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Dynamics of Neurodegeneration and of Potential Neuroprotection

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Abstract: Neurodegeneration constitutes a loss of neuronal cells in terms of ongoing injury to cell membranes and organelles. A loss of membranous constituents of the cell appears to account for a process of cerebral cortical atrophy consistent with a further injury to nuclei in the form of DNA fragmentation and induced apoptosis. One might recognize the development of neurofilament aggregation and of beta-amyloid fibrillogenesis in terms of a selective involvement of the neuronal cell body in the neurodegeneration. Alzheimer's disease constitutes a representation of onset dynamics with aging of the central nervous system in the ongoing continuum of further injury to the neuronal cell. A spectrum of dynamic changes would involve in particular a targeting of autophosphorylation systems based on membranes and constituting synaptic injury as a primary site of action. Synapses and cell organelles are a constituent system of dynamic turnover particularly susceptible to ongoing injury as represented and as further developed by such systems as protein molecular misfolding and oxidative stress, within an overall context of cytokine and chemokine action.

Key words: Neurprotection, dynamics, neuradegeneration

NEUROPROTECTION AS NEUROPREVENTION OF PROGRESSIVE ACCUMULATIVE ACTION OF PATHOGENIC RATHER THAN OF ETIOLOGIC AGENTS

Neuroprotection appears a form of neurorescue that arises from etiologic considerations of how injury to neurons progresses rather than originates [1, 2]. In this sense, antioxidant treatment would refer to the progressive accumulation of oxidative stress linked inherently to progression of the neuronal injury itself rather than to the generation of the cause of that neuronal injury.

A mixed cocktail preparation as neuroprotective measures against oxidative stress would appear primarily a closely related phenomenon that progressively scavenges derivatives of the oxygenation-promoting action of nitric oxide and peroxinitrite in reference particularly to lipid peroxidation.

It is perhaps in terms of microglially mediated inflammatory action on various lipid molecules that one might better delineate neuroprotective measures that are generated as self-progressive systems promoting not simply prevention of etiologic cause but particularly progression of etiologic transformation to pathogenetic involvement. Indeed, one might speak of an important host cell involvement in pathogenetic progression of etiologic cases of neuroinjury ranging from oxidative stress to structural lipid catabolism of neuronal cells and cellular subcomponents.

AFFERENT AND EFFERENT PATHWAYS IN ENTORHINAL CORTEX OF ALZHEIMER BRAINS

Transenterorhinal and entorhinal systems would constitute a focal point of transition of afferent to efferent pathways from sensory cortex to prefrontal cortex as a highly selective focus of involvement in Alzheimer's that perhaps relates to fundamental etiology and pathogenesis [3]. Essential intersections of afferent and efferent neuronal pathways as a source of increased susceptibility in Alzheimer's disease might involve modes of neurodegeneration as pathways of pathogenesis.

The preferential atrophy affects the Alzheimer brain in a manner that would be suggestive of a failure of interconnectivity between afferent and efferent pathways of neurodegeneration affecting neuroprotective measures.

The relations of Alzheimer's disease with Argyrophilic Grain Disease, Pick's disease, Parkinson's, Huntington's, may possibly implicate essential intersections between afferent and efferent pathways that progressively result in anterograde and retrograde neuronal degeneration and atrophy.

SYNAPTIC INHIBITION IN SYSTEM INVOLVEMENT IN NEURODEGENERATION

Synaptic inhibition appears a predictor of neuronal susceptibility allowing comparison between different parallel systems of neural projection as represented between the parahippocampus and the hilus of the dentate gyrus [4].

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A concept of parallel attributes between different projection fibers may very well account for an integrative series of pathways that comprehensively delineate whole parametric physiologic pathways that pathologically transform [5]. One might speak of how modes of parallelism would characterize evolving influence as related to neuronal susceptibility and synaptic inhibition in terms especially of cell cycle activation[6]. Pezrhaps it is strictly in terms of synaptic transmission that one might better characterize modes of neuronal susceptibility that arise and develop largely as individual neuronal cell loss.

NEURONAL CELL LOSS IN PREDETERMINED PROGRESSION OF THE CLINICAL DEMENTED STATE

Alzheimer's disease appears to have an onset of activity that predates clinical symptoms by several years [7,8].

One might consider the individual neurofibrillary tangles that progress in terms of an initial alteration in neuronal structure and appearance and that subsequently extend as a series of neuropathologic indices [9].

Amyloid deposition as an initially focal process of accumulation of the beta-amyloid fibrils would progress in terms of dynamics of cellular and vascular involvement.

An essential aspect of neuronal pathobiology would otherwise implicate alternate mechanisms to physico-chemical spread of the beta-amyloid deposition and of neurofibrillary tangles. Such a system would otherwise implicate at an early stage the hippocampal cortex as progressive transformation of vessels and neurons; these are not limited only to a few foci but extend globally to involve much of the brain [10] and would particularly implicate the proteome [11]. Vascular and neuronal lesions would be an evolving progression of lesions that might prove independent of actual mechanistic spread from a single initial pathologic focus.

Alzheimer-type lesions might be a manifestation of vascular interaction with neurons in terms not only of trophic effect or deficiency but particularly as an integral phenomenon of neuronal non-viability.

Neuronal loss might constitute a fundamental pathogenetic series of pathways as evolving systems of influence and self-definition in dynamics of a clinical demented state.

NEURONAL CELL LOSS VERSUS EVOLVING BRAIN ATROPHY

.Failure to detect early volumetric loss of the entorhinal cortex and hippocampus proper in Alzheimer's disease might relate to a non-atrophic pattern of progressive neuronal loss in the first instance [12] . Neurons might be lost in Alzheimer patients without a statistically significant element of cortical atrophy being detectable on imaging studies. One might speak of non-atrophic forms of Alzheimer's that are only partly characterized as early disease stage [13]. Indeed, neuronal loss in Alzheimer's would perhaps prove a correlate measure of a disease process that evolves largely as glial or neuropil shrinkage prior to massive loss of neuronal cell bodies.

EARLY ONSET DISEASE VERSUS EARLY DISEASE STAGE

Prediction of the development of the demented state would require not simply a risk factor profile but especially an assessment of the early stages of the clinical demented state [14]. Indeed, early-demented stages of the disease would prove an often -close correlate of modes of reaction or adjustment to the early and subsequent stages of brain involvement. Early stage progression would perhaps be linked to either early or later stage of onset of the demented state.

LARGE MOLECULAR COMPLEXES AS INTERACTIVE MEMBRANE-BASED HYPERPHOSPHORYLATION

Neurofibrillary tangles appear a characterization of tau hyperphosphorylation in a manner determining protein kinase activities [15]. Binding Complexes of Presenilin Binding Protein (CPBP) as a very large molecule might constitute dynamics of a hyperphosphorylation chiefly determined by molecular complex size. The localization of CPBP to brain regions particularly susceptible to Alzheimer disease pathology would perhaps indicate a selective response based on such large molecular complex size and progressing also in such terms. Presenilin as an attached molecule to neuronal membranes would also participate in dynamics of amyloid deposition affecting neuronal viability.

It might very well prove valid to consider essential adaptation of large molecular complexes that promote interactive membrane events in progression of the Alzheimer brain pathology and that involve aggregation-disaggregation [16] . Indeed, strict characterization of dynamic membrane interactions might not simply implicate a possible role for misfolded protein molecules[17]. but an accumulative phenomenon of interactive participation in various systems ranging from neurofibrillary tangle formation, dystrophy of neurites and neuropil threads.

Axonal pathology in Alzheimer's disease might very well involve a responsiveness to neuronal injury that hyperphosphorylates further tau molecules [18,19].

A central problem regarding loss of neuronal viability might indicate a multiplicity of events arising as strict progression of membrane-based hyperphosphorylation and as an interactivity of various protein kinases and also as membrane-based events of etiologic and pathogenic significance in Alzheimer's disease.

A GLIAL REACTION TO ARGYROPHILIC GRANULES IS ABSENT IN ALZHEIMER'S DISEASE

Localization of argyrophilic granules to the cortical grey matter in Alzheimer's disease might correspond to modes of biochemical handling linked to microtubule binding repeat patterns that distinguish in particular argyrophilic grain disease as an apparently distinct pathologic entity in its own right [20]. A concurrent glial participation with various argyrophlic granule -associated disorders ranging from Pick's disease to supranuclear palsy to motor neuron disease and multisystem disease as contrasted with Alzheimer's might perhaps indicate a nonspecificity for the diagnostic label of Argyrophilic Grain Disease linked to variable uptake dynamics of glial cells.

Glial cell participation in these disorders is one that is possibly related to dynamics of loss of neurons and of other processes whereby white matter becomes a reactive component to the primarily neuronal body involvement as distinct from Alzheimer's disease.

BEYOND SIMPLE SYSTEM TRACT INVOLVEMENT IN NEURODEGENERATION

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Oxidative stress injury and oxidative free radical action appear related to neurodegenerative disease and aging [21] . Indeed, one might recognize how aging predisposes to neurodegeneration affecting not only the dopaminergic system in Parkinson's disease but also a wide variety of cerebral cortical systems as represented by Alzheimer's disease, or the motor neuron system in amyotrophic lateral sclerosis. In this way, perhaps, one might very well classify neurodegenerative disease in terms of an oxidative stress injury that is or is not suppressible with agents such as carbosyfallerenes with their very large electronegative center and iron scavenging action.

Understanding neurodegeneration in terms of one integral mechanism of oxidative injury would better account for types of pathology that defy classification as specific features of any neurodegenerative state beyond simple concepts of just single system tract involvement.

A COMPARTMENTALIZED INITIAL STAGE OF OXIDATIVE STRESS INJURY

Antioxidant protection of neurons, as by melatonin, appears tied up with the permeability of the blood brain barrier to various antioxidants and also with a phenomenon of subcompartmentalization within neurons and the neuropil [22].

It would appear that subcompartmentalization of oxygen-free radicals and of anti-oxidants would proceed in a manner intrinsically related to peroxidation events affecting bilipid membranes of neurons and of neuronal organelles. One might speak of how oxidative stress injury is a compartmentalized form of injury that only subsequently extends to involve not only DNA and lipid membranes but also a series of subcellular organelles ranging from the Golgi apparatus to mitochondria.

PATTERN PROTOTYPE ORDERS OF SYNAPTIC FUNCTIONALITY

It would appear that different orders or levels of functionality operate in terms of clathrin-coated synaptic vesicle release and uptake in the cerebral cortex [23].One might implicate synaptophysin and also AP180 at different foci in the synapse that are activated separately or strictly in a sequential fashion rather than simultaneously. This perhaps appears particularly related to the presynaptic uptake of clathrin-coated synaptic vesicles from the synaptic cleft.

It is only in terms, however, of different orders of functionality that one would best account for the utilization and immunomarking of synaptophysin after a baseline functional level for AP180 is exceeded.

Baseline functionality of synapses might, in general terms, help account for various pattern progression traits of neurodegenerative disorders such as Parkinson's disease that predominately affect the extrapyramidal system but invariably progress later to implicate cortical circuits and induce dementia.

DNA FRAGMENTATION IS DISTINCT FROM APOPTOSIS

Ca2+-influx within neurons activates calpain in a manner that secondarily cleaves poly-ADP-ribose polymerase (PARP) based also on caspase-mediated action [24]. It would appear that PARP inactivation is a consequential step in accumulative fragmentation of neuronal DNA in a manner that intrinsically characterizes neurodegeneration of an apoptotic type. One might speak of how neuronal apoptosis is a consequence of beta-amyloidosis in a manner linked to formation and deposition of the amyloid in the senile plaques but also in the wall of blood vessels.

The oxidative free radicals generated by beta-amyloid deposition would result in apoptotic cell death characterizing neurodegeneration of an Alzheimer type distribution.

There would appear to operate two basic pathways, one linked to apoptosis and another to accumulative DNA fragmentation, that can apparently be distinguished from acute apoptotic neuronal cell death.

STABILIZING AND MATURING FUNCTIONALITY OF HYPERPHOSPHORYLATION IN NEUROFILAMENT REACTIVITY

NF 68 kDa Neurofilament accumulation in the cone growth of axons is transformed into stabilizing NFM (160

kDa) and NFH (200 kDa) neurofilament that progress to stabilization of and maturation of pre-existing connections [25].

Understanding such neurofilament transformation from accumulative to stabilizing to maturing structures might help redefine highly phosphorylated neurofilament [26] that progresses in reaction to ischemic injury of neurons. Aging as a competent but attenuated system of reactive neurofilament response to ischemic neuronal injury might perhaps also help characterize neurofilament transformations as plasticity events intrinsic to dendritic sprouting. Indeed, dendritic thickening might closely correlate with reactive synaptogenesis and to progressive phosphorylation of neurofilaments towards stabilization and maturing functionality [27].

NEURAL CELL ADHESION MOLECULE AND INTEGRIN ALPHAV UNDERLIE SURVIVAL OF SPROUTING NEURONS IN GDNF ACTION

Neuritic cone outgrowth appears to constitute a differentiation process related to integrin alphav and NCAM functionality related glial -cell-line-derived neurotrophic factor [28]. Such action would appear linked to dopamine turnover and motor activity that progresses in terms of dopaminergic neuronal survival and outgrowth.

It is perhaps in understanding how neural cell adhesion molecules cooperatively interact with integrin alphav that one would better realize how neuronal sprouting is an integral phenomenon of differentiation linked to cell sprouting on the one hand and to various other mechanisms of induced participation promoting cellular interactivity as a connectivity phenomenon [29].

Connectivity participation in dopaminergic neuronal survival would appear to involve a sprouting response intrinsic to such neuronal survival.

Neuronal migration, neurite outgrowth, synaptogenesis and intracellular signaling appear linked to basic neuritogenesis that ensures neuroprotection and optimizes neuronal survival [23].

IMMUNE REACTIVITY TO AMYLOID BETA IN ALZHEIMER DISEASE PROGRESSION

Lymphocytes reactive to Amyloid Beta appear to involve an immune response that modulates Alzheimer disease course [36]. The inflammatory and pro-oxidant features of the ongoing Alzheimer disease process appear linked to tumor necrosis factor alpha secretion and the recruitment of lymphocytes to Amyloid Beta in particular. T-cell involvement in this disease would involve upregulation of Amyloid Precursor Protein-derived peptides in a manner resulting in their multiplication and clonal expansion. Telomere shortening of T cells appears linked to immune alterations arising both in terms of native and also foreign antigens. T cell rather than B cell reactivity is tied up with serum levels of tumor necrosis factor alpha and with apoptosis. Immune reactivity in Alzheimer's disease appears a centrally operative modulator in disease progression in Alzheimer disease [31]

LOSS OF NEURONAL CELL MEMBRANE IN ALZHEIMER'S

A continuum of production of a process centrally operative as amyloid protein deposition but individually characterized by specific dynamics of evolution might define an Alzheimer process of generated fibrillogenesis that proceeds largely in terms of how molecules do aggregate intraneuronally [6].

Intraneuronal involvement in terms of neurofibrillary tangles and especially how such involved neurons are a transitional stage in an Alzheimer neurodegeneration continuum might significantly help establish progression of a brain atrophy that arises primarily intraneuronally and evolves subsequently transmembranously.

A transmembranous evolution of initially intraneuronal aggregation of amyloid type proteins [32]. ranging from neurofibrillary tangles to Lewy bodies might help define attributes of senile plaques that morphologically enlarge and mature in terms of the neuronal loss and of variable activity of microglia and astrocytes.

Understanding an essential evolutionary maturation of the senile plaque might in various ways help characterize a process of transmembranous involvement of neurons that extends towards the loss of neurons in a manner distinct from either neurofibrillary tangle formation or of Beta-amyloidosis. Aggregation of misfolded protein molecules would be only one aspect of an integral event of promoted transformation in a continuum of cellular membranous incorporation.

Synapses might be considered as primarily membranous, and would undergo oxidative/nitrative and lipid peroxidation to account for a cholinergic deficit in Alzheimer's that is primarily membranous in terms of a primary neuronal cell loss [33].

The neuronal cell membrane injury might be construed as a counterpart of the neurofilament/cytoskeletal involvement that in various ways would constitute a continuum in the establishment of Alzheimer's disease activity. This would apply particularly in the mode of subsequent development of nonlytic neuronal cell loss that involves loss of cell membrane.

DYSTROPHIC NEURITOGENESIS AS SELF-PROGRESSIVE

Class A and Class B Scavenger receptors on macrophages and microglia would perhaps help complete an aggregation phenomenon that is both chemotactic and

also chemically generative in terms of ongoing oxidative [30] and cytokine action [34,35]. A generating series of waves of cytokine activity involving Tumor Necrosis Factor alpha and various other neurotoxic agents would account for various modes of ongoing neurite injury that is often characterized by dystrophic type features [36]. Microglia would perhaps involve oxidative type stress injury in a manner linked to nitric oxide injury and involving possible interaction with a blood supply and with an endothelial cell vascular bed; these would all promote ongoing activity and induced damage to neurites [37,38]. Indeed, it would appear that an ongoing neuritogenesis subsequent to such neurite injury is itself a characteristic contributor to further neurite and neuronal injury in senile plaque formation and maturation in Alzheimer's disease.

Strict recognition of neuritogenesis as both a cause and a further effect of ongoing injury to neurites and neurons would combine dystrophy within a continuum of amplified effect. With each generating wave of repeated neuritogenesis, further neuronal cell body injury would progress along a continuum of dystrophic change that promotes formation of senile plaques towards an endstage burnout form.

CONVERSION OF NONFIBRILLAR TO FIBRILLAR AMYLOID DEPOSITION

Nonfibrillary amyloid deposition would be distinct from fibrillogenesis in terms of a dual axial development of disease pathways affecting either primary neuronal degeneration or primary axonopathy [39].

Amyloid fibrillogenesis in familial amyloidotic polyneuropathy might constitute a series of transformational changes whereby nonfibrillar amyloid deposition is directly toxic to axons. Fibrillogenesis of amyloid protein on the other hand would demarcate a process of primary neuronal body injury in subsequent disease progression as neurodegeneration [40].

In Alzheimer's disease, such fibrillogenesis would progress according to strict parametric attributes of the fibrillogenesis in amyloid deposition [324].

Nonfibrillar amyloid deposition is a potential starting point towards a process of fibrillogenesis that demarcates conversion of a primary axonopathy to a primary neuronal body degeneration of Alzheimer type.

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