COMPOSITIONS OF BIOCHEMICAL COMPOUNDS INVOLVED IN BIOENERGY METABOLISM OF CELLS AND METHOD OF USE

This invention relates to compositions of biochemical compounds involved in bioenergy metabolism of living cells and a method of use in prevention and therapy of diseases and other health conditions in humans and animals.

The fact that many human diseases develop at the level of cells is well established. Rudolph Virchow's "Cellular Pathology" [1854,] has become a leading principle of pathology. While the localization of the initiation of these diseases - the cell - was thereby defined, the variety of mechanisms that cause a cell to malfunction have remained insufficiently understood.

Life is not possible without sufficient bioenergy being created at the cellular level. In a series of metabolic pathways proteins, carbohydrates and fats are converted to Adenosine Thriphosphate (ATP). Optimum availability of cellular energy is a precondition for health. Under normal conditions, e.g. in a young and healthy individual, the cells of the body create an optimum amount of cellular energy to maintain the diversified functions of the body.

With advanced age and under pathological conditions, the cells of the body are frequently not able to provide sufficient energy to maintain physiological functions of the body, despite optimum intake of food. Moreover, several inherited disorders have been identified in which enzymes of the cellular energy metabolism are affected, leading to neurological disorders and other clinical manifestations.

One of these pathological mechanisms that have remained obscure is a deficiency or a lack of bioenergy in the cell. Under physiological conditions the bioenergy of a cell is provided from sugar, proteins and fats that is catabolyzed in the cell. The common pathways of catabolism of food and for the generation of bioenergy in form of ATP are the Tricarboxylic Acid Cycle or Citric Acid Cycle [Krebs Cycle] and subsequent cellular energy pathway, the cellular respiratory chain [Respiratory Chain] as well as the closely connected Urea Cycle.

CONFIRMATION COPY

The basic components of these biochemical pathways have been elucidated and they are summarized in Figure 1-3. While the biochemical structure of these compounds is known, they are currently not used in medicine as preventive and therapeutic agents. I did not find any textbook of medicine recommending the preventive and/or therapeutic use of these compounds for patients.

The possibility of a deficiency of one or more of the Krebs-Cycle, Respiratory Chain and the Urea Cycle compounds are further enhanced by the fact that these biochemical pathways involve a multitude of enzymatic steps. Just recently the first molecular diseases involving an enzyme deficiency of the Krebs-Cycle have been characterized. Genetic disorders for one or more of these enzymes and/or one or more of the coenzymes involved inevitably lead to a deficiency of one or more of the biochemical compounds of these pathways.

Recently, several of the coenzymes (e.g. thiamine, nicotinic acid, ascorbic acid, riboflavin, Mg^{++}) of the Krebs Cycle have been successfully used in the prevention and adjunct treatment of certain health conditions. However the biochemical compounds of the Krebs-Cycle itself, the Respiratory Chain and the closely related Urea Cycle are not.

It has been found (Stumpf et al. Friedreich attaxia: III. Mitochondrial Malic Enzym Deficiency, Neurology 1982; 32: 221-7) that many neuromuscular disorders may have underlying mitochondrial metabolic defects by reduction of mitochondrial malic enzym activity. It has further been found (Walker et al., Journal of Inherited Metabolism Disorder 12 (1989), 331-332; Gellera et al., Neurology 1990, 40 (3 Pt 1): 495-9; Bourgeron et al. Mutation of the fumerase gene in two siblings with progressive enzephalopathy and fumerase deficiency, Journal of Clinical Investigations 1994 June; 93 (6): 2514-8; Narajanan et al., congenital fumerase deficiency presenting with hypothonia and areflexia, Journal of Children Neurologie 1996 May; 11 (3): 252 - 55; Coughlin et al. Molecular analysis and prenatal diagnosis of human fumerase deficiency, Mol. Genet. Meta. 1998 April; 254 - 62; Zinn et al. Abnormalities in succinal purins in fumerase deficiency;) that fumerase deficiency have severe neurological impairment, that fumerase deficiency is an autosomal recessive enzephalopathy affecting both the mitochondrial and the cytosolic enzymes.

It has further been reported that aconitase deficiency and 2-ketogluterate dehydrogenase deficiency and succinate dehydrogenase deficiency may be responsible for neurodegenerative diseases (Drugge J. Med. Genet. 1995 May; 32 (5): 344-7 hereditary myopathy with legtic archdiocese, succinate dehydrogenase and aconitase deficiency; Dunkelman et al. Neuropediatric 2000 February; 31 (1): 35-8; 2 ketogluterate dehydrogenase deficiency with intermittents to ketoglutaric aceturia;). It has been suggested that encephallomyopathy, cardiomyopathy and other neurological disorders may be due to heretical or acquired mutations of DNA encoding enzymes catalyzing intermediate steps in bioenergy metabolism particularly in the Krebs-Cycle, the Respiratory Chain and the Urea Cycle. Many of theses neurological disorders have been found to be lethal.

It is obvious that the above described deficiencies are not limited to neurological orders but reflect the importance of bioenergy metabolism of cells and of deficiencies in the pathways of such metabolism which are the Krebs-Cycle, the Respiratory Chain and the Urea cycle. Deficiencies therein lead to lack of bioenergy which thereby does not cause only neurological effects but is responsible for all kind of human diseases including heart failure conditions. The most common form, idiopathic cardiomyopathy is caused by cellular malfunction of millions of cardiac myocytes. The most frequent cause of this malfunction is an insufficient availability of cellular energy depriving the myocytes of essential energy for the cardiac pumping function.

Therefore there is a need for methods and compositions to prevent and treat malfunctioning of bioenergy metabolism of cells.

Since it has been discovered that genetic defects affecting the Krebs-Cycle and other metabolic energy cycles of cells it seems to be obvious to find means and methods to repair inherited and acquired mutations of genes encoding for enzymes essential for the compensation of deficiencies in the Krebs-Cycle and other metabolic energy cycles. However also gene technology becomes more and more advanced it is still widely theoretic, malfunctioning and possibly causing so far unknown side affects.

On the other hand it seems to be obvious to compensate such deficiencies in bioenergy metabolism by administering such lacking components to the body.

However, since pathways of bioenergy metabolism, particularly the Krebs-Cycle has been discovered a long time ago bioenergy metabolism is a very complex process which takes place in mostly closed systems. In skeletal muscle, the primary role of the tricarboxylic acid cycle is to provide reducing equivalents to the electron-transport chain for ATP-synthesis and to function as a closed cycle with essentially complete oxidation for carbon dioxide of entering carbon skeletons. In the liver the tricarboxylic acid cycle function as an open cycle, with carbon skeletons entering and leaving the cycle at different sides to provide substrates for biosynthetic processes in the mitochondria and cytosol (Zinn et al., Fumerase Deficiency: The new cause of mitochondrial enzephallomyopathy, the New England Journal of Medicine, Volume 315, August 21, 1986).

Thus, deficiencies of the genuine biochemical components of the Krebs-Cycle, Urea Cycle and /or Respiratory Chain are not understood as a causative or contributing factor to the pathology of diseases. Moreover, there is currently no preventive or therapeutic formula known containing combinations of the biochemical compounds of these pathways. Although such deficiencies have been discovered many years ago there seems to be a prejudice to administer compounds to compensate such deficiencies due to the described fact that such cycles are closed or allow only entrances of limited chemical compositions like carbon skeletons.

Surprisingly I have found that certain compositions of compounds compensating enzyme deficiencies in metabolic cycles are able to repair genetic inherited or acquired defects although it is not known in which way such compounds are effective whether they enter such pathways or act in different ways. I have further found that it is not necessary to detect in which intermediate step of such cycles exists a deficiency and therefore compositions of compounds may be used covering possible enzyme deficiencies regardless where such deficiencies exist. Since I use such compositions which have no known side effects compounds which are not needed for compensation are excreted without any harm.

It is therefore the aim of this invention to find compositions and methods to overcome these deficiencies.

This invention features a composition of biochemical compounds involved in bioenergy metabolism of living cells and a method of use in prevention and therapy of diseases and other health conditions in humans and animals.

Since the lack of cellular bioenergy is an important pathological mechanism, there is a need for providing a composition of biochemical compounds involved in the Krebs-Cycle, the Respiratory Chain and / or the Urea Cycle.

This composition of biochemical compounds of these biochemical pathways could provide essential bioenergy molecules that would maintain an optimum level of cellular energy metabolism in the cells and thereby contribute to the prevention and therapy of organ malfunction and diseases.

I have not found any earlier description of such a composition of biochemical compounds nor of their therapeutic use in the scientific literature.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

This invention features the preventive and therapeutic use of biochemical intermediates of the Krebs-Cycle, and /or the Respiration Chain, and/or the Urea Cycle, alone or in combination with biochemical cofactors.

a) The Krebs-Cycle

The biochemical intermediates of the Krebs-Cycle are Citrate, Cis-Aconitate, Isocitrate, Oxalsuccinate, Alpha-Ketoglutarate, Succinyl-CoenzymA, Succinate, Fumarate, Malate, Oxalacetate as well as the biochemical compounds that are immediate precursors of the Krebs-Cycle, namely Acetyl-Coenzyme A and Pyruvate.

Due to the varying importance of these compounds for energy metabolism, they are divided into two categories for the purposes of this invention:

A. Category A (Table 1): Succinate, Fumarate, L-Malate, Alpha-Ketoglutarate.

B. Category B (Table 2): Citrate, Cis-Aconitate, Isocitrate, Oxalsuccinate, Succinyl-CoenzyniA, Oxalacetate as well as Acetyl-Coenzyme A and Pyruvate.

b) The Respiratory Chain

The biochemical compounds of the Respiratory Chain (Table 3) are Coenzyme Q-10 (Ubiquinone), Ubihydroquinone(Ubiquinol), other compounds of the ubiquinone / ubiquinol family of compounds, heme a (part of cytochrome a), herne b (part of cytochrome b) and heme c (part of cytochrome c).

c) The Urea Cycle

The biochemical compounds of the Urea Cycle (Table 4) are Citrulline, Argininosuccinate, Arginine, Ornithine and Aspartate

d) The Cofactors of Cellular Energy Metabolism

The biochemical cofactors of cellular energy metabolism (Table 5) are Lipoic Acid, Lipoamide, Acetyl-Lipoamide, Lysine, Carnitine, Ascorbate, Thiamine, Riboflavin, Nicotinic Acid, Niacinamide, Pantothenate, Nicotinamide-Adenine Dinucleotide (NAD), Reduced Nicotinamide Adenine Dinucleotide (NADH), Nicotinamide-Adenine Dinucleotide Phosphate (NADP), Reduced NADP (NADPH), Quinolinate (NAD/NADP precursor), Flavin-Adenine Dinucleotide (FAD), Reduced Flavin-Adenine Dinucleotide (FADH), Flavin Mononucleotide (FMN), Reduced Flavin Mononucleotide ($FMNH_2$), Adenosine Diphosphate (ADP), Adenosine Triphosphate (ATP), Guanosine Diphosphate (GDP), Guanosine Triphosphate (GTP), Magnesium (Mg^{++}), Calcium (Ca^{++}), Manganese (Mn^{++}), Copper Iron-Sulfate Molybdenum.

The compounds claimed in this patent have broad application in medicine. The compounds claimed in this patent can be used in maintaining and restoring cellular energy to essentially every cell system in the body. Thus, the compounds claimed here can be used for the prevention and therapy of a broad spectrum of diseases in humans as well as animals.

In a first embodiment of compositions chemical substances are claimed which are involved in the bioenergy metabolism of cells of the Krebs-Cyle, the Respiratory Chain and the Urea Cycle, all closely related comprising intermediates of such cycles and precursors and cofactors thereof in case it is not determined at which of the intermediates steps of the cycles such a enzyme deficiency exists.

In a further embodiment biochemical substances of the Krebs-Cycle are claimed as shown in table 1, category A.

In a further embodiment biochemical substances of other intermediate steps of the Krebs-Cycle are claimed.

In a further embodiment biochemical compounds of the Respiratory Chain (Table 3) are claimed including coenzymes.

In a further embodiment biochemical compounds of the Urea Cycle are claimed.

In a further embodiment cofactors which enhance enzymatic reactions of metabolism and their precursors, vitamins and prosthetic groups and enzyme activators are claimed.

Table 1: Krebs-Cycle Compounds Category A

Biochemical Substances	Units	Amount claimed
Succinate	mg	0.001 - 100,000
Fumarate	mg	0.001 - 100,000
L-Malate	mg	0.001 - 100,000
Alpha-Ketoglutarate	mg	0.001 - 100,000

Table 2: Krebs Cycle Compounds Category B

Biochemical Substances	Units	Amount claimed
Pyruvate	mg	0.001 - 100,000
Acetyl-Coenzyme A	mg	0.001 - 100,000
Citrate	mg	0.001 - 100,000
Cis-Aconitate	mg	0.001 - 100,000
Isocitrate	mg	0.001 - 100,000
Oxalsuccinate	mg	0.001 - 100,000
2-Oxo-Glutarate	mg	0.001 - 100,000
Succinyl-CoenzymA	mg	0.001 - 100,000
Oxaloacetate	mg	0.001 - 100,000

Table 3: Cellular Respiratory Chain Compounds

Biochemical Substances	Units	Amount claimed
Coenzyme Q-10 (Ubiquinone)	mg	0.001 - 100,000
Ubihydroquinone (Ubiquinol)	mg	0.001 - 100,000
Heme a (Part of Cytochrome a)	mg	0.001 - 10,000
Heme b (Part of Cytochrome b)	mg	0.001 - 10,000
Heme c (Part of Cytochrome c)	mg	0.001 - 10,000

Table 4: Cellular Urea Cycle Compounds

Biochemical Substances	Units	Amount claimed
Citrulline	mg	0.001 - 100,000
Argininosuccinate	mg	0.001 - 100,000
Arginine	mg	0.001 - 10,000
Ornithine	mg	0.001 - 10,000
Aspartate	mg	0.001 - 10,000

Table 5: Biochemical Cofactors of Cellular Energy Metabolism

Biochemical Substances	Units	Amount claimed
Lipoic Acid	mg	0.001 - 100,000
Lipoamide (Lipoic Acid + Lysine)	mg	0.001 - 100,000
Acetyl-Lipoamide	mg	0.001 - 100,000
Lysine	mg	0.001 - 100,000
Carnitine	mg	0.001 - 100,000
Ascorbate	mg	0.001 - 100,000
Thiamine	mg	0.001 - 100,000
Riboflavin	mg	0.001 - 100,000
Nicotinic Acid	mg	0.001 - 100,000
Niacinamide	mg	0.001 - 100,000
Pantothenate	mg	0.001 - 100,000
Nicotinamide-Adenine Dinucleotide (NAD)	mg	0.001 - 100,000
Reduced Nicotinamide Adenine Dinucleotide (NADH)	mg	0.001 - 100,000
Nicotinamide-Adenine Dinucleotide Phosphate (NADP)	mg	0.001 - 100,000
Reduced NADP (NADPH)	mg	0.001 - 100,000
Quinolinate (NAD/NADP precursor)	mg	0.001 - 100,000
Flavin-Adenine Dinucleotide (FAD)	mg	0.001 - 100,000
Reduced Flavin-Adenine Dinucleotide (FADH)	mg	0.001 - 100,000
Flavin Mononucleotide (FMN)	mg	0.001 - 100,000
Reduced Flavin Mononucleotide ($FMNH_2$)	mg	0.001 - 100,000

Adenosine Diphosphate (ADP)	mg	0.001 - 100,000
Adenosine, Triphosphate (ATP)	mg	0.001 - 100,000
Guanosine Diphosphate (GDP)	mg	0.001 - 100,000
Guanosine Triphosphate (GTP)	mg	0.001 - 100,000
Magnesium (Mg^{++})	mg	0.001 - 100,000
Calcium (Ca^{++})	mg	0.001 - 100,000
Manganese (Mn^{++})	mg	0.001 - 100,000
Copper	mg	0.001 - 1,000
Iron-Sulfate	mg	0.001 - 1,000
Molybdenum	mg	0.001 - 1,000

mg = milligrams

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A composition of chemical substances involved in the bioenergy metabolism of cells by the Krebs-Cycle, the respiratory chain and the Urea Cycle comprising one or more of the intermediates of the cycles and/or precursors and cofactors thereof for the improvement of cellular energy metabolism.

2. A composition of two or more of the following biochemical substances Succinate, Fumarate, L-Malate, Alpha-Ketoglutarate - irrespective of their amounts - for the improvement of cellular energy metabolism.

3. A composition of two or more of the following biochemical substances Citrate, cis-Aconitate, Isocitrate, Oxalsuccinate, Alpha-Ketoglutarate, Succinyl-CoenzymA, Succinate, Fumarate, L-Malate, Oxalacetate, Acetyl-Coenzyme A and Pyruvate - irrespective of their amounts - for the improvement of cellular energy metabolism.

4. A composition of two or more of the following biochemical substances Coenzyme Q-10 (Ubiquinone), Ubihydroquinone(Ubiquinol), other compounds of the ubiquinone / ubiquinol family of compounds, heme a (part of cytochrome a), heme b (part of cytochrome b) and heme c (part of cytochrome c) - irrespective of their amounts - for the improvement of cellular energy metabolism.

5. A composition of any or all of the following biochemical compounds Citrulline, Argininosuccinate, Arginine, Ornithine and Aspartate - irrespective of their amounts - for the improvement of cellular energy metabolism.

6. A composition accordingly to claim 1 - 5 further comprising of any or all of the following biochemical compounds Lipoic Acid, Lipoamide, Acetyl-Lipoamide, Lysine, Carnitine, Ascorbate, Thiamine, Riboflavin, Nicotinic Acid, Niacinamide, Pantothenate, Nicotinamide-Adenine Dinucleotide (NAD), Reduced Nicotinamide Adenine Dinucleotide (NADIJ), Nicotinamide-Adenine Dinucleotide

Phosphate (NADP), Reduced NADP (NADPH), Quinolinate (NAD/NADP precursor), Flavin-Adenine Dinucleotide (FAD), Reduced Flavin-Adenine Dinucleotide (FADH), Flavin Mononucleotide (FNIN), Reduced Flavin Mononucleotide ($FMNH_2$), Adenosine Diphosphate (ADP), Adenosine Triphosphate (ATP), Guanosine Diphosphate (GDP), Guanosine Triphosphate (GTP), Magnesium (Mg^{++}), Calcium (Ca^{++}), Manganese (Mn^{++}), Copper Iron-Sulfate Molybdenum - irrespective of their amounts - for the improvement of cellular energy metabolism.

7. A composition of biochemical substances according to claims 1-6 where this composition is provided to a patient in form of tablets, pills, injections, infusions, inhalations, suppositories or other pharmaceutically acceptable carriers and/or means of delivery.

8. A composition of biochemical substances according to claims 1-7 where the dosage of each of the biochemical substances chosen for the composition is sufficient to exert a preventive and / or therapeutic effect but below the level where it would cause side-effects.