



Disclosure of the major causes of mental illness—mitochondrial deterioration in brain neurons via opportunistic infection

Katsunari Nishihara^{*,1}

President of the Nishihara Institute, Hara Bldg 3F, 6-2-5 Roppongi, Minato-Ku, Tokyo, Japan

In conventional medicine psychoses are accepted to be quite different maladies from common intractable immune diseases, carcinomas or infectious maladies. From the viewpoint of cellular respiration of mitochondria, the author has investigated aging as well as malady conditions of cerebral neurons, hypothesizing them to be due to mitochondrial deterioration in neurons via intracellular infection by nonpathogenic common enteromicrobes induced by some anomalous energy (temperature) condition in the gut. By such intracellular infection, at first protein synthesis in the cytoplasm is disturbed, which induces mitochondrial mutation or other anomalies. Consequently, disturbance of the metabolic pathways of biogenic amines in mitochondria occurs, engendering the characteristic symptoms of psychoses. Integrating biomechanics, molecular biology, physiology, developmental morphology and clinical therapeutic research, the author reveals that psychoses are mere organ (brain neuron)-specific immune diseases, viz., intracellular infection via nonpathogenic common enteromicrobes, which bring about mitochondrial deterioration concomitant with the disturbance of monoamine metabolism in brain neurons. This paper also discusses the essential mitochondrial function of cellular life activity, namely remodelling to overcome aging.

Keywords: energy metabolism, intracellular infection, intractable immune disease, mitochondrial deterioration, monoamine, negative feedback regulation system, opportunistic infection, psychosis

1. INTRODUCTION

The author recognizes that cerebral neurons are originally constructed from the same cellular components and genes as those of other visceral epithelial as well as mesenchymal stem cells. Therefore, from the viewpoint of mitochondrial energy metabolism the living function of neurons is the same as that of other visceral as well as somatic organ cells, even though their specific function (transmitting neural impulses) is quite different from other organ cells. The brain neurons, fibroblasts in subcutaneous tissue as well as osteoblasts and intestinal chorioepithelial cells have been derived from a fertilized egg. Therefore, all cytoplasmic nucleic diploid genes as well as mitochondrial haploid genes in these cells are originally the same. Healthy mitochondrial function is a *sine qua non* for vivid cells. Therefore, all kinds of mitochondrial deterioration induce anomalies in metabolism, disturbing cell remodelling to overcome aging.

The author started research on “Disclosing causes and mechanism of development of mitochondrial mutation using yeast”, inducing respiration-deficient petite mutants by means of applying antibiotics for bacteria as well as for eukaryotes, based on his PhD thesis. After that he investigated not only the essential rôle of mitochondria in mammals but also the direct influence of environmental

energy upon animal cellular life activity. He also introduced the concept of environmental energy as well as mitochondrial energy metabolism into conventional life science and medicine, and showed how morphology, physiology, molecular genetics, biomechanics, bacteriology, virology, and clinical therapeutic medicine can be integrated to cure intractable immune maladies. The major causes of immune diseases were disclosed as being brought about by intracellular infection of nonpathogenic common enteromicrobes due to absorbing improper environmental energies. Through controlling environmental energy as well as intracellularly infecting common enteromicrobes, it has been shown that these maladies of intractable immune diseases, including psychoses and carcinoma, occur by *deterioration of mitochondrial function* via these microbes.

The author has shown that the major cause of mitochondrial mutation can be induced by cycloheximide, i.e. an inhibitor of cytoplasmic protein synthesis in eukaryota. The life system of higher mammals depends upon perfect mitochondrial function at the cellular level. For 60 years it has been well known that in a mental patient’s brain neurons malfunction; disorders of monoamine oxidase and in monoamines and amine-similar acetylcholine are observed, which are inside the

* E-mail: nishihara-ken@a.email.ne.jp

¹ President of the Japanese Association for Genuine Clinical Immunology.

mitochondrial membrane. Monoamines comprise several kinds of amino acid derivatives, viz., serotonin, noradrenaline, dopa, and dopamine as well as acetylcholine—the major neurotransmitters. *Mitochondria are the most important organelles in the mammalian life system.* Also, it is well known that in hepatic cells of alcoholics, infected leukocytes as well as organ cells intracellularly infected with rickettsia, mycoplasma, chlamydia and viruses, and mitochondrial mutation, dysfunction or morphological disorders are observed.

The author has deduced that the causes of mitochondrial deterioration can be ascribed to the following six items, each of which gives rise to functional disturbance of cell respiration in various organ cells, which in turn brings about specific functional disturbance of highly differentiated organ cells: (1) toxic substances, agricultural chemicals or insecticides; (2) improper nutrition (malnutrition) including lack of coenzymes and minerals, oxygen and water; (3) environmental energy anomalies, e.g. cold and hot stimuli, low atmospheric pressure, overloading by gravity, and chronic fatigue of mitochondria due to excessive movement; (4) infection by microbes, especially intracellular contamination (including by nonpathogenic enteromicrobes); (5) incompatible transplantation; and (6) biological energy anomalies associated with religion, spirituality and fear. It is obvious at subcellular levels that maladies can be induced by the deteriorated condition of mitochondria via the influences thus itemized. It follows that maladies can occur at the cellular level in all organ or tissue cells in the whole body via the blood circulation of granulocytes (leukocytes), which contain the deteriorated mitochondria. Dissemination into cerebral neurons is especially undesirable (Nishihara 2008b, 2009a).

2. DISCLOSURE OF THE MAJOR CAUSES OF MITOCHONDRIAL MUTATION BY MEANS OF MOLECULAR BIOLOGY

In today's clinical medicine, not only in mitochondrial diseases but in various immune diseases, mitochondrial mutations are commonly reported. The causes of these mutations are considered to be the effects of oxygen free radicals generated during the mitochondrial function of oxidative phosphorylation. However, the author is sceptical about this concept. The theme of his PhD thesis, written (in Japanese) about 40 years ago, was "Disclosure of Major Causes of Mitochondrial Mutation by Means of Molecular Biology". Only recently were some papers published in English on this topic (Nishihara, 2008b, 2009a). Part 1 of the thesis aimed to reveal the mechanism of mitochondrial mutation, deformities and deterioration in diseased cells. The author carried out the following model experiments using yeast (*Saccharomyces*

cerevisiae): (1) Development of a respiration-deficient strain using an inhibitor of protein synthesis in the cytoplasm (cycloheximide) and of mitochondria (chloramphenicol) in culture; (2) Measurement of the activities of mitochondrial DNA and RNA synthesis *in vitro* during development of the respiration-deficient strain. Part 2 concerned the interaction between nuclei and mitochondrial genes during the development of mitochondria. To reveal the developmental mechanism of mitochondrial mutants the author carried out molecular biology experiments using wild strains of yeast and several respiration-deficient strains of different genotypes, in which he observed *in vitro* the synthesis of DNA polymerase and RNA polymerase of mitochondria. Part 3 dealt with mitochondrial genes: observation of the activities of yeast mitochondrial ATPase with the administration of cycloheximide; cytoplasmic protein synthesis was measured.

From the experiments of Part 1 the following results were obtained: (i) using cycloheximide, a respiration-deficient strain (i.e., petite mutant) could be obtained at a high rate; (ii) using chloramphenicol, no marked development of a respiration-deficient strain was obtained; (iii) using streptovaricin, no marked development of a respiration-deficient strain was obtained; (iv) in yeast cultured in cycloheximide-containing medium, decreased activities of mitochondrial DNA polymerase, and no activities of mitochondrial RNA polymerase, were observed; (v) in yeast cultured in chloramphenicol-containing medium, markedly increased activities of mitochondrial DNA as well as of mitochondrial RNA were observed. From these results the author concluded that the petite (respiration-deficient) mutant can be developed by an inhibitor not of mitochondrial but of nucleic cytoplasmic protein synthesis, which would disturb mitochondrial DNA polymerase as well as RNA polymerase synthesis in the cytoplasm.

From the experiments of Part 2 (measurement of DNA/RNA synthesis) the following results on specific activities of wild-type strain and strains with mitochondrial mutation were obtained: (i) DNA synthesis of epistatic mutant 5d was extremely high; (ii) lowering of RNA synthesis was observed with 5d and segregational mutant 431; (iii) extreme inhibition by the operation of chloramphenicol and cycloheximide in RNA synthesis was observed with mutant 431. It was inferred from these results that the developmental mechanism of mitochondrial mutation was a disturbance of mitochondrial DNA and RNA polymerase due to cycloheximide.

From the experiments of Part 3 the following results were obtained: (i) inhibitor did not show any difference from that of the control; (ii) activities of yeast mitochondrial ATPase with administration of

chloramphenicol showed evident lowering; (iii) activities of yeast mitochondrial ATPase with administration of ethidium bromide showed evident lowering. With the above results, an interpretation would be allowed that coupling factor F1 (ATPase) is controlled by mitochondrial genes, and that its genetic information is translated by the protein synthesis system of mitochondria.

By revealing the functions of mitochondrial genetic information, it is expected to obtain clues to determine whether the morphological transformation of mitochondria in diseased or cancerous cells is derived from the disturbance of synthesis of DNA polymerase and RNA polymerase of mitochondria, which are encoded in nuclear genes. From these model experiments using yeast, one of the causes of respiration-deficient mutants was shown to be a disturbance of DNA polymerase as well as of RNA polymerase of mitochondria due to cycloheximide. After clinical studies to cure intractable immune diseases, instead of cycloheximide tremendous numbers of intracellularly infected nonpathogenic enterobacteria or viruses would induce severe disturbance of protein synthesis in the cytoplasm (Nishihara, 2009a). Hence, the author proposes that the major cause of intractable immune disease and mental illness is a result of mitochondrial deterioration due to entangled, complicated intracellular contamination by low virulence pathogenic as well as nonpathogenic common enteromicrobes such as viruses, mycoplasma, rickettsia, chlamydia and/or bacteria in various organ cells and in neurons.

3. THE ESSENTIAL ROLE OF MITOCHONDRIA AND INTRACTABLE DISEASES INCLUDING PSYCHOSES

The author proposes that the essence of living phenomena is the system of remodelling, which is closely connected with energy metabolism; with that, the living system can overcome aging. In conventional medicine, the essential rôle of mitochondria in human body cells has been almost completely overlooked. Mitochondria, having their own haploid genes, are presumed to be derived from the archetypical prokaryote; therefore, they can be seen as a relic of aerobic archaea. Prokaryotes generate energy for their own life system; however, multicellular eukaryote mammals generate 90% of their life energy in mitochondria and only 10% by glycolysis in the cytoplasm (Lehninger, 1964). By glycolysis, glucose is resolved into pyruvates, which are metabolized through the TCA (Krebs) cycle in mitochondria for *de novo* synthesis of ATP. Without mitochondrial energy metabolism the life system of mammals could not exist.

Multicellular mammalian life, which is integrated as a unified system, is completely dependent upon tremendous numbers of mitochondria in the 60×10^{12} cells in the body.

In order to more deeply understand health, maladies and the lifespan of mammals, consideration of the mitochondrial condition in all the cells is an ineluctable necessity. Surveying the human history of overcoming contagious and infectious diseases as well as the history of transition in therapeutic medicine applied to modern maladies, the present author has revealed that intractable immune diseases, including psychiatric disorders and carcinomas, are severe cases of maladies that have been known for 50 years as opportunistic infections or autotoxic diseases, histiocytosis, granulomatosis or sarcoidosis, which have been brought about by nonpathogenic common enteromicrobes, which usually infect intracellularly. Clinical research revealing and curing "intractable" immune diseases has already been reported in several papers by the present author (Nishihara, 2008a; 2009a, b). In conventional medicine very few clinicians pay attention to mitochondrial diseases or mitochondrial dysfunction, of which mitochondrial mutation might be the initial observable in diseased cells.

The life system of cells in mammals depends completely upon mitochondrial ability. Consequently mammalian health and aging as well as lifespan depend completely upon the condition of the mitochondria, whether healthy or deteriorated. Rickettsia, mycoplasma and chlamydia are contemporary living bacteria that resemble the archaic type of bacteria or mitochondria. They live solely as parasites in the cytoplasm of mammalian cells, just like mitochondria. Therefore, they can only infect intracellularly via leukocytes (granulocytes). Intracellularly contaminated granulocytes disseminate these bacteria into tissue or organ cells. These bacteria and viruses are so weakly toxic that they can infect intracellularly without apparent effect, which explains why in recent basic medicine, despite its embracing of bacteriology, virology and pathology, as well as in clinical therapeutic medicine, no one has considered intracellular infection by nonpathogenic common enteromicrobes, although they have been known as opportunistic infections for 50 years. In contrast, infections by pathogenic microbes are so toxic that when they contact an animal medium, maladies ensue immediately. Nevertheless, following intracellular infection by common enterobacteria mitochondrial deterioration occurs in various tissue or organ cells. From clinical therapeutic studies for intractable immune diseases (including psychiatric disorders and carcinomas), the author considers human diseases and healthy life as well as aging from the viewpoints of energy, biomechanics and mitochondrial deterioration (Nishihara and Tanaka, 1996; Nishihara, 1997; Tache and Morley, 1989, 1999, 2000, 2001, 2003a,b, 2004b, 2005, 2006, 2007a,b).

4. THE OVERALL SYSTEM IN MAMMALIA TO CONTROL MITOCHONDRIA IN WHOLE CELLS DIRECTLY

There should be special acceptors as well as regulators in multicellular organisms, especially mammals, which control energy metabolism over all cells in the body. The special supervising acceptors for systemic energy metabolism in whole cells in mammals are the suprarenal glands, which are themselves supervised by the hypophysis. The suprarenal glands secrete adrenaline as well as mineral- and glyco-corticosteroid hormones, which control mitochondrial energy metabolism in whole cells. The control of mitochondrial metabolism in whole cells is the most important system in mammals. The accepting apparatuses for the outputs of these hypophysis–suprarenal gland systems comprise the whole sensory organs of the somatic system, the whole gut visceral system (via the epithelial body), all kinds of hormonal glands, the thymus, Waldeyer's lymph–adenoid rings, gut-associated lymphoid tissue (GALT), and whole cells (except erythrocytes) in the body. The hypophysis secretes not only an adrenocorticotrophic hormone but various other kinds of hormone as well as cytokines and growth factors, as a regulator responding to the total stimuli influencing the living energy system of an animal.

Selye thought that there must be a close direct correlation between the immune system and the central nervous system because the hypophysis is a part of the limbic system of the cerebrum. However, the immune system incorporates cellular digestion as well as a remodelling system conjugated with the energy metabolism of mitochondria. The limbic system is a structural anatomical system. All neurons in the central nervous system also have their own cellular remodelling system (i.e., the cellular digestion system, namely, the immune system). Therefore, there is no correlation between them directly, but via the stimuli conversion system of nucleic neurons in the hypothalamus of the limbic system, by which total information from inside the body or outside is integrated in the cerebrum through the reticular formation via the central nervous system. Subsequently, the neurons of the limbic system secrete neurotransmitters, hormones, cytokines and growth factors and transfuse them to the hypophysis via axons (Nishihara, 2006). What are these total stimuli impinging on the animal? They are entities without mass (i.e., energy) and substance with mass (including oxygen, nutrition, parasitic microbes and toxins). Energy stimuli include heat and cold, thermal gradients and atmospheric pressure, light and electromagnetic waves, sound, moisture and biological energy (i.e., emotion, religion, spirituality, fear and wickedness).

Besides the acceptors and the common energy sensors mentioned above, mammals also have receptors

and incorporate organs of the branchial, respiratory and digestive gut systems of substance with mass, namely nutrition from foods, toxins, parasitic microbes (namely viruses, mycoplasma and bacteria) parasites, toxic proteins and amines. These receptors are the gut absorbing system and tonsilla or lymph–adenoid tissue and thymus, Peyer's patch, epithelial body, cervical sinus, hypophysis and suprarenal glands, which are almost all derived from branchial organs, and the gut–visceral system. The above-mentioned concept of receptors (acceptors) and regulators has been overlooked by conventional research. The hypophysis and suprarenal glands are acceptors not only for pressure, thermal stimuli, light and sound, but also for various kinds of substances with mass (e.g., parasitic viruses and bacteria as well as toxins). Peyer's patch is the acceptor for proteins, amines, toxins, viruses and bacteria. For the gut–visceral system, not only sensors for energy, namely the eye, ear and skin, but also the sensors associated with acceptors for substance with mass, namely the sensor of smell, the tongue, taste buds, hypophysis, thymus, GALT and suprarenal glands, which also constitute the incorporation system of nutrition and chemical substances, as well as viruses, bacteria and all other sensors, are subordinate to the gut–visceral system. The hypophysis and suprarenal glands, as well as the cervical sinus, are also receptors of energy. Conventionally, sensory organs are considered to be limited to capturing energy. However, all entities, with or without mass, entering the body from outside are accepted as well as absorbed and acknowledged by the somatic or visceral organs and transmitted through the nervous system as well as the bloodstream system over the whole body's organs and cells.

5. HUMAN-SPECIFIC INTRACTABLE IMMUNE DISEASES—THE HYPOTHESIS OF MITOCHONDRIAL DETERIORATION, ESTABLISHMENT OF THE MITOCHONDRIA-ACTIVATING THERAPEUTIC METHOD (MATM), AND DIAGNOSIS *EX JUVANTIBUS*

The present author has confirmed from clinical research that upon cooling the gut by just 1 °C from 37 °C, intracellular infection of leukocytes occurs via M cells in Peyer's patch, which develop into granulocytes. Granulocytes contaminated with numerous bacteria circulate in the whole body, disseminating bacteria into various organ cells, resulting in intracellular infection of these organs. The author hypothesizes that these intractable immune diseases are not autoimmune diseases but severe cases of formally accepted opportunistic infections, which are caused by intracellular infection by common nonpathogenic enteromicrobes (Nishihara, 2006). Contaminated granulocytes from the pus of periodontitis, the sputa of lung diseases or the sedimentation of the urine

of nephritis contain numerous moving bacteria, as can be observed highly magnified ($\times 2000$) in the light microscope. These intracellular infections deteriorate as well as mutate mitochondria, and result in functional disturbances of specialized organs, which appear to be immune diseases. The author hypothesizes that human-specific intractable immune diseases are severe cases of opportunistic infections or autotoxic diseases caused by intracellular infection of common nonpathogenic enterobacteria and/or enteroviruses as a result of lifestyle changes.

The author also hypothesizes that by intracellular infection of common enterobacteria and/or enteroviruses mitochondrial deterioration and mutation in the cytoplasm takes place. Subsequently, the author verified the intracellular infections of common enterobacteria, observing leukocytes as well as epithelial cells obtained from sedimentation of sputa of lung diseases or urine of nephritis using highly magnified ($\times 2000$) light microscopy or transmission electron ultramicroscopy (TEM). With these hypotheses and understanding, the author established the mitochondria-activating therapeutic method (MATM) (Nishihara, 2007a) to cure those diseases by means of prevention and recovery from intracellular infections in conjugation with nose breathing during sleep as well as warming the gut, recovering bone rest time by lying down, moderate eating and drinking with optimal mastication, treating periodontitis, optimal exposure to sunshine by sunbathing, and by administering suitable bifidus factors, effective antiviral agents as well as antibiotics. By these MATM remedies intracellularly infected microbes are controlled, mitochondrial mutation and/or deterioration are easily countered and the specific functions of specialized organ cells are restored completely. In most of the cases, the patients who had been diagnosed with intractable immune diseases in authorized hospitals showed evident recovery by these curative methods. From the complete cures of intractable immune diseases, namely complete recovery of deteriorated mitochondria in diseased cells via these MATM remedies, the hypotheses are verified as diagnosis *ex juvantibus*; i.e., diagnosis based on the results of treatment (Nishihara, 2009a). If intracellular infection occurs in some organ, the function of the cells of the organ deteriorates because of the dysfunction of mitochondria caused by contaminating bacteria or viruses. This is an immune disease (Nishihara, 2004a). These intracellular parasites of specific cells hinder the energy metabolism of mitochondria, leading to deterioration of organ function and to intractable immune diseases. Immune diseases hinder cellular renewal (remodelling), which is conjugated with the faculty of energy metabolism of mitochondria, which is a major cause of cellular aging.

The causes of most immune diseases are a deterioration of the mitochondrial function by various energies as well as by intracellularly-infected bacteria or viruses; that is, parasites. Intracellular contamination of specially differentiated cells (e.g., neurons or hormonal glands) by parasitic microbes of the gut, regardless whether aerobic or anaerobic, disturbs the specialized function of mitochondria. This is the immune disease condition at the subcellular level (Nishihara, 2004a). Cytoplasmic protein synthesis would be disturbed via intracellular infection instead of cycloheximide, which is an inhibitor of protein synthesis of eukaryotae, consequently mitochondrial mutation as well as deterioration occur (Nishihara, 2008b).

6. CHARACTERISTIC SYMPTOMS OF PSYCHOSIS

Psychoses are commonly accepted as quite different kinds of maladies compared with immune diseases, carcinoma, and infections because of quite different symptoms or syndromes. However, from the viewpoint of investigating maladies at the subcellular level, viz., mitochondria-based pathology, mental illness is a similar pathological condition to other immune diseases or carcinomas. Then, what is the difference of their symptoms and syndromes from other maladies? The answer is quite simple: the symptoms depend exclusively upon disturbed characteristic functions of cerebral neurons and glia; that is, neural cells and their relatives in the brain, which have been disturbed, exhibiting special symptoms when intracellular infection in cerebral neurons by common enteromicrobes occurs. In common immune diseases (e.g., intracellular infection of Langerhans cells in the pancreas), specialized cytokine insulin synthesis is disturbed by enteromicrobes. As a result, insulin deficiency occurs.

In atopic dermatitis, various kinds of mesenchymal cells in subcutaneous tissue are contaminated by enteromicrobes, intracellular inflammation occurs, and the electron-transmitting system of mitochondria is disturbed by bacteria, producing incomplete metabolites, which induce itching and aching. The actual condition of atopic dermatitis is intracellular infection in ectodermal epithelial and subcutaneous cells. Mental illness is just the same infection as in neurons (which are derived from ectodermal epithelial cells and subepithelial glia cells). Therefore, the diseases of atopic dermatitis and mental illness are quite similar but also quite different in symptoms and syndromes. In some severe cases of atopic dermatitis, schizophrenia is often concurrent. The therapeutic methods are rather similar. The present author has treated and cured so many cases of mental illness. All stimuli affecting creatures (e.g., neural and physicochemical, nutritional, toxic, bacterial and parasitic), as well as psychological stresses, are transmitted through the

thalamus into the hypothalamus by means of the neuromuscular system and via the cardiovascular system through the choroid plexus, which is composed of ependymocytes and pia mater, in which there are no blood–brain barriers. These stimuli are transmitted to the nuclei of the hypothalamus.

There, in neurons of nuclei neural stimuli are then converted into hormones, cytokines and growth factors, which are the direct control system of intracellular respiration of mitochondria in 60×10^{12} cells. They are carried through the axon to the portal vein in the anterior lobe of the hypophysis and are delivered to all systemic hormonal organs. After that, the intermediary informational substances (hormones, cytokines and growth factors as well as nutrition) are delivered over the whole body to mitochondria in these cells. This is the hypophysis–systemic hormonal system. All metabolism based on cellular respiration in all cells, each having 800~3,000 mitochondria, are directly controlled by the intermediaries, namely the humoral information system of hormones, cytokines, growth factors, nutrition, and toxins as well as parasitic microbes.

7. HYPOTHESIS CONCERNING THE CAUSES OF INTRACTABLE PSYCHOSES

In conventional medicine it is well known that in cerebral neurons, in cases of major mental illness (patients of depression and schizophrenia as well as dementia), deficiency of monoamines (i.e., serotonin and adrenaline), a surplus of dopamine, and lack of acetylcholine (monoamine-resembling chemicals) are commonly observed. These phenomena imply that in these patient's cerebral neurons, metabolic disorders or dysfunction in monoamines as well as in acetylcholine occur. Many researchers have recognized these facts since several decades ago. However, no one considers why these disorders occur. Several kinds of neurotransmitters are derivatives of amino acids, which are metabolized not only by mitochondria, but also by intracellularly infected bacteria. The present author has hypothesized (Nishihara, 2009a) that by intracellular infection of cerebral neurons via opportunistic infection by nonpathogenic enteromicrobes, disorders in metabolic pathways for monoamines as well as acetylcholine and other biogenic amines take place.

Mitochondria as well as bacteria are good at monoamine metabolism. Therefore, if intracellular infection of common enteromicrobes easily occurs in cerebral neurons, various kinds of mental illness can easily occur, and the name of a disease is decided according to the site of the supposedly relevant brain neurons. Brain neurons are the “muscle system”, and through muscle movements calculations and thinking come into existence.

Therefore, if an infant exhibits febrile convulsions, he likely has an intracellular infection by enteromicrobes in cerebral neurons. The present author has also disclosed, as mentioned above, through developmental research on the hypophysis, the origin of which is derived from oral mucosa, that the common enteromicrobes in oral as well as in Waldeyer's adenoid tissue can enter by granulocytes through the hypophysis, pituitary glands or choroid plexus, which have no blood brain barrier, or the supra-hypophysis artery, which continues to the hypophysis portal vein into the cerebrospinal fluid. Consequently, granulocytes disseminate them into neurons. In vivid, vital cells, regardless of any kind of specifically differentiated cells, too many kinds of metabolic pathways in mitochondria are working.

In brain neurons the monoamine metabolic path is well functioning in a healthy condition. However metabolic maps of mitochondria in opportunistically infected neurons are completely disturbed. For example, considering the metabolism of monoamines, tyrosine is transformed into dopa, dopamine, noradrenaline and adrenaline and tryptophan is transformed into serotonin under normal conditions. However, if neurons are contaminated with large numbers of bacteria (several thousands) or viruses (several hundreds of thousands)—that is, comparable to the population of mitochondria—the monoamine metabolic path deteriorates and the amounts of dopa and dopamine become unstable. Neurotransmitters noradrenaline or adrenaline become oxidized or hydroxidized into amphetamine or methamphetamine, which is a stimulant. The mental illness induced by intracellular infection by common enteromicrobes (typically facilitated by ice-cream ingestion, mouth breathing during sleep, nonstop speaking and bone rest shortage due to short slumber), characterized by hallucination or auditory hallucination, is caused by deficient mitochondrial function of the infected cells. The metabolism of the neurotransmitter serotonin is disturbed by contaminating enteromicrobes, one consequence of which is that serotonin changes into hallucinogenic LSD.

8. DISCLOSURE OF THE CAUSES OF PSYCHOSES, INCLUDING PSYCHOSOMATIC DISORDERS

In conventional medicine we have had a serious issue concerning psychoses, including psychosomatic disorders, dementia, schizophrenia, manic depressive, epilepsy, migraine, neurosis, mental retardation, paracenesesthesia, and/or cenesthopathy. Even though many histopathological studies have been conducted, few traces of contamination of microbes in cerebral neurons have been reported. Clinically, it is well known that meningitis, encephalitis, febrile convulsion and epileptic convulsion easily take place, especially in children, by some kind of viral or

bacterial infection. The author discloses the mechanism of intracellular infection in brain neurons from the viewpoint of development of the frontal lobe of the hypophysis, which is derived from the Rathke's pouch, the upper floor of the primordial oral cavity. From the hypophysis, pineal gland and choroid plexus contaminated leukocytes spread through suprahypophysis arteries, as well as vertebral arteries allowing nonpathogenic common enteromicrobes in the contaminated leukocytes to enter into the cerebrospinal fluid. Therefore, cerebritis is induced quite easily by contaminated leukocytes, which enter into the cerebrospinal fluid in the brain, because the hypophysis has no blood-brain barrier to shut out microbes containing leukocytes.

The central nervous systems is constructed from neurons, neuroglia and a tremendous network linking them. The brain is the muscle movement system with various kinds of sensory organs. All stimuli (i.e., energy and substance with mass) are concentrated into the hypothalamic nuclei of neurons via the reticular formation of the medulla oblongata. In the reticular formation there are noradrenergic, cholinergic, dopaminergic and serotonergic neurons, which comprise a neural network covering all brain regions. All stimuli come from the eyes, ears, nose, tongue, skin and gut, as well as gravity, moisture, the atmosphere and stimuli of substance with mass (i.e., nutrition, toxic matter and others). These are transmitted through axons and other networks into nuclei in the hypothalamus via the nuclei in the reticular formation, in which neurons, hormones, cytokines, growth factors, neurotransmitters and others are generated by means of the stimuli conversion system of mitochondria. In the diencephalon in the limbic system there are the hypothalamic nuclei of neurons, which activate, control and integrate the peripheral automatic mechanisms, endocrine activity, and many somatic functions, e.g., a general regulation of water balance, body temperature, sleep and food intake, and the development of the secondary sex characteristics; the axons continue to the hypophysis pendent on its floor.

If intracellular infections occur in the hypothalamic nuclei, by common enteromicrobes with no pathogenicity, psychophysiological disorders (e.g., anorexia nervosa, polyphagia, and insomnia) arise, which are considered intractable in conventional medicine. If they occur in the nuclei of reticular formation, panic disorder, hyperventilation syndrome and/or cardiac neurosis take place. These infections can only occur via granulocytes thorough the portal vein of the hypophysis, where no blood-brain barrier exists. Roughly speaking, monoamine (i.e., serotonin, noradrenaline and dopamine) deficiency induces depression and dopamine excess induces

schizophrenia and manic sensations. Therefore, it is reasonable that if intracellular infection occurs in serotonergic, noradrenergic and/or dopaminergic neurons, depression takes place. In case of dopamine excess, also induced by intracellular infection in dopaminergic neurons, manic disorders or schizophrenia takes place. Both are treated by means of effective antibiotics as well as antiviral agents concomitant with serotonin-dopamine antagonists or selective serotonin reuptake inhibitors (Nishihara, 2009b).

9. PSYCHOSES VIA MITOCHONDRIAL DETERIORATION IN CEREBRAL NEURONS BY INTRACELLULAR OPPORTUNISTIC INFECTIONS

The author proposes that the cause of mental illness is an intracellular infection of nonpathogenic enteromicrobes in cerebral neurons (just like intractable immune diseases in other organs or tissues), which brings about the deterioration of mitochondrial functions. Mitochondria metabolize biogenic amines in healthy neurons; however, intracellularly infected microbes in neurons disturb the normal amino acid metabolic processes. This condition leads to psychoses. All specifically differentiated cells have their characteristic functions, which are supported by their mitochondria. Brain neurons are categorized as a tremendous system of specialized neurons and several kinds of neuroglia in various regions of the cerebrum (the limbic system, the thalamus, the hypothalamus, the cerebral cortex and the cerebellum). However, it is well known that in all cases of mental illness, disorders in monoamine oxidases, which are located on the membrane of mitochondria, take place. Monoamine neurotransmitters in brain neurons are serotonin, noradrenaline, adrenaline, dopa, dopamine, glutamic acid, glycine and GABA (γ -amino butyric acid). Besides them there are cholinergic transmitters as well as adenosine and peptides. From several kinds of amino acids, biogenic amines are changed by decarboxylation into neurotransmitters. Therefore, some kinds of biogenic amines are physiologically especially important. From choline, glycine is produced and glycine is essential for mitochondrial reproduction. GABA is produced from glutamic acid by decarboxylation, and dopa, noradrenaline and adrenaline are produced from the amino acid tyrosine. Serotonin is produced from tryptophan. The metabolism of amino acids or biogenic amines is carried out by mitochondria in normal cells and they are a strong point target for bacteria. Therefore, if intracellular infection by common enterobacteria occurs their metabolism is easily disturbed and a decrease or increase of dopa or dopamine occurs in the cytoplasm of neurons; these conditions may be considered as psychosis and mental illness at the cellular

level. If adrenaline changes into amphetamine or methamphetamine in the cytoplasm due to intracellularly contaminated enterobacteria, hallucinations occur (Nishihara, 2009b).

10. FINAL DISCUSSION AND CONCLUSION

The author has elucidated the essential entities of mental illness, which have a tremendous variety of symptoms, including loss of logical thinking and behaviour, uncontrollable convulsions and/or hallucinations, brought about by intracellular infection of cerebral neurons via common enteromicrobes without pathogenicity. These microbes quite resemble the mitochondria, which have been parasites in the cytoplasm of eukaryotae for $ca 2 \times 10^{10}$ years. By intracellular infections in eukaryotic mammalian neurons via nonpathogenic microbes (i.e., mitochondria-resembling bacteria and low-virulence viruses) at first protein synthesis is disturbed, which induces mitochondrial mutation or anomalies, consequently disturbance of the metabolic pathway of monoamines takes place, which give rise to the characteristic symptoms of psychoses. Hallucinogens and stimulants are produced by oxidation or hydroxylation of monoamines by intracellularly parasitic enterobacteria.

Methamphetamine and amphetamine, stimulants developed from adrenaline and LSD, are turned from serotonin to the hallucinogens also via parasitic enteromicrobes. The control centre of the substance-distributing system (distributing substances in blood and lymphofluid into cells) is the direct regulation system of mitochondria in whole body cells. This control centre is the hypophysis–systemic humoral system. Dysfunction of this system by intracellular infection or by toxic substances or malnutrition (e.g., a complete lack of vitamins B or C), or by improper energy absorbance (such as cold or heat), induces systemic dysfunction of mitochondria in whole body cells.

In conclusion, the author proposes that the cause of human-specific mental illness and consequent aging is mitochondrial deterioration due to intracellular infection by common enteromicrobes, just like common intractable immune diseases. By applying the mitochondria-activating therapeutic method (MATM), mental illness can be treated and recovered manifestly by means of recovering mitochondrial functions in neurons, by which their aging is prevented.

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