, causing a shrinking of the cells and a resultant loosening of the intercellular tight junctions. This permits compounds within the bloodstream to enter the vascular system within the central nervous system.

In accordance with one embodiment of the method of the invention, a sugar is administered orally and one or more chemical compounds that is, or are, to produce a desired biologic effect in an animal is co-administered with the sugar. Typically, the animal is a patient in need of a therapeutic effect of a therapeutic chemical agent. The patient may be any animal patient, including human patients and veterinary patients such as dogs, cats, horses, cattle, sheep, goats, pigs, and ferrets. The sugar is any sugar that can be absorbed into the bloodstream when administered orally. Therefore, any sugar that is absorbed in the tissues of the intact or diseased mouth, oropharynx, or gastrointestinal tract is suitable for use in accordance with the method of the invention.
In another embodiment, the method of the invention is a method for transporting a chemical compound across the blood-brain barrier of an animal. In accordance with this embodiment, a chemical compound is administered, a sugar is orally co-administered with the chemical compound in an amount sufficient to cause the blood-brain barrier to be opened, and the chemical compound is permitted to cross the blood-brain barrier.

In another embodiment, the method of the invention is a method for opening the blood-brain barrier of an animal. In accordance with this embodiment, a sugar is orally administered to an animal in an amount sufficient to open the blood-brain barrier and the sugar is permitted to cause the blood-brain barrier to be opened.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the method of the invention is a method for increasing the biologic effect of a chemical compound in an animal by administering the compound, orally co-administering with the compound a sugar that is absorbed into the bloodstream from the gastrointestinal tract in an amount sufficient to augment the biologic effect of the compound, and permitting the compound to exert its biologic effect.

In accordance with the invention, the chemical compound may be one that exerts its effect by its interaction with or action upon tissues within the central nervous system, such as the brain or the spinal cord. The biologic effect may be a therapeutic effect, or it may be for diagnostic or experimental purposes. Preferably, in the absence of a generalized opening of the blood-brain barrier, the chemical compound is completely or partially inhibited from crossing the blood-brain barrier. When co-administered with an agent that opens the blood-brain barrier, such as with an orally administered sugar in accordance with the method
of the invention, the chemical compound enters the central nervous system in an increased amount and its biologic effect is enhanced.

The animal may be a patient, such as a human or veterinary patient. Typically, the patient is a mammal but may also be non-mammalian such as a reptile, an amphibian, a bird, or a fish. Most commonly, the animal is either a person or a domesticated animal such as a house pet like a dog, cat, or bird, or a farm animal, such as a horse, cow, sheep, goat, or pig. When the animal is a ruminant, it is preferable that following oral administration the sugar is absorbed into the bloodstream before it reaches the rumen.

The chemical compounds that are suitable for use with the method of the invention include, but are not limited to, amino acids, peptides, lipids including simple lipids like fats, fatty acids, and waxes, and conjugated lipids like lecithins, phospholipids, and cerebrosides, carbohydrates, vitamins, minerals, ionic salts, minerals, herbs, and enzymes. Examples of particular compounds that are suitable as the chemical compound of the invention include beta carotene, xanthophyll, lecithin (phosphatidylcholine), tri-calcium phosphate, fat soluble vitamins A, D, E, and K, water soluble vitamins B and C, tryptophan, melatonin, pyroxidine, selenium, choline, tyrosine, tryptophan, arginine, hydroxyproline, potassium glutinate, calcium carbonate, sodium or potassium chloride, cysteine, and omega 3 and omega 6 fatty acids.

The chemical compound is administered in an amount sufficient to cause a biochemical effect in the body of the patient and may vary depending upon such variables as the particular compound administered, the condition that it is being administered to treat, the severity of the symptoms that the patient has, the biologic effect or the intensity of the biologic effect.
that is desired, and the amount of sugar that is co-administered with the chemical compound.

The route of administration of the chemical compound is immaterial to the method of the present invention. For example, the compound may be administered by intravenous, intraarticular, or subcutaneous injection, or by other enteral or parenteral routes, such as by ingestion, suppository, transdermal, or intranasal routes.

Sugars that are suitable for the method of the invention include all sugars that are absorbable from the alimentary canal to enter the bloodstream of the patient. Classes of suitable sugars include pentose, hexose, and heptose monosaccharides, disaccharides, trisaccharides, polysaccharides, amino sugars, deoxy sugars, and sugar alcohols. Particular sugars that may be used in the method of the invention include erythritol, xylitol, galactose, lactose, xylose, dulcitol, myoinositol, fructose, mannitol, sorbitol, glucose, arabinose, cellobiose, maltose, raffinose, rhamnose, melibiose, ribose, adonitol, arabitol, fucose, lyxose, trehalose, melezitose, sucrose, glucosamine, mannosamine, galactosamine, mannolactose, gluconolactose, and maltodextrins.

The sugar may be in any form in which it can be orally administered so as to be available to be acted upon by gastrointestinal digestive and/or absorptive processes. The sugar may be in solution or suspension in a liquid, such as an aqueous liquid, or may be in solid form, such as in a solid crystalline form, either in isolation or in a mixture, such as with other solid or liquid foodstuffs. Preferably, the sugar is administered as a pure sugar, either in a crystalline form or a saturated or supersaturated solution.

The absorption of the sugar from the alimentary canal to the bloodstream may be by passive diffusion, facilitated diffusion, or active transport from the lumen
of the gastrointestinal tract into the vascular system. The absorption may occur in any portion of the alimentary canal from the mouth to the anus. The absorption of the sugar in accordance with the method of the invention may be through intact or diseased mucosal tissues of the mouth, pharynx, esophagus, stomach, small intestine, and large intestine.

The amount of sugar administered in accordance with the method of the invention is an amount effective to increase the biologic effect of a co-administered chemical compound. Preferably, the amount of sugar administered is an amount sufficient to cause the blood-brain barrier to be temporarily opened. Generally, in a human, the minimal dosage is about 1 to 1.25 grams of sugar. In other animals, the dosage will vary depending on the weight of the animal. Depending, however, on the particular sugar administered and the efficiency of absorption of that sugar, the minimum amount of sugar to be administered in accordance with the invention may be higher or less than 1 gram. The maximal amount of sugar to be administered likewise depends on the particular sugar administered and the efficiency with which it is absorbed. High levels of sugars that are slowly or incompletely absorbed from the gastrointestinal tract, such as sorbitol or rhamnose, may cause gastrointestinal disturbances such as bloating or diarrhea, and may provide an undesirable source of nutrients to intestinal bacterial flora. Because of this, it is preferred to use a sugar that is completely, or almost completely, absorbed from the gut. Examples of preferred sugars include monomers like glucose, fructose, and galactose, and dimers composed of these sugars, such as maltose and sucrose, and, less preferably, digestible oligosaccharides and polymers made from these sugars.

Other than for the purpose of avoiding adverse reactions, such as nausea, heat sensation, flushing, or ringing of the ears, that may be associated with ingesting large
amounts of sugars, there is no upper limit to the amount of sugar that may be orally administered in accordance with the invention. However, to avoid such adverse reactions, it is preferred that the amount of easily digestible sugar, such as glucose, fructose, galactose, maltose, or sucrose, be less than or equal to about 6 grams.

In view of the above paragraph, a preferred dose range for fully digestible sugars such as glucose, fructose, galactose, maltose, and sucrose, is between .5 to 10 grams, most preferably between 1.25 and 6 grams. However, if desired and if the presence of adverse reactions is acceptable, the dosage may be much higher. For incompletely absorbed sugars, such as rhamnose and lactose, especially in lactose-intolerant individuals, it is generally necessary to use higher doses than with the fully digestible sugars. However, such doses typically produce undesirable adverse reactions, especially gastrointestinal upsets, bloating, and diarrhea.

The term "co-administered," when used in this specification and in the claims, refers to administering the sugar and the chemical compound at the same time or at different times, but close enough in time so that the sugar can augment the biologic effect of the compound. Generally, sugar is rapidly removed from the bloodstream to enter the cells of the body. Consequently, when the sugar is administered before the therapeutic compound, it is preferred that the chemical compound be administered within about 30 minutes following sugar administration.

In diabetics and other individuals in which sugar transport from the bloodstream is delayed, the administration of the chemical compound may be delayed if desired for up to several hours following sugar administration.

When the chemical compound is administered before the sugar, the time in which the sugar must be administered will vary depending on the particular
chemical compound and how long it remains in the bloodstream. For compounds that are eliminated rapidly, it might be necessary to administer the sugar within 30 minutes after administration of the compound. On the other hand, for compounds that remain in the bloodstream for extended periods of time, the sugar may be administered several hours after administration of the compound.

The methods of the invention may be used for experimental, diagnostic, or therapeutic purposes. For example, the method of the invention may be used to increase the uptake of beta carotene from the bloodstream to the brain, for experimental or therapeutic purposes related to the effect of beta carotene on the treatment of skin diseases or on hair growth in balding men. Lecithin, choline, or phospholipids, either alone or with other chemical compounds, may be used in accordance with the method of the invention to investigate or treat central nervous injuries or diseases such as Alzheimer's Disease, stroke, Lou Gehrig's disease, and cerebral palsy. Ocular diseases or disorders related to vision may be investigated or treated with Vitamin E and/or beta-carotene co-administered with a sugar as disclosed herein. Mental illness such as depression may be investigated or treated with chemical agents known to have an effect on these diseases, such as lithium, amino acids like tyrosine and tryptophan, or other psychotropic agents. Other examples of diseases that can be treated or investigated in accordance with the method of the invention are disclosed in European Patent No. 652012A1, Canadian Patent No. 2,103,339, Japanese Patent Application No. 01-186086, and U.S. Patent Application 08/554,410.

The following non-limiting examples provide further description of the invention.
Example I

Four Sprague-Dawley rats, weighing between 200 and 220 grams, are gavaged with 2 ml of a concentrated fructose solution. An additional four Sprague-Dawley rats to be used as negative controls are gavaged with 2 ml of water. After 30 minutes, the rats from both groups are anesthetized with isofluorane and C^{14}-labeled aminoisobutyric acid (AIB) is injected into a femoral vein. One hour later, while still anesthetized, the chest is opened, the heart is removed, and a saline solution is perfused through the aorta to wash blood from the brain. The washing of the blood from the brain is performed so that any radioactivity later found in the brain is due to transit of the AIB into the brain itself, rather than being due to the presence of AIB in the blood of the brain capillaries. The brain is then removed, homogenized, and an aliquot is assayed for radioactivity in a liquid scintillation counter.

Radioactivity is found to be much higher in the brains of the rats receiving the fructose solution compared that found in the brains of the control rats receiving water without the fructose.

Further modifications, uses, and applications of the invention described herein will be apparent to those skilled in the art. It is intended that such modifications be encompassed in the following claims.
CLAIMS

1. A method for increasing the therapeutic response to a chemical compound comprising administering the compound to a patient in need thereof, orally co-administering a sugar that is absorbable from the alimentary tract to the patient in an amount sufficient to augment the therapeutic effect of the compound, and permitting the compound to exert its therapeutic effect.

2. The method of claim 1 wherein the sugar is a pentose, hexose, or heptose monosaccharide, a disaccharide, a trisaccharide, a polysaccharide, an amino sugar, a deoxy sugar, or a sugar alcohol.

3. The method of claim 2 wherein the sugar is selected from the group consisting of erythritol, xylitol, galactose, lactose, xylose, dulcitol, myoinositol, fructose, mannitol, sorbitol, glucose, arabinose, cellobiose, maltose, raffinose, rhamnose, melibiose, ribose, adonitol, arabinol, fucose, lyxose, trehalose, melezitose, sucrose, glucosamine, mannosamine, galactosamine, mannolactose, gluconolactose, and maltodextrins.

4. The method of claim 3 wherein the sugar is selected from the group consisting of glucose, fructose, galactose, maltose, and sucrose.

5. The method of claim 1 wherein the sugar is administered as an oral solution or suspension.

6. The method of claim 1 wherein the sugar is administered in a solid form.

7. The method of claim 1 wherein the absorption of the sugar occurs in the small intestine.
8. The method of claim 1 wherein the patient is a human.

9. The method of claim 8 wherein the amount of the sugar administered is between about one to six grams.

10. The method of claim 1 wherein the chemical compound exerts its therapeutic effect by an action within the central nervous system.

11. The method of claim 1 wherein the therapeutic effect of the chemical compound is increased when the compound enters the central nervous system.

12. The method of claim 1 wherein the increase of the therapeutic response by the co-administered sugar is by causing the chemical compound to enter the central nervous system at levels that are higher than occur without the co-administration.

13. The method of claim 1 wherein the administration of the chemical compound is within about 30 minutes following administration of the sugar.

14. The method of claim 1 wherein the administration of the sugar is during the time that the blood level of the chemical compound is elevated due to the administration of the chemical compound.

15. The method of claim 14 wherein the sugar is administered within about thirty minutes following administration of the chemical compound.

16. A method for transporting a chemical compound across the blood-brain barrier of an animal comprising administering the chemical compound to the
animal, orally co-administering a sugar in an amount sufficient to cause the blood-brain barrier to be opened, and permitting the chemical compound to cross the blood-brain barrier.

17. The method of claim 16 wherein the sugar is selected from the group consisting of erythritol, xylitol, galactose, lactose, xylose, dulcitol, myoinositol, fructose, mannitol, sorbitol, glucose, arabinose, cellobiose, maltose, raffinose, rhamnose, melibiose, ribose, adonitol, arabitol, fucose, lyxose, trehalose, melezitose, sucrose, glucosamine, mannosamine, galactosamine, mannolactose, gluconolactose, and maltodextrins.

18. The method of claim 16 wherein the purity of the sugar is at least about 93%.

19. The method of claim 16 wherein the animal is a human.

20. A method for opening the blood-brain barrier of an animal comprising orally administering to the animal a sugar in an amount sufficient to open the blood-brain barrier and permitting the sugar to cause the blood-brain barrier to be opened.

21. The method of claim 20 wherein the sugar is selected from the group consisting of erythritol, xylitol, galactose, lactose, xylose, dulcitol, myoinositol, fructose, mannitol, sorbitol, glucose, arabinose, cellobiose, maltose, raffinose, rhamnose, melibiose, ribose, adonitol, arabitol, fucose, lyxose, trehalose, melezitose, sucrose, glucosamine, mannosamine, galactosamine, mannolactose, gluconolactose, and maltodextrins.
22. The method of claim 20 wherein the animal is a human.

23. The method of claim 22 wherein the amount of sugar administered is between about one to six grams.