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Neurodegeneration as mitochondrial pathology: Signaling mechanisms and new routes for life-time diagnostics and targeted therapy (review)

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Structural and functional alterations of mitochondria have been shown to be responsible for a wide variety of clinical disorders that are referred to as “mitochondrial diseases”. It is now obvious that many factors are involved in transport of mitochondrial proteins including cytokines, chaperones, chemokines, neurosteroids, ubiquitin and many others. At the same time, the participation and the role of biogenic amines and peptide hormones (which are produced by the diffuse neuroendocrine system cells located in different organs) in endogenous mechanisms of mitochondrial diseases are still unknown. Taking into account the wide spectrum of biological effects of biogenic amines and peptide hormones, and especially their regulatory role for intracellular communication, it seems important to analyze the possible participation of these molecules in the pathogenesis of mitochondrial disorders as well as to draw up a new way for elaboration of a new markers for lifetime diagnosis, definition of prognosis and efficiency of specific therapy in neurodegenerative diseases.

Keywords: *Mitochondrial diseases, biogenic amines, peptide hormones, diffuse neuroimmunoendocrine system, lifetime diagnostics, neurodegeneration*

INTRODUCTION

Mitochondria are a key beachhead of cell pathology

Mitochondria are the sites of crucial cellular functions in eukaryotic cells responsible of converting energy derived from chemical fuels by harnessing this energy for biological purposes through a chemiosmotic coupling. Moreover, mitochondria have also been suggested as an important source of cellular second-messenger molecules (reactive oxygen intermediates and others), which are involved in many gene regulatory pathways. In metabolically active cells, mitochondria are the most abundant organelles, and up to 10-20% of the total intracellular proteins have been estimated to be present within this organelle (Devine and Kittler, 2018).

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In spite of mitochondria having their own DNA encoding mt tRNA, mt rRNA and several polypeptides, they import virtually all of their proteins from the cytoplasm. This import process faces the challenge to route the proteins to their correct submitochondrial compartment, and this process required that most of them must be transported across two membranes. This challenge is met by the joint action of two distinct protein transport systems, one in the outer membrane and the other in the inner membrane.

Primary defects in mitochondrial function are involved in over 100 diseases, and the list continues to grow. Structural and functional alterations of mitochondria have been shown to be responsible for a wide variety of clinical disorders that are referred to as "*mitochondrial diseases*" or "*mitochondrial cytopathies*" (Schapira, 1993; Luft, 1994). It has become apparent that genetic defects in the synthesis of mitochondrial proteins may be the underlying cause of diseases affecting organ systems including the nervous system, skeletal and cardiac muscle, liver and others.

It is now obvious that many factors are involved in transport of mitochondrial proteins including cytokines, chaperones, chemokines, neurosteroids, ubiquitin and many others (Mihara and Omura, 1996; Kroemer et al., 1998; Gale and McColl, 1999). At the same time the participation and the role of biogenic amines and peptide hormones (highly active biologically substances, which are produced by neuroendocrine cells located in different organs) in endogenous mechanisms of mitochondrial diseases are still unknown.

Taking into account the wide spectrum of biological effects of biogenic amines and peptide hormones, and especially their regulatory role for intracellular communication, it seems important to analyze the possible participation of these molecules in the pathogenesis of mitochondrial disorders, especially for neurodegenerative diseases.

The aim of this paper is to analyze the possible role of regulatory peptides and related molecules in endogenous mechanisms of neurodegenerative processes and to identify avenues for further research.

Diffuse neuroimmunoendocrine system: Evolution of knowledge

In last two decades there are more and more evidences that identical peptide hormones and biogenic amines are synthesized by different cells having neuronal, immune or endocrine assignment. Historically, Pearse was the first who in the late 1960's suggested that a specialized, highly organized cell system should exist in organisms, whose main feature was the ability of component cells to produce peptide hormones and biogenic amines.

His concept was based on an extensive series of experiments for distinguishing endocrine cells in different organs, identifying endocrine cell-generated products and performing a thorough cytochemical and ultrastructural analysis of these cells.

Pearse has obtained that a variety of cell types, widely dispersed throughout the organism, have a common ability of absorbing monoamine precursors (5-hydroxytryptophan and L-dihydroxyphenylalanine) and decarboxylating them, thus producing biogenic amines. That ability accounts for the term APUD, an abbreviation of "Amine Precursor Uptake and Decarboxylation" used by Pearse to designate this cell series (Devine and Kittler, 2018; Phu et al., 2020).

To date, the APUD series includes over 60 types of endocrine cells located in gut, pancreas, urogenital tract, airway epithelium, pineal gland, thyroid gland, adrenals, adenohypophysis and hypothalamus, carotid body, skin, sympathetic ganglia, thymus, placenta and other organs. Meanwhile the advent of radioimmunological methods and the rapid development of immunohistochemistry resulted in the establishment of a completely unexpected phenomenon, i.e., the same biogenic amines and peptide hormones were identified in neurons and endocrine cells. Just in this year 25 years have passed since Roger Guillemin has been awarded by Nobel Prize and presented his Nobel Prize Lecture entitled "Peptides in the brain. New endocrinology of the neuron" (Ramage et al., 1993).

The accumulated data did not fit the traditional concepts of hierarchical dependence within two main regulatory systems, viz., the nervous and endocrine systems. It became more and more data that the mechanism of biological regulation should be based on the coordinated functional interaction between the endocrine system and the central and peripheral nervous system considering the common type of information perception and transmission at subcellular, cellular and tissue levels.

Many studies on identification of the same and similar physiologically active substances, acting within the nervous system as neurotransmitters and neurohormones, and locally or remotely as hormones within the endocrine system, enables both system to be incorporated into the universal ***diffuse neuroendocrine system (DNES)*** (Hernandez et al., 1999a)**.** Actually, it should be possible to unite in the organisms the structurally isolated nervous and endocrine systems by means of functional relationships between biogenic amines and regulatory peptides and, to a certain extent, to provide a basis for the concept of integrated functions. Located in practically all organs and producing biologically active substances, the DNES cells play role of regulators of homeostasis acting via neurocrine, endocrine and paracrine mechanisms (Hernandez et al, 1999b).

Later it was shown that the nervous and immune systems have well-established and very closed related interrelations for regulate systemic homeostasis that involves the production and secretion of a variety of cellular mediators known as ***regulatory peptides*** (peptide hormones, cytokines, chemokines, integrins and others) (Schapira, 1993). Peptide hormones, cytokines and other related molecules regulate homeostasis in the tissue of origin, either via local actions or by recruitment of external systems that facilitate restoration of local homeostasis.

The studies on isolated-cell systems have confirmed that many regulatory peptides and biogenic amines are expressed within the brain. There are many peptidergic neurons and glial cells in the brain which can produce peptide hormones and biogenic amines; also besides neurons, immune cells, such as macrophages, T-lymphocytes, eosinophilic leukocytes and mast cells, which invade the brain after injury or inflammation, are a rich source of cytokines and other active molecules (Luft, 1994; Mihara and Omura, 1996; Molnar and Kovaes, 2017).

Such chemical common character of three regulatory systems, namely nervous, endocrine and immune systems stimulated the development of new research field called ***neuroimmunoendocrinology*** which mainly studied the mutual interrelationships between these regulatory systems (Kroemer et al., 1998). It seems to be necessary to underline that numerous investigations in this field of study fail to take one phenomenon into account which we consider as very important fact.

There is a following circumstance - **the nervous and immune cells together with APUD cells represent in most visceral organs, where they are available to produce many peptides and biogenic amines which are identical to the same in the brain and central organs of immune and endocrine systems**.

Therefore the close interrelations between three regulatory systems provide with anatomical/functional property - immune and nervous system have their representation in visceral organs through the peptidergic/aminergic neurons (and/or nerve fibers) as well as through the immunocompetent cells producing different peptide molecules; in its turn, the endocrine system represents in central nervous system and immune organs through APUD cells (e.g. hypothalamic neurosecretory cells and others).

Thus, obviously that cell types of all three classical regulatory systems (nervous, endocrine and immune) represent in each visceral organ, including the central organs of homeostatic regulation (e.g. brain, thymus, thyroid, etc).

Hence it follows to be possible to unite peptidergic/aminergic neurons, APUD cells and peptide-producing immunocompetent cells into a single common functional system and to extend the term ***diffuse neuroendocrine system (DNES)*** to the new term ***diffuse neuroimmunoendocrine system (DNIES)***.

Exactly the DNIES is a field of the study for neuroimmunoendocrinology as a new scientific biomedical discipline which integrates our knowledges about signalling mechanisms of homeostatic regulation.

Neuropathology of Alzheimer's and Parkinson's diseases

The most important diseases among all mitochondrial disorders are the neurodegenerative diseases, including most notably Alzheimer's disease (AD) and Parkinson's disease (PD). AD is characterized by a progressive loss of memory, resulting in dementia and death. AD affects over 20 million people worldwide and its incidence is expected to double over the next 30 years (Price, 1999).

A triad of neuromorphophysiological features characterize AD and include amyloid-β plaques (senile plaques), neurofibrillary tangles and extensive neural loss particularly in the hippocampus and cerebral cortex (Dickson, 1997); these changes are associated with dementia and characteristic neurobehavioral consequences. The signs of the disease differ among individuals with the majority of cases arising sporadically and commonly they have a late life onset (after 65 years of age); in a less common form of familial AD, the onset of the condition is typically much earlier (40-50 years of age) (Price, 1999).

Parkinson's disease (PD) is a major neurodegenerative disorder with a prevalence of roughly 150 cases for every 100,000 elderly people. The condition is characterized by the progressive deterioration of the dopamine containing neurons in the pars compacta of the substantia nigra in the brain stem; the loss of these catecholaminergic neurons is associated with a variety of sensory and motor impairments which lead to tremor, rigidity and akinesia (Li and Song, 2020).

For an individual to manifest signs of PD it is estimated that the nigro-striatal dopaminergic neuronal population must be depleted by at least 80%. Thus, in most cases the initiating factor for PD probably precedes the overt signs of parkinsonism by 5-10 years (Li and Song, 2020).

Pathogenesis of neurodegenerative diseases: Related molecules and cellular bases. Cytokines

Major cytokines for brain function are neurotrophins (BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor and GDNF, glial-derived neurotrophic factor) and neuropoietins (especially interleukin-6, IL-6). They participate in the mechanisms of growth and differentiation of neurons and in neurotransmission (Merrill and Jonakait., 1995). The most abundant source of cytokines, particularly after local damage, appears to be activated microglia, although neurons, astroglia, perivascular and endothelial cells can also express cytokines (Kunkl et al., 2020). Studies on the localization and expression of peptide hormones and cytokines in response to specific stimuli have important implications for their actions in the CNS.

For example, it is clear now that cytokine expression is upregulated rapidly in situations of tissue stress, and that cytokines have important actions that are consistent with their role in restoration of tissue homeostasis. Cytokines have been reported to influence many central neurotransmitters, including noradrenaline, serotonin, GABA and expression of a number of neuropeptides (somatostatin, substance P, opioids, VIP, etc.) in several brain regions (Neumann and Wekerle, 1998). However, the interrelationships between each of these varied neurotransmitter responses and their relevance to specific cytokine actions have yet to be defined.

Similarly, a number of second messenger systems in neurons are affected not only by cytokines, but melatonin and other hormones and mediators, including activation of cAMP, increased activity of protein kinase C, synthesis of nitric oxide, release of arachidonic acid and Ca^{2+} flux (Mrak et al., 1997; Borjigin and Snyder, 1999). Thus, now it seems likely that the behavior of practically all molecules involved in pathogenesis of AD and other mitochondrial diseases may be under control of regulatory peptides.

Several cytokines have been reported to influence neuronal differentiation and growth as well as to acutely modify synaptic plasticity in brain slice preparations. For many cytokines and other peptide molecules, conflicting data exist, indicating that many can exert neurotrophic, neuroprotective and neurotoxic actions. As reported, transgenic mice overexpressing IL-6 in astrocytes show marked neurodegeneration, and inhibition of action of IL-1 and IL-6 markedly inhibits the neurodegenerative processes (Griffin et al., 1995). IL-1 induces expression of β-amyloid precursor protein (β-APP) and adhesion molecules in neural tissue (Morganti-Kossmann et al., 1992).

Many hormones influence cytokine actions: glucocorticoids are potent inhibitors of the synthesis and actions of cytokines; also, melanocyte stimulating hormone and vasopressin attenuate actions of cytokines in the brain, and these peptides, as well as lipocortin, have been implicated in impaired febrile responses to cytokines in ageing animals (Rothwell and Hopkins, 1995).

The pathological presentation of AD, the leading cause of senile dementia, involves regionalized neuronal death and an accumulation of intracellular and extracellular filamentous protein aggregates which form lesions termed neurofibrillary tangles and senile plaques, respectively (Dickson, 1997). Several independent parameters have been suggested as the primary factor responsible for this pathogenesis, including apolipoprotein ε genotype, hyperphosphorylation of cytoskeletal proteins, or metabolism of amyloid β.

Amyloid β (Aβ). The view that a relationship exists between amyloid deposits and neurofibrillary lesions remains an important unresolved issue in our understanding of the pathogenesis of AD (Auld et al., 1998; Selkoe, 1998; Iadanza et al., 2018).

Amyloid plaques (AP), which are a classical neuropathological characteristic of AD, have been reproduced in transgenic mice. These mice exhibit selective neuronal death in the brain regions that are most affected in AD, suggesting that AP formation is directly involved in AD neuron loss (Calhoun et al., 1998). On the other hand, non-Aβ component of AD amyloid (NAC) is the second component in the amyloid from brain tissue of patients afflicted with AD (Ueda et al., 1993).

Its precursor protein (NACP) was shown to be a brain-specific protein. NACP was more abundant in the neocortex, hippocampus, olfactory bulb, striatum, thalamus and cerebellum. Confocal laser microscopic analysis revealed that anti-NACP immunostaining was colocalized with synaptophysin - immunoreactive presynaptic terminals, therefore NACP is a synaptic protein, suggesting that synaptic aberration observed in senile plaques might be involved in amyloidogenesis in AD (Iwai et al., 1995).

Tau-protein. There are some data indicating that even small numbers of neurofibrillary lesions are pathological and may represent the early stages of AD. There are also many neurodegenerative diseases with numerous positive filamentous lesions: AD, Parkinson's disease (PD), Down syndrome, myotonic dystrophy, and others.

Tau is a microtubule-associated protein that is involved in microtubule assembly and stabilization (Gao et al., 2018). In adult human brain, six isoforms of tau are expressed, which are produced by alternative splicing of mRNA from a single gene located on the long arm of chromosome 17. Tau protein mRNA is expressed predominantly in neurons, with recent reports indicating its additional presence in oligodendrocytes.

Within nerve cells tau protein is present mainly in axons (Congdon and Sigurdsson, 2018). In some recent studies the expression of tau-protein has also been shown in cultured skin fibroblasts from Alzheimer's disease patients (Blass et al., 1991). A number of studies have characterized tau filaments in various diseases by electron microscopy and immuno-electron microscopy (Spillantini and Goedert, 1998). Currently, three types of filament morphologies can be distinguished and they have a diagnostic significance (for example, type I more often can be identified in AD, type II more characteristic feature for PD).

Tau pathology is one of the central neuropathological characteristic of a number of neurodegenerative disorders since the events leading to the formation of tau filaments are sufficient to produce nerve cell degeneration (Lee and Trojanowski, 1999). Therefore, an important direction for further study is to find either endogenous and exogenous ways to prevent tau filament formation. In this connection, one of the possible ways to prevent tau filament formation and development of amyloid plaque could be to identify the endogenous mechanisms of interpeptide communications.

It appears that biologically active substances (neuropeptides, cytokines, etc.) have several, probably distinctive, actions on the nervous system: as communicators to the brain of systemic injury and other disorders; as modulators of brain responses to peripheral organs; as neuromodulators and neurotransmitters of the CNS control of systemic host defence responses to disease and injury; and as molecules that inhibit or mediate neurodegeneration and repair in the brain. The relevance of peptide molecules and related protein actions to a variety of neurological disorders is now being determined, and has opened a potentially fruitful area of research and therapeutic development.

Synuclein proteins. Several mitochondrial neurodegenerative disorders are characterized by intracellular protein accumulations or inclusions, such as the Lewy bodies (LB) in PD. α-synuclein is a proposed component of LB. It was shown immunohistochemically, that indeed LB in brains of sporadic PD patients are strikingly synuclein-positive (Spillantini et al., 1997). In addition to synuclein, LB contain ubiquitin, ubiquitin C-terminal hydrolase, and proteasomal subunits, major components of the cellular protein degradation pathway (Alves-Rodrigues et al., 1998; Pallares-Trujillo et al., 1998). The following areas of the brain are often involved in this pathological process: the striatum (putamen), substantia nigra, locus coeruleus, inferior olive, pons, and cerebellum.

Synuclein proteins are produced by three genes (Clayton and George, 1998). They share a structural resemblance to apolipoproteins. α-synuclein is distinguishable from the other synucleins. It uniquely has a histidine at residue 50 (β has a unique histidine at 65). Recent reports of synuclein immunoreactivity in LB suggest the presence of α but not β synuclein (Clayton and George., 1998). The structure, function and localization of the synucleins might be subject to regulation by signals associated with synaptic activity and neuritic growth.

In general, the distribution of α-synuclein in the brain is similar to the distribution of brain pathology in AD (Alves-Rodrigues et al., 1998). Additional portions of the synuclein protein are present in amyloid plaques in AD. A significant increase in cytosolic synuclein immunoreactivity in frontal cortical extracts in early AD cases was reported; it seems possible that α-synuclein might potentiate the long-term development of AD (Dehghani et al., 2020).

Chemokines. Chemokines and chemokine receptors in the CNS are constitutively expressed at low levels in astrocytes, microglia and neurons of the developing and adult brain and they are induced by inflammatory mediators (Mennicken et al., 1999). Furthermore, chemokines and their receptors are upregulated in various neuropathology including brain tumours and AD (Asensio and Campbell, 1999). Cell culture studies support a role for chemokines in the differentiation and migration of brain cells.

For example, IL-8 enhances the survival of neurons and the number of microglial and astroglial cells in rat hippocampal cultures, and it influences neuronal growth in the human brain (Asensio and Campbell 1999). Chemokines also modulate angiogenesis or neovascularization in lesion brain areas. Moreover, an upregulation of the CXCR2 protein (receptor for IL-8) occurs in senile plaques adjacent to the hippocampus in the brains of AD patients. Because IL-8 promotes survival of hippocampal neurons, a possible involvement of IL-8/CXCR2 in compensatory and reparative mechanisms in the Alzheimer’s brain should be considered (Mennicken et al., 1999).

Integrins. Integrins are the major family of cell surface receptors that mediate attachment to the extracellular matrix, and specific classes of integrins also mediate important cell-cell adhesive interactions. These integrin-mediated adhesive interactions are intimately involved in the regulation of many cellular functions, including embryonic development, tumor cell growth, programmed cell death, hemostasis and many others (Clark and Brugge, 1995).

It appears that multiple receptor systems can synergize with integrins to regulate cell proliferation, motility, secretion, and other cellular events. The signalling proteins activated by these synergistic agents are common to many receptor pathways. Thus, although unique pathways may be activated by individual classes of receptors, cross talk between integrins and other receptor pathways is critically involved in the integration of signals that converge on cells in their natural environments *in vivo*.

Chaperones. Molecular chaperones (Hsp28, αB-crystallin) are also involved in AD (Martinus et al., 1995). Detailed insights into the role of molecular chaperones have come from studies of mitochondrial protein biogenesis, a process in which chaperones act as unfoldases, pulling devices, and foldases. One of the chaperones is mitochondrial import stimulation factor (MSF) (Hachiya et al., 1993). It seems this factor is a conformational modulator of mitochondrial precursor proteins. Other studies showed that some heat shock proteins (Ssa1p, Ssa2p and especially Hsp70) are involved in the import of proteins into mitochondria, as well as into the endoplasmic reticulum and nuclei (Kang et al., 1990; Lithgow et al., 1993).

Neurosteroids. It is now established that the brain itself also synthesizes steroids *de novo* from cholesterol in a variety of vertebrates (Paul and Purdy, 1992). In the brain, glial cells play a major role in neurosteroid formation and metabolism (Kreutzberg, 1996). Purkinje cells produce neurosteroids (pregnenolone and progesterone). These cells demonstrate immunopositive staining with antibody to key steroidogenic enzyme cytochrome P450scc (Tsutsui and Ukena, 1999).

Progesterone (one of the main neurosteroids) is shown to be produced from pregnenolone by Schwann cells in peripheral nerves, and some observations indicate a role for locally produced progesterone in myelination, demonstrate that progesterone is not simply a sex steroid, and suggest a new therapeutic approach to promote myelin repair (Koeniget al., 1995). Mitochondria of C6-2B glioma cell line participate in the biosynthesis of pregnenolone converting (22R)-22-hydroxycholesterol to pregnenolone by a mechanism blocked by aminoglutethimide (Papadopoulos et al., 1992).

Oxygen radicals. Many diseases related to aging may involve oxygen radicals at some stage in their development. In these diseases, it has been proposed that mutations of mthDNA and changes in cellular bioenergetics contribute in some way to the aging process and to the development of degenerative diseases (Shigenaga et al., 1994).

Though only recently uncovered as a physiologic messenger, nitric oxide (NO) is increasingly appreciated as a major regulator in the nervous, immune, and cardiovascular systems (Nathan, 1992). Besides mediating normal functions, NO has been implicated in many different pathophysiologic states including neurodegenerative diseases (Ames et al., 1993).

Of all the organs in the body, the central nervous system (CNS) takes more than its share of oxidative abuse (Bolanos et al., 1997). The reasons for this are several-fold. The brain although constituting only a small percentage (in the human about 2%) of the body weight consumes a disproportionately large amount (in the human about 20%) of the O_2 inhaled. Given that by-products of O_2 are toxic, it is not suprising that neural tissue may thus be destroyed at a more rapid rate than other organs.

Mitchondrial DNA (mtDNA) has more than 10 times the level of oxidative DNA damage than does nuclear DNA (Ames et al., 1993). This increase may be due to a lack of mtDNA repair enzymes, a lack of histones protecting mtDNA, and the proximity of mtDNA to oxidants generated during oxidative phosphorylation. The cell defends itself against this high rate of damage by a constant turnover of mitochondria, thus presumably removing the damaged mitochondria that produce increased oxidants.

Despite this turnover, oxidative lesions appear to accumulate with age in mtDNA at a higher rate than in nuclear DNA. Oxidative damage could also account for the mutations in mtDNA that accumulate with age (Smith et al., 1995).

That oxidative stress may be a culprit in neuronal loss in AD has been emphasized in recent years and the evidence is becoming progressively stronger that radicals are involved in the neural pathogenesis of AD (Reiter, 1995). The free radicals that have been incriminated as causing neuronal loss are believed to be generated by Aβ (Smith et al., 1995).

According to the free radical theory of PD, dopaminergic neurons are lost as a consequence of their relatively high exposure to reactive oxygen species, most notably H_2O_2 which is produced during both the enzymatic, via monoamine oxidase activity, and non-enzymatic, due to the autooxidation, destruction of dopamine (Fahn and Cohen, 1992).

Not only does oxidative stress destroy the dopaminergic neurons but it also compromises mitochondrial oxidative phosphorylation leading to decreased energy output by these organelles and eventually to secondary death of the cells.

Glutamate. There is an increasing amount of experimental evidence that oxidative stress is a causal, or at least an ancillary, factor in the neuropathology of several adult neurodegenerative disorders (Reiter, 1998).

At the same time, excessive or persistent activation of glutamate/gated ion channels may cause neuronal degeneration in these same conditions. Glutamate and related acidic amino acids are thought to be the major excitatory neurotransmitters in brain and may be utilized by 40 percent of the synapses (Coyle and Puttfarcken, 1993). Thus, two broad mechanisms, oxidative stress and excessive activation of glutamate receptors, are converging and represent sequential as well as interacting processes that provide a final common pathway for cell vulnerability in the brain.

The broad distribution in brain of processes regulating oxidative stress and mediating glutamatergic neurotransmission may explain the wide range of disorders in which both have been implicated. Yet differential expression of components of the processes in particular neuronal systems may account for selective neurodegeneration in certain disorders.

Although NO participates in normal synaptic transmission, excess levels of NO are neurotoxic. NO stimulates glutamate neurotoxicity which may contribute to dysfunction in neurodegenerative diseases such as Alzheimer's and Huntington's diseases.

Evidence is now emerging that activation of glutamate-gated cation channels may be an important source of oxidative stress and that these two mechanisms may act in a sequential as well as a reinforcing manner, leading to selective neuronal degeneration. Understanding the relation between oxidative stress and glutamate neurotransmission could lead to the development of pharmacologic interventions that disrupt this chain of pathological events without impairing excitatory neurotransmission.

Calcium homeostasis. Brain ageing is associated with a marked decline in mental faculties. One hypothesis postulates that sustained changes in the regulation of intracellular Ca^{2+} concentration are the major cause of neuronal degeneration (Choi, 1995). This "calcium hypothesis" is supported by demonstration of the impairment in aged neurons of molecular cascades that regulate intracellular Ca^{2+} concentration.

The conceptual pillars of this point of view are: dysfunction of intracellular Ca^{2+} homeostasis, and neuronal loss (Verkhratsky and Toescu, 1998). This view of the ageing brain is that the decrease in cognitive function results mainly from neuronal death and that this leads to a decrease in the number of brain cells. Strong support for this hypothesis has come from studies of neurodegenerative diseases, such as AD. In AD there is a profound loss of neurons that correlates well with the decrease in learning abilities and memory function (Dickson, 1997). In addition, a key element of AD pathology, the accumulation of Aβ, has been shown to disrupt neuronal intracellular Ca^{2+} homeostasis (Verkhratsky and Toescu, 1998).

Brain contains a huge population of glial cells that are responsible for the regulation of the brain microenvironment. They can also play an important role in the integrative function of neurons by controlling the concentrations of neurotransmitters and neuromodulators, and thus affecting synaptic transmission. Glial cells, especially astrocytes, rely heavily on neuronal intracellular Ca^{2+} homeostasis, signaling that is involved in most of their response to neurotransmitters (Kreutzberg, 1996).

Apoptosis. In any case, the death of neurons is a final stage of neurodegenerative diseases and this phenomenon is known as apoptosis (Sastry and Rao, 2000). During the development of the vertebrate nervous system, up to 50 percent or more of neurons normally die soon after they form synaptic connections with their target cells (Raff et al., 1993). *Bcl*-2 and related proteins have become a major focus of efforts to unravel the intracellular molecular events that regulate cell survival, and cause cell death (Davies, 1995).

Clarification of the repertoire and functional significance of the interactions between these proteins, and identification of the chain of molecular events in which they fit, will greatly increase our understanding of the apoptotic process. Moreover, neurons are particularly useful for studying the regulation of cell survival and apoptosis because, being postmitotic cells, experimental analysis is not complicated by cell proliferation. Furthermore, the roles of *bcl*-2 related proteins in certain neurons might have important therapeutic implications for neurodegenerative diseases (Hockenbery et al., 1993).

The intracellular membrane-bound protein *bcl*-2 is probably associated with the cytoplasmic surface of the nuclear envelope, endoplasmic reticulum, and mitochondria (Monaghan et al., 1992). Experimental over-expression of *bcl*-2 prevents the death of neurons deprived of particular neurotrophic factors *in vitro*, and rescues developing neurons that would otherwise die *in vivo*.

The intracellular localization of *bcl*-2 to the inner mitochondrial membrane (Hockenbery et al., 1990), endoplasmic reticulum membrane and the nuclear envelope has led to several hypothesis about how it might work. The localization of *bcl*-2 in mitochondria has raised the possibility that it might protect against apoptosis by altering mitochondrial function.

The localization of *bcl*-2 to major sites of oxygen free-radical generation, and evidence that reactive oxygen species might be involved in causing apoptosis in neurons (Jacobson et al., 1993) and other cells have raised the possibility that *bcl*-2 might prevent apoptosis by either acting as an antioxidant or by inhibiting production of free radicals (Fadeel et al., 1999).

Hormones in brain: Localization and role for central nervous functions

Melatonin. During the last decade a great deal of attention has been focused on melatonin, one of the hormones of the DNES, which for many years was considered exclusively as a secretory product of pineal gland (Reiter, 1973; 1992). As soon as highly sensitive antibodies to indolealkylamines became available (Grota and Brown, 1974), melatonin was identified not only in pineal gland, but also in extrapineal tissues, i.e., retina, cerebellum, gut mucosa, airway epithelium, kidney and other tissues (Kvetnoy, 1999) as well as in non-neuroendocrine cells such as mast cells, natural killer cells, eosinophilic leukocytes, platelets and endothelial cells (Kvetnoy, 1999) and in bone marrow cells (Tan et al., 1999).

Also it has now been shown that many cells in different organs possess melatonin receptors and a variety of melatonin receptors have been identified in many areas of human brain (Pang et al., 1993). The above list of cells which contian melatonin indicates that this MT indoleamine has a unique position among the hormones, being found in a variety of organ systems including the CNS.

Functionally, melatonin-producing cells are likely to be part and parcel of the DNES as a universal system of response, control and organismal protection. Taking into account the large number of melatonin-producing cells, the wide spectrum of biological activities of melatonin and especially its properties as a regulator of biological rhythms and antioxidant, extrapineal melatonin may be an important paracrine molecule to ensure optimal cellular function and protection.

The identification of melatonin in pineal gland and in extrapineal tissues stimulated interest in the physiology of this hormone and a wide spectrum of biological activities of melatonin have been uncovered. Some of these functions include the control of biological rhythms, seasonal reproductive events, stimulation of immune processes, cytostatic and antiproliferative effects in vitro and in vivo (Reiter, 1992).

Additionally, another unexpected function of melatonin was uncovered. Thus, the indole has been shown to be a free radical scavenger and antioxidant (Reiter, 1997; Reiter et al, 1993; 1998). Melatonin is now known to be a potent hydroxyl radical scavenger and under some circumstances, it protects against free radical damage more effectively than the well-known scavenger glutathione (Cuzzocrea et al., 1999). Melatonin is now known to scavenge the highly toxic hydroxyl radical, the peroxynitrite anion, singlet oxygen and NO.

Also, secondarily, it reportedly scavenges the superoxide anion radical (Cuzzocrea et al., 1999). Additionally, it stimulates mRNA levels for superoxide dismutase and the activities of glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase (all of which are antioxidative enzymes), thereby increasing its antioxidative capacity (Reiter et al., 1998). Also, melatonin inhibits nitric oxide synthase, a pro-oxidative enzyme and stimulates the rate limiting enzyme in glutathione synthesis, α-glutamyl-cysteine synthase (Barlow-Walden et al., 1995).

There is ample evidence that the brain of PD patients exhibits signs of enhanced oxidative stress. Acuna-Castroviejo et al. (Acuna-Castroviejo et al., 1997) have investigated the ability of melatonin to protect the brain against the toxic effects of MPTP, a drug that produces Parkinson like signs. In this model system, melatonin was strongly protective. Also, Mayo and co-workers (Mayo et al., 1998) assessed the ability of MT to protect against dopamine autoxidation-induced protein damage using the oxygen radical absorbance capacity assay.

The results showed that melatonin reduces the degree of oxidation of the fluorescent protein which is the basis for the assay indicating that melatonin prevents macromolecular damage that is a result of dopamine autooxidation. The authors surmised that this was due to the free radical scavenging capacity of melatonin and they suggested that the indole may have beneficial effects in reducing oxidative damage in the brain of PD patients.

While oxidative stress may be one feature that links many neurological deficits, it is also obvious that these diseases have extremely complex etiopathologies and it is unlikely that a single agent will totally combat their development. Moreover, there is an urgent need to understand the mechanisms underlying the degeneration of neurons.

Melatonin as a potential treatment to defer neurodegenerative diseases is of interest for several reasons: the endogenous production of this molecule falls with age coincident with the onset of many of the age-associated neurodegenerative conditions (Reiter et al., 1998); melatonin readily crosses the blood-brain barrier and after its exogenous administration it is found in high concentrations in the brain, sometimes exceeding those in the blood manifold (Reiter, 1995); melatonin is a ubiquitously acting free radical scavenger and antioxidant (Reiter et al., 1993) which in models of neurological diseases has proven effective in reducing oxidative damage and preserving neurological function (Reiter, 1998).

The importance of the study of melatonin as a promising molecule to understand better the pathogenesis of AD and PD is illustrated by the recent fact that soluble forms of full-length β-amyloid precursor protein (β-APP) of the Aβ-peptide were detected in secretory granules of chromaffin cells (Efthimiopoulos et al., 1996), where melatonin and dopamine are also synthesized (Kvetnoy, 1999).

Moreover, it was shown that stimulation of APP secretion was paralleled by a stimulation of secretion in catecholamines and chromogranin A, indicating that secretion of APP was mediated by chromaffin granules. Because, secretion of APP from primary chromaffin cells was time-dependent, we surmise that melatonin may have a direct effect on this process.

Serotonin (5-hydroxytriptamine; 5-HT). 5-HT neuron and neurotransmitter loss in normal ageing and neuropsychiatric diseases of late life may contribute to behavioral changes commonly observed in the elderly population (Meltzer et al., 1998). Extensive evidence implicates a deficit in serotoninergic neurotransmission in the development of major depression. The concentrations of 5-HT is reduced by 18% in the frontal cortex and by 21-37% in hippocampal cortex, hippocampus and striatum in AD (Reinikainen et al., 1990). It has been further suggested that the age-related changes in 5-HT neurons may predispose the elderly to depression. There is also increasing evidence that a disturbance in serotoninergic function may play a role in cognitive impairment in AD.

Catecholamines (CA). There are many data showing a significant loss of dopamine (DA) immunopositive neurons in the brain of PD patients (Li and Song , 2020). Also a reduction of DA concentrations (18-27% compared with normal level) have been noted in AD patients in the temporal cortex and hippocampus (Reinikainen et al., 1990).

Immunocytochemical techniques have been used to compare the proportion of neurons expressing CA in the different brain areas of neurologically normal elderly humans to that of age-matched AD patients (Yew et al., 1999). The CA cells in the frontal cortex of the AD patients were found to be significantly decreased; the CA are present in both cortical neurons and astrocytes. (Reinikainen et al., 1990) showed that in AD patients the concentration of noradrenaline was reduced (18-36% compared with normal patients) in frontal and temporal cortices, and in putamen.

Histamine. Histamine is known to be a neurotransmitter, but it has not been clearly implicated in major diseases. All histaminergic neurons reside in the posterior hypothalamus and innervate most brain areas, which is compatible with the concept that histamine is involved in general central regulatory mechanisms. A sensitive high-performance liquid chromatographic fluorimetric method was used to measure histamine content in post mortem brain in AD patients and age-matched controls (Zlomuzica et al., 2016). At the same time the cellular storage sites and distribution of histaminergic fibers were examined with a specific immunohistochemical method.

The histamine content was significantly reduced in the hypothalamus (42% of control value), hippocampus (43%) and temporal cortex (53%) of AD brains. Histamine concentration in other cortical areas, putamen and substantia nigra were not significantly altered. Histamine-containing nerve fibers were found in the hippocampus, parahippocampal gyrus and subiculum of both AD brains and controls.

No histamine-containing mast cells were seen in these temporal structures. Histamine in the human temporal lobe is stored in nerve fibers originating from the posterior hypothalamus, and not in mast cells. A reduction in brain histamine levels may contribute to the cognitive decline in AD directly or through the cholinergic system. Thus, development of drugs that penetrate the blood-brain barrier and increase histaminergic activity may be beneficial in AD (Zlomuzica et al., 2016).

Somatostatin (ST). ST was originally isolated from hypothalamic extracts (Brazeau et al., 1973). It has subsequently been shown to be present in neurons and endocrine cells throughout the brain and gut (Figlewicz et al., 1987). Numerous central effects of ST have been described, although there appear to be some conflicts in the literature.

The consensus appears to be that main neurobiological effect of ST results in a generalized arousal, with concomitant enhancement of grooming and exploratory activities. Metabolically, it has been shown to inhibit the hyperglycemic response to a variety of stressors (Brown et al., 1979).

Disturbances in ST synthesis and secretion may play a role in the pathogenesis of various neurological diseases. Recent data suggest a disturbance of some brain ST neurons in AD, moreover, some endocrine activities known to be regulated by ST, such as growth hormone, thyroid-stimulating-hormone, somatomedins, as well as insulin and glucose, also seem to be affected in some patients (Reubi and Palacios, 1986). It is speculated that these changes are due to a global CNS and endocrine ST defect in AD and that the described endocrine imbalances may indirectly be responsible for at least part of the CNS pathology.

A deficiency in ST is the most consistently described neurochemical alteration in AD attributable to intrinsic cortical neurons (Beal et al., 1986). ST concentrations are depleted in cerebral cortex in both AD and in the dementia that accompanies PD (Beal, 1990). ST neurons in both illness are markedly dystrophic and may be reduced in number. Li et al. (1996) tried to verify if there is a difference in the number of ST neurons in the cortex between normal ageing versus AD patients and, secondly, if any of these neurons were dying via apoptosis.

In their specimens, immunohistochemistry revealed that there was no difference in the number of ST-containing neurons between the two study groups. Moreover, the bulk of the apoptotic cells that were idenified using the sensitive immunocytochemical TUNEL method, none contained ST (Li et al., 1996). It is concluded that while there is apoptotic cell death in normal ageing and AD, it does not seem to occur in neurons which contain ST in any significant amount.

A novel role for receptor-associated protein in ST modulation and it's implications for AD was shown recently. It is known that receptor-associated protein appears to play an important role in low-density lipoprotein receptor-related protein (LRRP) trafficking. Since ligands for the LRRP have been implicated in AD and normal functioning of this protein is indispensable for CNS development, deficient LRRP expression may result in CNS alterations (Solarski et al., 2018). In this study, receptor-associated protein-knockout mice were behaviorally tested and nervous system integrity was assessed via in situ hybridization and immunocytochemical/laser confocal microscopy methods.

In wild-type mice, the LRRP was found to be highly co-expressed with ST in hippocampal and neocortical inhibitory neurons. LRRP-knockout mice, however, showed a significant decrease in number of ST-expressing neurons in the CA1 region and ST expression within these neurons. The decreased number of ST neurons significantly correlated with cognitive impairment observed in the receptor-associated protein in modulating the functioning of ST-producing neurons. Furthermore, this has implications for AD pathogenesis, in which altered regulation of both ST and the known LRRP ligands are a consistent finding.

Endogenous oppiates. Yew et al. (1999) obtained only minimal difference in the proportion of cortical neurons expressing leu-enkephalin between normal and AD patients.

Hypothalamic and pituitary peptides. The neuropathological hallmarks of neurodegenerative diseases are very prominent in the hippocampus (Kraskovskaya et al., 2017), a brain site that is pivotal for regulation of the synthesis of the hypothalamic and pituitary hormones. An alteration of neuroendocrine processes is supported by a significantly reduction of adrenocorticotropin hormone (ACTH) levels in cerebrospinal fluid in AD patients as compared with the controls (Suemaru et al., 1993).

Several studies indicate a reduction in corticotropin-releasing hormone (CRH) immunoreactivity in the cerebral cortex of AD patients (De Souza et al, 1986; Vandael and Gounko, 2019), particularly in temporal, frontal, and occipital areas. Nevertheless, these findings are not specific to AD. In fact, reduced levels of CRH in cerebrospinal fluid were also demonstrated in patients with vascular dementia (Suemaru et al., 1991), and reduced CRH immunoreactivity in cerebral cortex was found in PD.

An attenuated growth hormone-releasing hormone (GHRH)–induced growth hormone response specific to AD has been demonstrated (Chiso et al., 1993). Furthermore, a reduction in cerebrospinal fluid levels of antidiuretic hormone was observed not only in AD patients, but also in patients with frontal lobe dementia (Petrella et al., 2019). No alteration in the synthesis of thyrotropin-releasing hormone and prolactin was found in AD or PD (Dysken et al., 1990).

Substance P (SP). SP was first isolated and chemically characterized from hypothalamus. Immunohistochemical findings indicate that many nerve fibers from the amygdalo-fugal pathway, probably via the stria terminalis, contain SP, and enter the bed nucleus of the stria terminalis (Sakanaka et al., 1981) and lateral hypothalamus (Sakanaka et al., 1982).

Besides, the neurons with SP immunoreactivity have been observed in the arcuate nucleus, ventral and dorsal premammillary nucleus, dorsomedial nucleus, in the medial preoptic area, the periventricular nuclei of the dorsal tuberal region, and the lateral hypothalamus (Ljungdahl et al., 1978; Ronnekleiv et al., 1984).

These cells lack a projection to the median eminence but probably subserve important roles in integrating information from within the limbic system, including neuroendocrine regulation (Aronin et al., 1986). An important ultrastructural observation is that terminals containing SP form axodendritic synapses in the tuberoinfundibular region (Tsuruo et al., 1983).

SP immunoreactivity is present also in anterior pituitary and in median eminence (Sakanaka et al., 1981; Tsuruo et al., 1983). It seems to be possible that SP plays a role as a paracrine regulator of intrabrain hormonal status (Aronin et al., 1986). Immunocytochemical studies (Yew et al., 1999) have not documented a difference between the number and/or functional activity of cortical SP-immunoreactive neurons in healthy and AD patients in the same age.

Neurotensin (NT). Like SP, NT was also first isolated from hypothalamus. Numerous cells containing NT have been found in the paraventricular and periventricular cell groups and in the lateral hypothalamus. Both magno- and parvocellular neurons are labeled with NT in the paraventricular nucleus, which may indicate that NT-stained cells are components of the hypothalamic-anterior pituitary axis and the neurohypophyseal tract (Jennes et al., 1982).

Scattered NT-positive cells have been observed in other hypothalamic regions, with the exception of the supraoptic, suprachiasmatic, and ventromedial nuclei (Kahn et al., 1980). Dense fiber labeling is located in the paraventricular and periventricular zones and, importantly, in the median eminence (Kahn et al., 1982).

Some hypothalamic neurons that are positive for NT may also contain CA. These cells are distributed in the periventricular and arcuate regions (Liu et al., 2017). Like SP, NT immunoreactivity has been identified in anterior pituitary cells (Goedert et al., 1982). The role of NT in central neural functions is not defined; one idea is that this peptide together with SP may regulate the content of other peptides in the brain (Aronin et al., 1986).

Cholecystokinin (CCK). The presence of cholecystokinin (CCK) in high concentrations in a number of brain areas, its colocalization with DA in some central neurons, the distinct behavioral effects it has, and the alterations in certain neurotransmitter systems that are seen following its peripheral or central administration, all implicate CCK as a neuromodulator or neurotransmitter (Figlewicz et al., 1987).

High concentrations of CCK in the CNS occur in the cortex, caudate nucleus and olfactory bulb (Goltermann, 1982). The effects of CCK in the CNS may involve its interaction with major neurotransmitter pathways. CCK injection into the lateral hypothalamus increases DA and noradrenaline bindings in the nucleus accumbens (Dumbrille-Ross and Seeman, 1984). There are some data indicating a decrease in the number of CCK immuno-positive neurons in cortex of post mortem AD brain (Plagman et al., 2019).

Bombesin (BOM). BOM immunoreactivity is localized in nerve cells in different areas of brain, but the largest amount of this peptide is present in the hypothalamus and brain tissue closely to fourth ventricle (Figlewicz et al., 1987) . Like many other gut peptides (e.g. CCK), found in brain, BOM has been shown to reduce meal size. Additionally, it has important neurobiological effects. Brown (1983) reported that BOM activates the adrenal medulla and results in markedly elevated plasma adrenaline levels, with secondary increases in plasma glucose and glucagon. Because noradrenaline is reduced in AD (Reinikainen et al., 1990), it is possible, that BOM may have therapeutical significance in maintaining normal levels of noradrenaline.

Neuropeptide Y (NPY). It is known, that NPY found in high concentrations in cerebral cortex and is contained in cortical neurons (Figlewicz et al., 1987). NPY-containing nerve fibers also innervate small blood vessels. NPY is colocalized with catecholamines in some areas of brain (Everitt et al., 1984), and chemical depletion of catecholamines results in depletion of NPY in some, but not all, neurons (Lundberg et al., 1985).

Beal et al. (1986) measured concentrations of this peptide in postmortem tissue from AD patients and controls using a sensitive and specific radioimmunoassay. High-performance liquid chromatography showed that more than 95% of immunoreactivity co-migrated with synthetic standards in both AD and control frontal cortex. Significant reductions in neuropeptide Y immunoreactivity were found in cortex, the hippocampus, and the locus ceruleus. The regions particularly affected included the temporal lobe, frontal lobe, and occipital cortex.

A reduction in immune function has been found in patients with a major depressive disorder and in persons undergoing severe life stress (Merrill and Jonakait, 1995). Irwin et al. (1991) investigated the association between NPY and natural killer (NK) cytotoxicity in AD depression. Circulating concentrations of NPY in plasma were inversely correlated with NK activity in AD patients. These findings suggest that the release of NPY may be associated with the modulation of NK cytotoxicity.

Insulin (INS). Earlier it was impossible to imagine the active production of insulin outside of pancreas, especially in CNS, but in the last few years new evidence has indicated that insulin and its receptors are present in the brain. Insulin was detected in brain by radioimmunoassay, biochemical and immunochemical methods (Baskin et al., 1987).

Immunohistochemical localization of insulin-containing neurons has been shown in many areas of brain, but the olfactory bulbs and hypothalamus consistently have the highest concentrations of insulin. Insulin provides for glucose utilization in brain tissue as well as is an important regulatory peptide in the CNS participated in many physiological processes (e.g. insulin inhibits firing of neurons in the hippocampus and hypothalamus).

Several lines of evidence indicate that insulin may influence synaptic activity. Insulin modulates monoamine uptake in cultured neuronal cells (Boyd et al., 1985) and stimulates synaptosomal uptake of neurotransmitter amino acids (Sun et al., 2018).

Insulin increases catecholamine turnover and release from brain cells and has also been shown to stimulate Na, K-ATPase activity in hippocampus. Acquired disturbances of several aspects of cellular metabolism appear pathologically important in sporadic AD.

Among these, brain glucose utilization is reduced in the early stages of the disease and the regulatory enzymes important for glucose metabolism are reduced (Fine et al., 2017). In the brain, INS, insulin-like growth factors and their receptors regulate glucose metabolism and promote neuronal growth. INS and c-peptide concentration in the brain is decreased with ageing and AD (Fine et al., 2017).

Weak INS-immunoreactivity could be demonstrated histochemically in pyramidal neurons of controls, whereas in AD a stronger INS-immunoreactivity was found. Brain INS receptor densities in AD were decreased compared to middle-aged controls, but increased in comparison to age-matched controls. INS growth factor-I receptor densities were unchanged in ageng and in AD. Tyrosine kinase activity, a signal transduction mechanism common to both receptor systems, was reduced in AD in comparison to middle-aged and age-mathced control groups (Yew et al., 1999; Fine et al., 2017). These data are consistent with a neurotrophic role of INS in the human brain and a disturbance of INS signal transduction in AD brain and favor the hypothesis that INS dependent functions may be of pathogenetic relevance in sporadic AD.

Glucagon (GLU). In addition to being found in the pancreas and gut, GLU immunoreactivity has been demonstrated in brain, where the highest concentrations appear to be in the hypothalamus with intermediate amounts in the midbrain and low amounts in cortex (Figlewicz et al., 1987).

There are not many research data to establish a possible function of GLU in the CNS. GLU immunoreactivity is released from a synaptosomal preparation of thalamus, hypothalamus, and brain stem in response to K^+ (Tominaga et al., 1984).

These data support a potential role of CLU as neurotransmitter or neuromodulator, which could be involved in the cascade of molecular reactions that regulate intracellular Ca^{2+} concentration. Many data testify to dysfunction of intracellular Ca^{2+} homeostasis to result in neuronal loss (Choi, 1995; Verkhratsky et al., 1998).

Endothelins (ET). ET are a potent vasoactive peptides produced by endothelial cells that elecits prolonged constriction in most smooth muscle preparations and dilation in others (Rubanyi and Botelho, 1991). Of three isopeptides, ET-1 is the only form constitutively released and may modulate vascular tone via binding to one of several receptor subtypes in smooth muscle. ET-1 immunoreactivity in the AD brain was significantly increased in frontal and occipital cortex that those in the control brain and a significant correlation was found between frontal and temporal lobe of AD brains (Minami et al., 1996). These findings may explain the clinico-radiological results that the cerebral blood flow is decreased in AD patients, the mechanism of which is still unknown.

Chromogranin A (CGA). CGA belongs to a multifunctional peptide family widely distributed in secretory vesicles in neurons and neuroendocrine cells. Within the brain, CGA is localized in neurodegenerative areas associated with reactive microglia. CGA stimulated microglial cells to secrete heat-stable diffusible neurotoxic agents and also induced a marked accumulation of NO and tumor necrosis factor by microglia (Gasparini et al., 1998). It seems to be possible, that CGA represents an endogenous factor that triggers the microglial activity responsible for the pathogenesis of neuronal degeneration.

CONCLUSION: *Further investigations of brain hormones for improvement of diagnosis and therapy of neurodegenerative diseases*

In spite of many reports on the study of the behavior and role of different biologically active substances in the pathogenesis of mitochondrial diseases, most of them are devoting to concret one or two types of molecules. Thus, a complex studies, in which the behaviour of many molecules was studied at the same time and at the same patients are absent.

We guess, that it is now essential to identify not only those cytokines and other molecules above and their actions that are associated directly with physiological regulation and disease processes, but also their mechanisms of communications and joint actions. A clear understanding of these processes, combined with development of methods to manipulate them, is likely to offer significant therapeutic potential in the successful treatment of mitochondrial diseases.

It is necessary to underline, that while the patient is alive, the distinction between different forms of dementia rests with clinical assessment. The diagnosis of a specific form of dementia as AD manifestation is confirmed only at autopsy. This circumstance dictates the necessity of the search of in lifetime markers for diagnosis and prognosis of AD and relative mitochondrial diseases.

It seems to be possible, because recently the results of some investigations (Gasparini et al., 1998; Miklossy et al., 1999) suggest that AD might be the disease not only the central nervous system, but might be a systemic disorder. If so, the use of human peripheral cells and tissue biopsies could provide a promising tool for lifetime diagnosis of AD and other neurodegenerative diseases.

We suppose, that the further investigations in this direction should include the following steps to understanding better the inter- and intracellular mechanisms of neurodegenerative pathology as well as for elaboration of a new promising life-time marker of these diseases. The main of these steps are following:

- ***to study the molecular bases of AD and PD associated with defects of the mitochondrial machinery of protein translocation*** (i.e. to complete the sequence of the hTom20 gene; to elucidate the chromosome location of the gene and processed pseudogenes; to identify polymorphism of the hTom20 gene in general population as well as in patients with AD and PD; to identify new subunits of the translocase of the mitochondrial outer membrane (Tom complex), and to characterize their respective genes).
- ***immunocytochemical mapping and image analysis of microscopic manifestations of AD and PD*** (to identify localization of the most key molecules which are involved in pathogenesis of neurodegenerative diseases in human brain; to study in detail a functional morphology of cells and tissue structures imunocytochemically positive to molecules above and to compare them to the pathological lesions on light and electron-microscopical levels in post-mortem brain in AD and PD patients).
- ***development of a new methods for lifetime diagnosis and treatment of AD and PD*** (taking into account an important role of MT as scavenger of free radicals, it seems to be very promising to clarify the role of MT in intracellular mechanisms of neurodegenerative diseases and to elaborate it as a new in lifetime marker for diagnostics of AD and PD. To achieve this aim the objectives below should be solved: 1) to identify the key molecules of these disorders (i.e. β-APP, tau-protein, ubiquitin, dopamine, NO-synthase) and MT in human blood lymphocytes from healthy volunteers and patients with AD and PD, and thus to show that blood lymphocytes could be used as a suitable object for lifetime diagnosis of AD and PD; 2) to carry out the quantitative immunocytochemical analysis of concentration of β-APP, tau-protein, ubiquitin, dopamine, NO-synthase and MT in the lymphocytes from AD and PD patients; 3) to determine the excretion in urine of the products of MT interactions with free radicals: cyclic 3-hydroxymelatonin (3-HMT), N^1-acetyl-N^2-formyl-5-methoxykynuramine (AMFK), N^1-acetyl-5-methoxykynuramine (AMK) (Lee et al., 2016) as well as 6-sulfatoxymelatonin (aMT6s) in AD and PD patients; 4) to identify of polymorphisms and mutations in Tom20 gene in humal blood lymphocytes of general population and patients with AD and PD; 5) to study correllations between expression of Tom20 gene, β-APP, tau-protein, ubiquitin, dopamine, NO-synthase and MT in human lymphocytes of healthy people as well as of AD and PD patients and compare them with excretion indices of the same groups; 6) on the basis of data of the research above to clarify the biological role of MT in intracellular mechanisms of neurodegenerative diseases and to elaborate aMT6s as a new non-invasive marker for lifetime diagnosis, definition of prognosis and efficiency of specific therapy in individual AD and PD patients).

Thus, there is no doubt, that DNIES and its hormones being a multifunctional biologically active molecules and located everywhere in the organism, including brain play an important role in pathogenesis of AD, PD, and other neurodegenerative and mitochondrial diseases. The further investigations in this field of study it seems to be very effective as well as for elucidation of molecular and cellular bases of pathological mechanisms of neuronal degeneration and moreover for elaboration of optimal methods of diagnosis and therapy of many diseases.

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REFERENCES

Acuna-Castroviejo D., Coto-Montes A., Monti M.G. et al. (1997) Melatonin is protective against MPTP-induced striatal and hippocampal lesions. *Life Sci.*, **60:** 23-29.

Alves-Rodrigues A., Gregori L., Figueiredo-Pereira M.E. (1998) Ubiquitin, cellular inclusions and their role in neurodegeneration. *Trends Neurosci.*, **21:** 516-520.

Ames B.N., Shigenaga M.K., Hagen T.M. (1993) Oxidants, antioxidants, and the degenerative diseases of aging. *Proc. Natl. Acad. Sci. USA*, **90:** 7915-7922.

Aronin N., Coslovsky R., Leeman S.E. (1986) Substance P and neurotensin**:** their role in the regulation of anterior pituitary function. *Annu. Rev. Physio.l*, **48:** 537-549.

Asensio V.C., Campbell I.L. (1999) Chemokines in the CNS**:** plurifunctional mediators in diverse states. *Trends Neurosc.i*, **22:** 504-512.

Auld D.S., Kar S., Quirion R. (1998) β-Amyloid peptides as direct cholinergic neuromodulators**:** a missing link? *Trends Neurosci.*, **21:** 43-49.

Barlow-Walden L.R., Reiter R.J., Abe M. et al. (1995) Melatonin stimulates brain glutathione peroxidase activity. *Neurochem. Int.*, **26:** 497-502.

Baskin D.G., Figlewicz D.P., Woods S.C. et al. (1987) Insulin in the brain. *Annu. Rev. Physiol.*, **49:** 335-347.

Beal M.F., Benoit R., Mazurek M.F. et al. (1986) Somatostatin-28 (1-12)-like immunoreactivity is reduced in Alzheimer's disease cerebral cortex. *Brain Res*, **368:** 380-383.

Beal M.F. (1990) Somatostatin in neurodegenerative illnesses. *Metabolism*, **39 (9, Suppl 2):** 116-119.

Blass J.P., Baker A.C., Ko L. et al. (1991) Expression of "Alzheimer antigens" in cultured skin fibroblasts. *Arch. Neurol.*, **48:** 709-717.

Bolanos J.P., Almeida A., Stewart V. et al. (1997) Nitric oxide-mediated mitochondrial damage in the brain: mechanisms and implications for neurodegenerative diseases. *J. Neurochem.*, **68:** 2227-2240.

Borjigin J., Li X., Snyder S.H. (1999) The pineal gland and melatonin: molecular and phar-macologic regulation. *Annu. Rev. Pharmacol. Toxicol*., **39:** 53-65.

Boyd F.T., Clarke D.W., Muther T.F., Raizada M.K. (1985) Insulin receptors and insulin modulation of norepinephrine uptake in neuronal cultures from rat brain. *J. Biol. Chem.*, **260:** 15880-15884.

Brazeau P., Vale W., Burgus R. et al. (1973) Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. *Science*, **179:** 77-79.

Brown M., Rivier J., Vale W. (1979) Somatostatin: central nervous system actions on glucoregulation. *Endocrinology*, **104:** 1709-1715.

Brown M.R. (1983) Central nervous system sites of action of bombesis and somatostatin to influence plasma epinephrine levels. *Brain Res.*, **276:** 253-257.

Calhoun M.E., Wiederhold K-H., Abramowski D. et al. (1998) Neuron loss in APP transgenic mice. *Nature*, **395:** 755-756.

Chiso E., Nicolosi M., Arvat E. et al. (1993) Growth hormone secretion in Alzheimer's disease: studies with growth hormone releasing hormone alone and combined with pyridostigmine or arginine. *Dementia*, **4:** 315-320.

Choi D.W. (1995) Calcium: still center-stage in hypoxic-ishemic neuronal death. *Trends Neurosci.*, **18:** 58-60.

Ciesielski-Treska J., Ulrich G., Taupenot L. et al. (1998) Chromogranin A induces a neurotoxic phenotype in brain microglial cells. *J. Biol. Chem.*, **273:** 14339-14346.

Clark E.A., Brugge J.S. (1995) Integrins and signal transduction pathways: the road taken. *Science*, **268:** 233-238.

Clayton D.F., George J.M. (1998) The synucleins: a family of proteins involved in synaptic function, plasticity, neurodegeneration and disease. *Trends Neurosci.*, **21:** 249-254.

Congdon E.E., Sigurdsson E.M. (2018) Tau-targeting therapies for Alzheimer disease. *Nat Rev Neurol.*, **14(7):** 399-415.

Coyle J.T., Puttfarcken P. (1993) Oxidative stress, glutamate, and neurodegenerative disorders. *Science*, **262:** 689-695.

Cuzzocrea S., Tan D-X., Costantino G. et al. (1999) The protective role of endogenous melatonin in carrageenan-induced pleurisy in the rat. *FASEB J.*, **13:** 1930-1938.

Davies A.M. (1995) The bcl-2 family of proteins, and the regulation of neuronal survival. *Trends Neurosci.*, **18:** 355-358.

Davis R.E., Miller S., Herrnstadt C. et al. (1997) Mutations in mitochondrial cytochrome c oxidase genes segregate with late-onset Alzheimer disease. *Proc. Natl. Acad. Sci. USA*, **94:** 4526-4531.

De Souza E.B., Whitehouse P.J., Kuhar M.J. et al. (1986) Reciprocal changes in corticotropin-releasing factor (CRF)-like immunoreactivity and CRF receptors in cerebral cortex of Alzheimer's disease. *Nature*, **319:** 593-595.

Dehghani Z., Meratan A.A., Saboury A.A., Nemat-Gorgani M. (2020) α-Synuclein fibrillation products trigger the release of hexokinase I from mitochondria: Protection by curcumin, and possible role in pathogenesis of Parkinson's disease. *Biochim. Biophys. Acta Biomembr.*, **1862(6):** 183251.

Devine M.J., Kittler J.T. (2018) Mitochondria at the neuronal presynapse in health and disease. *Nat. Rev. Neurosci.*, **19(2):** 63-80.

Dickson D.W. (1997) The pathogenesis of senile plaques. *J. Neuropathol. Exp. Neurol.*, **56:** 321-339.

Dines K.C., Powell H.C. (1997) Mast cell interactions with the nervous system: relationship to mechanisms of disease. *J. Neuropathol. Exper. Neurol.*, **56:** 627-640.

Dumbrille-Ross A., Seeman P. (1984) Dopamine receptor elevation by cholecystokinin. *Peptides*, **5:** 1207-1212.

Dysken M.W., Falk A., Pew B. et al. (1990) Gender differences in TRH-stimulated TSH and prolactin in primary degenerative dementia and elderly controls. *Biol. Psychiatry*, **28:** 144-150.

Efthimiopoulos S., Vassilacopoulou D., Ripellino J.A. et al. (1996) Cholinergic agonists stimulate secretion of soluble full-length amyloid precursor protein in neuroendocrine cells. *Proc. Natl. Acad. Sci. USA*, **93:** 8046-8050.

Everitt B.J., Hokfelt T., Terenius L. et al. (1984) Differential co-existence of neuropeptide Y (NPY)-like immunoreactivity with catecholamines in the central nervous system of the rat. *Neuroscience*, **11:** 443-462.

Fadeel B., Zhivotovsky B., Orrenius S. (1999) All along the watchtower: on the regulation of apoptosis regulators. *FASEB J.*, **13:** 1647-1657.

Fahn S., Cohen G. (1992) The oxidant stress hypothesis in Parkinson's disease: evidence supporting it. *Ann. Neurol.*, **32:** 804-812.

Figlewicz D.P., Lacour F., Sipols A. (1987) Gastroenteropancreatic peptides and the central nervous system. *Annu. Rev. Physiol.*, **49:** 383-395.

Fine J.M., Forsberg A.C., Stroebel B.M. et al. (2017) Intranasal deferoxamine affects memory loss, oxidation, and the insulin pathway in the streptozotocin rat model of Alzheimer's disease. *J. Neurol. Sci.*, **380:** 164-171.

Gale L.M., McColl S.R. (1999) Chemokines: extracellular messengers for all occasions. *Bio-Essaya*, **21:** 17-28.

Gao Y., Tan L., Yu J.T., Tan L. (2018) Tau in Alzheimer's Disease: Mechanisms and Therapeutic Strategies. *Curr. Alzheimer Res.*, **15(3):** 283-300.

Gasparini L., Racchi M., Binetti G. et al. (1998) Peripheral markers in testing pathophysiological hypotheses and diagnosing Alzheimer's disease. *FASEB J.*, **12:** 17-34.

Goedert M., Lightman S.L., Nagy J.I. et al. (1982) Neurotensin in the rat anterior pituitary gland. *Nature*, **298:** 163-165.

Goltermann N.R. (1982) In vivo biosynthesis of cholecystokinin in hog cerebral cortex. *Peptides*, **3:** 101-104.

Green D.R. (1998) Apoptotic pathways: the roads to ruin. *Cell*, **94:** 695-698.

Griffin S.W.T, Sheng J.G., Roberts G.W., Mrak R.E. (1995) Interleukin-1 expression in different plaque types in Alzheimer's disease: significance in plaque evolution. *J. Neuropathol. Exp. Neurol*., **54:** 276-281.

Grota L.J., Brown G.M. (1974) Antibodies to indolealkylamines: serotonin and melatonin. *Can. J. Biochem.*, **52:** 196-203.

Hachiya N., Alam R., Sakasegawa N. et al. (1993) A mitochondrial import factor purified from rat liver cytosol is an ATP-dependent comformational modulator for precursor proteins. *EMBO J.*, **12:** 1579-1586.

Hernandez J.M., Giner P., Hernandez-Yago J. (1999b) Gene structure of the human mitochondrial outer membrane receptor Tom20 and evolutionary study of its family of processed pseudogenes. *Gene*, **239:** 283-291.

Hernandez J.M., Hernandez C.S., Giner C.P. et al. (1999a) Identification of Ψ3Tom20, a novel processed pseudogene of the human Tom20 gene, and complete characterization of Ψ1Tom20 and Ψ2Tom20. *Mol. Gen. Genet.*, **262:** 207-211.

Hockenbery D, Nunez G, Milliman C et al. (1990) Bcl-2 is an inner mitochondrial membrane protein that blocks programmed cell death. *Nature*, **348:** 334-336.

Hockenbery D.M., Oltvai Z.N., Yin X-M. et al. (1993) Bcl-2 functions in an antioxidant pathway to prevent apoptosis. *Cell*, **75:** 241-251.

Iadanza M.G., Jackson M.P., Hewitt E.W. et al. (2018) A new era for understanding amyloid structures and disease. *Nat. Rev. Mol. Cell. Biol.*, **19(12):**755-773.

Irwin M., Brown M., Patterson T. et al. (1991) Neuropeptide Y and natural killer cell activity: findings in depression and Alzheimer caregiver stress. *FASEB J.*, **5:** 3100-3107.

Ishii M., Hiller A.J., Pham L. et al. (2019) - amyloid-beta modulates low-threshold activated voltage-gated L-type calcium channels of arcuate neuropeptide y neurons leading to calcium dysregulation and hypothalamic dysfunction. *J. Neurosci.*, **39(44):** 8816-8825.

Iwai A., Masliah E., Yoshimoto M. et al. (1995) The precursor protein of non-Aβ component of Alzheimer's disease amyloid is a presynaptic protein of the central nervous system. *Neuron*, **14:** 467-475.

Jacobson M.D., Burne J.F., King M.P. et al. (1993) Bcl-2 blocks apoptosis in cells lacking mitochondrial DNA. *Nature*, **361:** 365-369.

Jennes L., Stumpf W.E., Kalivas P.W. (1982) Neurotensis: topographical distribution in rat brain by immunohistochemistry. *J. Comp. Neurol.*, **210:** 211-224.

Kahn D., Abrams G.M., Zimmerman E.A. et al. (1980) Neurotensin neurons in the rat hypothalamus: an immunocytochemical study. *Endocrinology*, **107:** 47-54.

Kahn D., Hou-You A., Zimmerman E.A. (1982) Localization of neurotensin in the hypothalamus. *Ann. NY Acad. Sci.*, **400:** 117-131.

Kang P.J., Ostermann J., Shilling J. et al. (1990) Hsp70 in the mitochondrial matrix is required for translocation and folding of precursor proteins. *Nature*, **348:** 137-143.

Koenig H.L., Schumacher M., Ferzaz B. et al. (1995) Progesterone synthesis and myelin formation by Schwann Cells. *Science*, **268:** 1500-1503.

Kraskovskaya NA, Kukanova EO, Linkova NS et al. (2017) Tripeptides Restore the Number of Neuronal Spines Under Conditions of *In Vitro* Modeled Alzheimer's Disease. *Bulletin of Experimental Biology and Medicine*, **163(4):** 550-553.

Kreutzberg G.W. (1996) Microglia: a sensor for pathological events in CNS. *Thends Neurosci.*, **19:** 312-318.

Kroemer G., Dallaporta B., Resche-Rigon M. (1998) The mitochondrial death/life regulator in apoptosis and necrosis. *Annu. Rev. Physiol.*, **60:** 619-642.

Kunkl M., Frascolla S., Amormino C. et al. (2020) T Helper Cells: The Modulators of Inflammation in Multiple Sclerosis. *Cells*, **9(2): pii:** E482.

Kvetnoy I.M., Sandvik A.K., Waldum H.L. (1997) The diffuse neuroendocrine system and extrapineal melatonin. *J. Mol. Endocrinol.*, **18:** 1-3.

Kvetnoy I.M., Yuzhakov V.V., Raikhlin N.T. (1997) APUD cells: modern strategy of morphofunctional analysis. *Microsc. Anal.*, **48:** 25-27.

Kvetnoy I.M. (1999) Extrapineal melatonin: location and role within diffuse neuroendocrine system. *Histoch. J.*, **31:** 1-12.

Larrson L-I. (1980) On the possible existence of multiple endocrine, paracrine and neurocrine messengers in secretory system. *Invest Cell Pathol.*, **3:** 73-85.

Lee K., Zawadzka A., Czarnocki Z. et al. (2016) Molecular cloning of melatonin 3-hydroxylase and its production of cyclic 3-hydroxymelatonin in rice (Oryza sativa). *J. Pineal. Res.*, **61(4):** 470-478.

Lee VM-Y., Trojanowski Q. (1999) Neurodegenerative tauopathies: human disease and transgenic mouse models. *Neuron*, **24:** 507-510.

Li P., Song C. (2020) Potential treatment of Parkinson's disease with omega-3 polyunsatu-rated fatty acids. *Nutr. Neurosci.*, 1-12. doi: 10.1080/1028415X.2020.1735143

Li W.P., Lai H.W., Cheng S.Y., Yew D.T. (1996) Somatostatin-positive neurons in the different parts of the brain in normal aging and Alzheimer's disease. *Biol. Signals*, **5:** 343-348.

Lithgow T., Ryan M., Anderson R.L. et al. (1993) A constitutive form of heat-shock protein 70 is located in the outer membranes of mitochondria from rat liver. *FEBS Lett.*, **332:** 277-281.

Liu Q., Hazan A., Grinman E., Angulo J.A. (2017) Pharmacological activation of the neurotensin receptor 1 abrogates the methamphetamine-induced striatal apoptosis in the mouse brain. *Brain Res.*, **1659:** 148-155.

Ljungdahl A., Hokfelt T., Nillson G. (1978) Distribution of substance P-like immunoreactivity in the central nervous system of the rat. I. Cell bodies and nerve terminals. *Neuroscience*, **3:** 861-943.

Luft R. (1994) The development of mitochondrial medicine. *Proc. Natl. Acad. Sci. USA*, **91:** 8731-8738.

Lundberg J.M., Saria A., Franco-Cereceda A. et al. (1985) Differential effects of reserpine and 6-hydroxydopamine on neuropeptide Y (NPY) and noradrenaline in peripheral neurons. *Arch. Pharmacol.*, **328:** 331-340.

Lynn W.S., Wong P.K.Y. (1995) Neuroimmunodegeneration: do neurons and T cells use common pathways for cell death. *FASEB J.*, **9:** 1147-1156.

Martinus R.D., Ryan M.T., Naylor D.J. et al. (1995) Role of chaperones in the biogenesis and maintenance of the mitochondrion. *FASEB J.*, **9:** 371-378.

Mayo J.C., Sainz R.M., Uria H. et al. (1998) Melatonin prevents apoptosis induced by 6-hydroxydopamine in neuronal cells**:** implications for Parkinson's disease. *J. Pineal. Res.*, **24:** 179-192.

Meltzer C.C., Smith G., DeKosky S.T. et al. (1998) Serotonin in aging, late-life depression, and Alzheimer's disease: the emerging role of functional imaging. *Neuropsychopharmacology*, **18:** 407-430.

Mennicken F., Maki R., de Souza E.B., Quirion R. (1999) Chemokines and chemokine receptors in the CNS: a possible role in neuroinflammation and patterning. *Trends Pharmacol. Sci.*, **20:** 73-78.

Merrill J.E., Jonakait G.M. (1995) Interactions of the nervous and immune systems in development, normal brain homeostasis, and disease. *FASEB J.*, **9:** 611-618.

Mihara K., Omura T. (1996) Cytoplasmic chaperones in precursor targeting to mitochondria: the role of MSF and hsp70. *Trends Cell Biolm.*, **6:** 104-108.

Miklossy J., Taddei K., Martins R. et al. (1999) Alzheimer disease: curly fibers and tangles in organs other than brain. *J. Neuropathol. Exp. Neurol.*, **58:** 803-814.

Minami M., Kimura M., Iwamoto N., Arai H. (1996) Endothelin-1-like immunoreactivity in cerebral cortex of Alzheimer-type dementia. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **19:** 509-513.

Molnar M.J., Kovacs G.G. (2017) Mitochondrial diseases. *Handb. Clin. Neurol.*, **145:** 147-155.

Monaghan P, Robertson D, Amos TAS et al. (1992) Ultrastructural localization of bcl-2 protein. *J. Histochem. Cytochem.*, **40:** 1819-1825.

Morganti-Kossmann M.C., Kossmann T., Wahl S.M. (1992) Cytokines and neuropathology. *Trends Pharmacol. Sci.*, **13:** 286-291.

Mrak R.E., Griffin S.T., Graham D.I. (1997) Aging-associated changes in human brain. *J. Neuropathol. Exp. Neurol.*, **56:** 1269-1275.

Nathan C. (1992) Nitric oxide as a secretory product of mammalian cells. *FASEB J.*, **6:** 3051-3064.

Neumann H., Wekerle H. (1998) Neuronal control of the immune response in the central nervous system: linking brain immunity to neurodegeneration. *J. Neuropathol. Exp. Neurol.,* **57:** 1-9.

Pallares-Trujillo J., Lopez-Soriano F.J., Argiles J.M. (1998) The involvement of the ubiquitin system in Alzheimer's disease (review). *Int. J. Mol. Med.,* **2:** 3-15.

Pang S.F. Dubocovich M.L., Brown G.M. (1993) Melatonin receptors in peripheral tissues: a new area of melatonin research. *Biol. Signals,* **2:** 177-180.

Papadopoulos V., Guarneri P., Krueger K.E. et al. (1992) Pregnenolone biosynthesis in C6-2B glioma cell mitochondria: regulation by a mitochondrial diazepam binding inhibitor receptor. *Proc. Natl. Acad. Sci. USA,* **89:** 5113-5117.

Paul S.M., Purdy R.H. (1992) Neuroactive steroids. *FASEB J.,* **6:** 2311-2322.

Pearse A.G.E. (1968) Common cytochemical and ultrastructural characteristics of cells producing polypeptide hormones (the APUD series) and their relevance to thyroid and ultimobranchial C-cells and calcitonin. *Proc. Roy. Soc. B.,* **170:** 71-80.

Pearse A.G.E. (1969) The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. *J. Histochem. Cytochem.,* **17:** 303-313.

Petrella C., Di Certo M.G., Barbato C. et al. (2019) Neuropeptides in Alzheimer's Disease: An Update. *Curr. Alzheimer Res.,* **16(6):** 544-558.

Phu L., Rose C.M., Tea J.S. et al. (2020) Dynamic Regulation of Mitochondrial Import by the Ubiquitin System. *Mol. Cell.,* **77(5):** 1107-1123.e10.

Plagman A, Hoscheidt S, McLimans KE et al. (2019) Cholecystokinin and Alzheimer's disease: a biomarker of metabolic function, neural integrity, and cognitive performance. *Neurobiol Aging.,* **76:** 201-207.

Polak J.M., Bloom S.R. (1986) Immunocytochemistry of the diffuse neuroendocrine system. In: J.M.Polak, S.Van Noorden (eds.) *Immunocytochemistry: modern methods and applications*. John Wright & Sons: 328-348.

Price D.L. (1999) New order from neurological disorders. *Nature.* **399 (Suppl):** A3-A5.

Raff M.C., Barres B.A., Burne J.F. et al. (1993) Programmed cell death and the control of cell survival: lessons from the nervous system. *Science,* **262:** 695-700.

Raikhlin N.T., Kvetnoy I.M. (1994) The APUD system (diffuse endocrine system) in normall and pathological states. *Physiol. Gen. Biol. Rev.,* **8(4):** 1-44.

Ramage L., Junne T., Hahne K. et al. (1993) Functional cooperation of mitochondrial protein import receptors in yeast. *EMBO J.,* **12:** 4115-4123.

Reinikainen K.J., Soininen H., Riekkinen P.J. (1990) Neurotransmitter changes in Alzheimer's disease**:** implications to diagnostics and therapy. *J. Neurosci. Res.,* **27:** 576-586.

Reiter R.J., Guerrero J.M., Garcia J.J., Acuna-Castroviejo D. (1998) Reactive oxygen intermediates, molecular damage, and aging. Relation to melatonin. *Ann. NY Acad. Sci.,* **854:** 410-424.

Reiter R.J., Poeggeler B,. Tan D-X. et al. (1993) Antioxidant capacity of melatonin: a novel function not requiring a receptor. *Neuroendocr. Lett.,* **15:** 103-116.

Reiter R.J. (1973) Comparative physiology: pineal gland. *Annu Rev Physiol,* **35:** 305-328.

Reiter R.J. (1992) The ageing pineal gland and its physiological consequences. *BioEssays.,* **14:** 169-175.

Reiter R.J. (1995) Oxidative processes and antioxidative defense mechanisms in the aging brain. *FASEB J.,* **9:** 526-533.

Reiter RJ.. (1997) Aging and oxygen toxicity: relation to changes in melatonin. *Age,* **20:** 201-213.

Reiter R.J. (1998) Oxidative damage in the central nervous system: protection by melatonin. *Prog. Neurobiol.,* **56:** 359-384.

Reubi J.C., Palacios J. (1986) Somatostatin and Alzheimer's disease: a hypothesis. *J. Neurol.,* **233:** 370-372.

Ronnekleiv O.K., Kelly M.J., Eskay R.L. (1984) Distribution of immunoreactive substance P neurons in the hypothalamus and pituitary of the rhesus monkey. *J. Comp. Neurol.,* **224:** 51-59.

Rothwell N.J., Hopkins S.J. (1995) Cytokines and the nervous system. II. Actions and mechanisms of action. *Trends Neurosci.,* **18:** 130-136.

Rubanyi G.M., Botelho H.P. (1991) Endothelins. *FASEB J.,* **5:** 2713-2720.

Sakanaka M., Shiosaka S., Takatsuki K. et al. (1981) Experimental immunohistochemical studies on the amygdalofugal peptidergic (substance P and somatostatin) fibers in the stria terminalis of the rat. *Brain Res.,* **221:** 231-242.

Sakanaka M., Shiosaka S., Takatsuki K. et al. (1982) Origins of substance P-containing fibers in the lateral septal area of young rats: immunohistochemical analysis of experimental manipulations. *J. Comp. Neurol.,* **212:** 268-277.

Sastry P.S., Rao K.S. (2000) Apoptosis and the nervous system. *J. Neurochem.,* **74:** 1-20.

Schapira A.H.V. (1993) Mitochondrial cytopathies. *Curr. Opin. Neurobiol.,* **3:** 760-767.

Selkoe D.J. (1998) The cell biology of β-amyloid precursor protein and presenilin in Alzheimer's disease. *Trends Cell Bio.l,* **8:** 447-453.

Shigenaga M.K., Hagen T.M., Ames B.N. (1994) Oxidative damage and mitochondrial decay in aging. *Proc. Natl. Acad. Sci. USA,* **91:** 10771-10778.

Silver R., Silverman A-J., Vitkovic L., Lederhendler I.I. (1996) Mast cells in the brain: evidence and functional significance. *Trends Neurosci.,* **19:** 25-31.

Smith M.A., Sayre L.M., Monnier V.M., Perry G. (1995) Radical AGEing in Alzheimer's disease. *Trends Neurosci.,* **18:** 172-176.

Solarski M., Wang H., Wille H., Schmitt-Ulms G. (2018) Somatostatin in Alzheimer's disease: A new Role for an Old Player. *Prion.,* **12(1):** 1-8.

Spillantini M.G., Goedert M. (1998) Tau protein pathology in neurodegenerative diseases. *Trends Neurosci.,* **21:** 428-433.

Spillantini M.G., Schmidt M.L., Lee VM-Y. et al. (1997) α-Synuclein in Lewy bodies. *Nature,* **388:** 839-840.

Suemaru S., Hashimoto K., Ogasa T. et al. (1991) Cerebrospinal fluid and plasma corticotropin-releasing hormone in senile dementia. *Life Sci.,* **48:** 1871-1879.

Suemaru S., Suemaru K., Hashimoto K. et al. (1993) Cerebrospinal fluid corticotropin-releasing hormone and ACTH, and peripherally circulating choline-containing phospholipid in senile dementia. *Life Sci.,* **53:** 697-706.

Sun P., Ortega G., Tan Y. et al. (2018) Streptozotocin impairs proliferation and differentiation of adult hippocampal neural stem cells *in vitro*-correlation with alterations in the expression of proteins associated with the insulin system. *Front. Aging Neurosci.,* **10:**145.

Sundler F., Bottcher G., Ekblad E., Hakanson R. (1989) The neuroendocrine system of the gut. *Acta Oncol.,* **283:** 303-314.

Tan D.X., Manchester L.C., Reiter R.J. et al. (1999) Identification of highly elevated levels of melatonin in bone marrow: its origin and significance. *Biochim. Biophys. Acta,* **1472:** 206-214.

Tominaga M., Kaneda H., Marubashi S. et al. (1984) Synaptosomal localization and release of glucagon-like materials in the rat brain. *Brain Res. Bull.,* **12:** 373-375.

Tsuruo Y., Kawano H., Nishimaya T. et al. (1983) Substance P-like immunoreactive neurons in the tuberoinfundibular area of rat hypothalamus. Light and electron microscopy. *Brain Res.,* **289:** 1-9.

Tsutsui K., Ukena K. (1999) Neurosteroids in the cerebellar Purkinje neuron and their actions (review). *Int. J. Mol. Med.,* **4:** 49-56.

Ueda K., Fukushima H., Maslian E. et al. (1993) Molecular cloning of a novel component of amyloid in Alzheimer's disease. *Proc. Natl. Acad. Sci. USA,* **90:** 11282-11286.

Vandael D., Gounko N.V. (2019) Corticotropin releasing factor-binding protein (CRF-BP) as a potential new therapeutic target in Alzheimer's disease and stress disorders. *Transl. Psychiatry,* **9(1):** 272.

Verkhratsky A., Toescu E.C. (1998) Calcium and neuronal ageing. *Trends Neurosci.,* **21:** 2-7.

Yew D.T., Li W.P., Webb S.E. et al. (1999) Neurotransmitters, peptides, and neural cell adhesion molecules in the cortices of normal elderly humans and Alzhemer patients: a comparison. *Exp. Gerontol.,* **34:** 117-133.

Zlomuzica A., Dere D., Binder S. et al. (2016) Neuronal histamine and cognitive symptoms in Alzheimer's disease. *Neuropharmacology,* **106:** 135-45.

Neurodegenerasiya mitoxondrial patologiya kimi: Siqnal mexanizmləri və *life-time* diaqnostika və *target* terapiyasina yeni yanaşmalar

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Mitoxondrilərin struktur və funksional dəyişikliklərin "mitoxondrial xəstəliklər" adlandırılan çoxsaylı kliniki pozulmaların yaranmasının səbəbi olması məlumdur. Hal-hazırda mitoxondrial zülalların nəqlində bir çox amillərin, o cümlədən sitokinlərin, şaperonların, hemokinlərin, neyrosteroidlərin, ubikvitin və digərlərinin iştirakı şübhə doğurmur. Eyni zamanda mitoxondrial xəstəliklərin endogen mexanizmlərində biogen aminlərin və peptid hormonlarının (müxtəlif orqanlarda olan diffuz neyroendokrin sisteminin hüceyrələrində yaranırlar) iştirakı və rolu hələ də məlum deyil. Biogen aminlərin və peptid hormonlarının geniş spektrə malik bioloji effektlərini və xüsusilə hüceyrədaxili kommunikasiyada onların tənzimləyici rolunu nəzərə alaraq, bu molekulların mitoxondrial pozulmaların patogenezində mümkün iştirakının təhlil edilməsini, eləcə də neurodegenerativ xəstəliklərdə *lifetime* diaqnostika üçün yeni markerlərin işlənib hazırlanması, spesifik terapiyanın proqnozunun və effektivliyinin müəyyən edilməsi üçün yeni yanaşmaların işlənməsini mühüm tədqiqat hədəfləri kimi təqdim edirik.

Açar sözlər: *Mitoxondrial xəstəliklər, biogen aminlər, peptid hormonları, diffuz neuroimmunoendokrin sistem, life-time diaqnostikası, neyrodegenerasiya*

Нейродегенерация как митохондриальная патология: Сигнальные механизмы и новые пути для *прижизненной* диагностики и *таргетной* терапии

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Структурные и функциональные изменения митохондрий ответственны за широкий спектр клинических нарушений, которые называют “митохондриальными заболеваниями”. В настоящее время, очевидно, что в транспорте митохондриальных белков, таких как цитокины, шапероны, хемокины, нейростероиды, убиквитин и многие другие, участвуют многие факторы. В то же время участие и роль биогенных аминов и пептидных гормонов (которые продуцируются клетками диффузной нейроэндокринной системы, находящимися в различных органах) в эндогенных механизмах возникновения митохондриальных заболеваний до сих пор неизвестны. Учитывая широкий спектр биологических эффектов биогенных аминов и пептидных гормонов, и, особенно, их регуляторную роль во внутриклеточной коммуникации, представляется важным проанализировать возможное участие этих молекул в патогенезе митохондриальных нарушений, а также искать инновативные пути разработки новых маркеров для прижизненной диагностики, определения прогноза и эффективности специфической терапии при нейродегенеративных заболеваниях.

Ключевые слова: *Митохондриальные заболевания, биогенные амины, пептидные гормоны, диффузная нейроиммуноэндокринная система, life-time диагностика, нейродегенерация*