International Journal of Molecular Medicine and Advance Sciences 2 (2) : 177-183, 2006

Initiating Events in Brain Aging Integral to Predetermined Neurodegeneration of Alzheimer Type

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Abstract: Cognitive decline constitutes an outcome phenomenon arising in terms of integral evolution of pathways determining viability of neuronal networks rather than of individual neuronal subsets. Indeed, synaptic integrity would promote a generalized preservation of pathways as predilected systems of neuroprotection against such system degeneration. One might view Alzheimer neurodegeneration as a characterization of system involvement that either initially determines evolution of cell death pathways or else primarily targets systems of interconnectivity between neuronal subgroups. It is in terms of both initiation and subsequent progression that differential systems of influence predetermine cascade pathways of development of neurodegenerative events as inherently integral events. Neurodegeneration, as pathways of promotion that are primarily concerned with initiating events and particularly Alzheimer disease, would possibly arise within a biologic context of brain aging. Genetic and sporadic predisposition would allow the further definition of characteristics of a disease process that initiates a heightened susceptibility primarily affecting also systems of interaction of hemodynamic dysregulation and glucose non-utilization. It is in the basic constitutional development of injury to neuronal networks that aging of the brain would possibly predetermine the further transformation of pathway events as Alzheimer neurodegeneration. The specific inter-relationships of brain aging with Alzheimer-type atrophy might involve particularly modes of initiation of damage to synapses as primarily network dysfunctionality. Alzheimer-type development of atrophy relates to regional phenomena that evolve as initiating events that further characterize biologic attributes of the synapse. Neuritogenesis is itself a product of characterized synapse maintenance or dysfunction that further develops in predetermined ways to induce injury as neuritic plaques and neurofibrillary tangles. It might be significant to consider cognitive decline as an outline evolving system that in Alzheimer brains would be further characterized as initial establishment of synaptic dysfunction. Primary determinants in development of Alzheimer's disease would paradoxically characterize brain aging as a generic system of promotion of innumerable pathways of possible neuronal network injury. Potential development of predeterminants would allow the definition of attributes of neuronal networks beyond simple neuronal subsets and in terms particularly of modes of interaction of synapse and neurites as dystrophy and dysfunctionality phenomena.

Key words: Alzheimer type, brain, integral, initiating events, predetermined

INTEGRAL INVOLVEMENT AND SUSCEPTIBILITY

Prenylation[1] or differential receptivity to glutamate in the context of a possible excitotoxicity pathogenesis[2-4] might perhaps be expected to constitute paradoxical systems of selective vulnerability that would subsequently involve a nonselective progressive series of neuronal cell death pathways. Alternatively, brain cholesterases may serve as a central point rallying various hypotheses regarding the etiopathogenesis of Alzheimer's disease[5]. Pathologic involvement of specific subsets of neurons does not necessarily involve subsequent pathologic involvement of other neuronal subsets within an integral system of central neurodegeneration. Aging has been suggested as the greatest risk factor for Alzheimer's disease[6]. One might speak of how systems of viability of neurons are not primarily concerned with concepts of vulnerability but with a paradoxical system of prevention of contextual initial development of such neuronal vulnerability. Beta-amyloid 42 appears a decisive factor for age of onset in familial Alzheimer disease[7]. It is in this sense that one might speak of a viable versus nonviable neuron in terms specifically arising as degrees of susceptibility for a lesion that only indirectly relates to diagnosis of compromised viability of the individual neuron.

In terms related to specific ways in the development of an initial form of neuronal involvement, one might perhaps consider neuronal receptivity as an overall

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process of neuronal selective vulnerability that paradoxically translates in terms of specific aspects of initiation rather than of progression of the initial neuronal lesion. Early endosomes are a point of convergence involving amyloid precursor protein processing; endosomal pathology and enlargement correlate with Beta-amyloid overproduction and accumulation in sporadic Alzheimer disease[8].

PROGRESSION OF ALZHEIMER MORPHOLOGIC PATHOLOGY

Familial forms of Alzheimer disease might constitute intrinsic pathobiology of the early onset of an organic dementia as a largely neuronal receptivity or response[9]. Dual enhancement of a mutually suppressive series of effects involving neuronal receptivity and neuronal response would tend to become more overt as long term potentiation. It might be significant to consider mutations of Presenilin 1 as a main determinant of how Ca2 + flux and Ca^{2+} availability impair potentiation or predisposition to progression of the Alzheimer process.

The strict question of spread pathobiologically of the Alzheimer process from hippocampus to cerebral neocortex might constitute a phenomenon whereby the morphologic lesions of the Alzheimer process correlate strictly with evolving and primarily established lesions rather than with actual or spatial pathobiologic spread.

In this sense, pathophysiologic and pathobiologic forms of spread of the Alzheimer process are phenomena only loosely linked with one another. Indeed, in a real sense, the morphologic aspects of pathologic involvement in the Alzheimer brain might constitute a closed system of self-progression that paradoxically is initiated strictly in terms of the existence of morphologic lesions of this type. Synaptic damage and loss affect degree of dementia in Alzheimer disease, with loss of spines and of total dendritic area[10].

INTRANEURONAL DEPOSITION OF BETA-AMYLOID

A coordinated system of secretion of both Presenilin 2 with Amyloid Precursor Protein towards the lumen of the endoplasmic reticulum of neurons might constitute a pathobiologic basis for deposition of beta-amyloid 1-42 in Alzheimer's disease[11]. This may arise from dysregulation rather than from increased dynamics of production of either Presenilin 2 or of Amyloid Precursor Protein.

An interaction of Presenilin 2 with Amyloid Precursor Protein would proceed as an integral process of secretion into the lumen of the endoplasmic reticulum. One might envision aspects of essential failure of cooperative secretion of Presenilin 2 and of Amyloid Precursor Protein in the deposition of beta-amyloid intraneuronally in cases of Alzheimer disease.

Beta-amyloidosis in the Alzheimer brain might effectively result from failed cooperative secretion of Amyloid Precursor Protein with Presenilin 2 into the lumen of the endoplasmic reticulum. In this sense, perhaps, a system of failed secretion of Amyloid Precursor Protein would actively generate beta-amyloid 1-42 within the strict context of failed secretion transformed to intraneuronal deposition of such beta-amyloid.

BETA-AMYLOID DEPOSITION AND DEPLETION

Failed deposition of beta-amyloid 1-42 with either onset or persistence of the Alzheimer disease process in patients with mutations of Presenilin-1 gene might constitute a flexible system of deposition[12]. This would progress regardless of pathologic effects attributable directly to either the deposition process itself or to the dynamics of interaction of Beta-amyloid 1-42.

A system of segregation of Beta-amyloid fibrils would perhaps allow the active deposition within the strict context of an initial intracellular mechanism that evolves only as a purely neurodegenerative process. In this way, a purely degenerative process involves only the neurons initially affected by deposition of Beta-amyloid as an intracellular series of mechanisms.

One would, in familial cases, have to account for the progression of Beta-amyloidosis as a genetic disorder that only secondarily constitutes effective neurodegeneration.

IS AMYLOIDOGENESIS A CHARACTERISTIC ETIOLOGIC FORM OF NEURODEGENERATION?

Biologic manipulation of amyloid protein may induce a state of fibrillogenesis that is significant in terms of molecular intermediate configuration[13]. This would be cooperative with ApoE4 within the context of turnover dynamics of synthesis and accumulation of amyloid protein, on the one hand and of secretion and enzymatic cleavage on the other.

The various isoforms of amyloid protein range particularly from 39 to 40 to 42 and might relate particularly to how the Amyloid Precursor Protein is handled as modes of production and source of the Amyloid.

One might consider sources such as nonreplicating smooth myofibers of the vascular media and nonreplicating neurons in neuritic plaques as fundamental biologic events intrinsically arising from a disease process of Alzheimer type. Aging associated inflammatory and

oxidative cerebral stress would trigger beta-amyloid deposition[14].

Nonproliferation may constitute a central process of tendencies toward Beta-Amyloidosis in Alzheimer's that biologically constitutes alternate systems of cellular processing expressed as fibrillogenesis.

Beta-amyloidosis may involve deposition that is implicated in non-replication of vascular media myofibers and of neurons as beta-amyloidogenesis and fibrillogenesis. Cytoskeletal perturbations influence soluble beta-amyloid associated cell death involving proteolysis of microtubule-associated proteins and synergistic activation of calpain and caspase-3[15].

One would tend to equate in approximate terms amyloidogenesis and amyloid deposition in vascular walls and in neuritic plaques with an ongoing biologic process of fibrillogenesis of amyloid isoforms in Alzheimer's disease.

Perhaps it would be legitimate to consider tunica media myofibers and neurons as parameters of an essential non-replicative process that paradoxically constitutes biology of disease progression in Alzheimer's disease.

ALZHEIMER'S DISEASE AS INTEGRAL MULTIPLICITY OF PATHWAYS OF NEURONAL NON-VIABILITY

A central aspect in Alzheimer disease pathogenesis revolves around an essential multiplicity of pathways of pathologic involvement that are paradoxically integral as a single disease process[16]. In terms particularly of senile (neuritic) plaques and of congophilic angiopathy, it would perhaps appear that the amyloidogenesis in Alzheimer's is itself a multiplicity of integral pathways in evolution. The function of mitochondrial Beta amyloid and whether it is produced locally in the mitochondrion is unclear[17].

Even the essential differentiation of amyloid deposition would involve predilected modes of vascular wall degeneration that are distinct from the diffuse and classic neuritic plaque in terms of integration of neuronal and vascular wall myofiber involvement.

Amyloidogenesis might constitute, in Alzheimer's disease, possible variability of neurodegeneration in terms of essential constituents of the neuron and of the vascular wall myofiber that specifically links abnormal vascular permeability to genesis of the neuritic plaque as a possibly perivascular lesion. Age and region-specific changes in the proteolytic clearance of Beta-amyloid may represent a centrally operative mechanism determining susceptibility in Alzheimer disease[18].

As a primarily perivascular lesion the neuritic plaque would involve trophic factor deprivation that allows a lesion to progressively become more focally demarcated and perivenous.

In terms of dynamics of vessel wall damage, one might consider a progression of changes from diffuse to classic neuritic plaque formation arising from integral participation multifocally and also along multiple pathways but involving an overall unified scheme of neuronal cell loss. The classic range of lesions of neuritic plaque type, congophilic angiopathy and neurofibrillary tangles would constitute a single endpathway with loss of homeostatic systems of viability of neurons.

Depletion of neuronal viability would be accompanied by compensatory systems for injury of potentially widely diverse nature. The Apolipoprotein E e4 allele increases risk of Alzheimer disease and cardiovascular pathology[19].

Amyloidogenesis would constitute mechanistic progression and integration of such multiple pathways of pathogenesis in Alzheimer's disease.

ACTIVATION PROGRESSION OF THE NEURODEGENERATION

Temporal factors of progression appear to implicate in particular apoptosis as a system of neurodegeneration and as a susceptibility of pathways of injury[16]. Inflammatory processes early in life might promote development of both cardiovascular disease and Alzheimer disease[20]. Postmortem time delay before examination of the brain might cooperatively act in concert with decreased neuronal viability systems in inducing or promoting DNA breaks. A laminar-like distribution of in situ end labeling might largely serve as a reflection of agonal processes of ischemia that are semi-chronic rather than acute. Indeed, one might perhaps view the decreased neuronal viability in Alzheimer's as only one aspect of a multifaceted process of compromised viability implicating activation by glia and particularly microglia inducing neurodegeneration[21].

Protein conformational transition to form beta-amyloid sheets may precede aggregation of protein molecules as implicated in neurodegeneration[22].

One might ascribe much of the progressiveness of the neurodegeneration in Alzheimer's to a series of activation pathways that involve concurrent and serial interactions between glia and microglia and also neurons[18]. Diabetes associated comorbidities of hypertension, dyslipidemia or hyperinsulinism may constitute important risk factors for Alzheimer disease with aging[23].

Also, Alzheimer's disease might be better viewed as an activation of progressiveness of neurodegeneration allied closely to DNA breaks.

SYNAPTIC DESYNCHRONY IN SYNAPTIC VESICLE EXOCYTOSIS AND ENDOCYTOSIS

Synaptic desynchrony affecting presynaptic vesicle endocytosis and exocytosis might constitute a central mechanism of cognitive decline leading to dystrophic neuritogenesis and neurodegeneration[24-26]. It is perhaps in terms of central disturbances of presynaptic vesicle endocytosis with exocytosis that one might consider neurodegeneration with neuronal cell loss that is particularly linked to dynamics of neurofibrillary tangle formation and to neuritic plaque formation and as a dystrophic neuritogenesis[27].

A process of dystrophy might constitute a regenerative neuritogenesis that is abnormally induced and proves persistently progressive.

The subfield variability in disease involvement of hippocampus versus neocortex or visual/parietal cortex or entorhinal cortex as a whole would appear a fundamental expression of a primary synaptic release disturbance. Synaptic desynchrony would perhaps constitute a common endpathway expression of various events of pathogenesis in the final development of cognitive decline and of brain atrophy of Alzheimer type.

DISTURBED Ca2 + HOMEOSTASIS WITHIN NEURONS

A net calcium ion increase within neuronal cells might operate to influence essential dynamics of Ca^{2+} flux into these cells that would perhaps modify mechanics of NMDA and AMPA/kainate receptivity[28]. A system of Ca2 + ion receptivity would appear one intrinsically based not only on the GluR subunit composition of these receptors but in particular on how such GluR subunit composition would interact with currently net levels of intracellular Ca2 + within the neuron.

A low intracellular AMPA/kainate receptors, with consequent compensatory increase in Ca2 + would tend to decrease the GluR2 subunit component of the AMPA/kainate receptors, with consequent compensatory increase in Ca2 + influx within that neuron, as would be expected in the hippocampus and entorhinal neurons in Alzheimer's.

No active participation in the effective prevention of Ca2 + influx might operate in Alzheimer's, a phenomenon perhaps linked to AMPA/kainate receptors highly localized to dendritic spines of pyramidal cortical neurons.

There might operate not simply an excitotoxicity of neurons but a dual phenomenon of neuronal injury and defective synaptic neurotransmission based on disturbances of Ca2 + ion flux. This, in turn, might tend to self-perpetuate due to a variable responsiveness of levels of GluR2 subunit component of NMDA and particularly AMPA/kainate receptors. Peroxisomal proliferation may induce neuroprotection from beta-amyloid associated degeneration by preventing cytoplasmic calcium increase and also production of reactive oxygen species[29]. The neurofibrillary tangles might form part of the spectrum of neuropathology in Alzheimer's as a phenomenon specifically arising as a hyperphosphorylation of tau filaments and increased compensatory influx of Ca^{2+} ions into such neurofibrillary tangle-containing cells. Interleukin 6 would induce a calcium influx through NMDA receptors mediated by the JAKs/STATs pathway that subsequently modifies tau hyperphosphorylation patterns[30].

The neurodegeneration in Alzheimer's disease would constitute a final form of neuronal injury that arises from a multiplicity of pathways that pathogenetically are centered on disturbance of influx of Ca2 + into neurons and also on trans-synaptic neurotransmission. An amyloid cascade hypothesis contrasts with a metabolic/signal transduction hypothesis in the multifactorial pathogenesis of Alzheimer's disease[31].

DYSTROPHIC SYNAPTOGENESIS AND DYSTROPHIC NEURITOGENESIS

Secretion of Amyloid Precursor Protein might constitute a marker of pathways of development that relate particularly with neuritogenesis and neuronal viability as functional synaptic neurotransmission[32]. Amyloid precursor protein and its C-terminal proteolytic fragments may be tightly coupled with intracellular adaptors to control cell signaling[33]. Both neuritogenesis and mechanisms of preservation of viability of neurons might effectively develop as inherently related homeostatic mechanisms arising from such secretion of Amyloid Precursor Protein. An evolving system of trophic neuronal effect might operate as a particular attribute of synaptic neurotransmission via neuronal secretion of Amyloid Precursor Protein.

Synaptic neurotransmission and synaptogenesis might constitute attempted preservation of viability of neurons once these are injured.

Destabilization of the microtubule network appears significant in causing neuronal dysfunction[34]. The dystrophic nature of neuritogenesis in Alzheimer's disease might arise as an evolving dystrophic synaptogenesis constituting in turn a central pathway of neurodegeneration and of neuropathology of Alzheimer type, affecting in particular presenilin 1 function in protein trafficking[35].

Amyloid Precursor Protein would be reflected in amyloid fibrillogenesis[36] and beta-sheet formation

specifically arising as a dystrophic synaptogenesis of neurons related to neuritogenesis in Alzheimer's disease.

VOLUME DENSITY AND AREA DENSITY OF NEURONS AS A CRITICAL ESTIMATE OF NEURONAL NETWORK ATTRIBUTES

A neuronal count would perhaps be a significant estimate of the network system of commitment of neurons within a context of volume based neuronal density, as attempted by stereology[37]. It is perhaps significant to consider neuronal density as an inherent function of neuronal volume that is in turn an inherent function of volume density of groups of neurons. The neuronal network dimensions would reflect how neuronal volume relates area density to volume density of neurons. Perhaps, volume density and area density of neurons would be significant relative to each other as an essential process beyond simple neuronal cell loss in the Alzheimer brain.

This would critically assess a fundamental property of the neuronal network as functional and dysfunctional attributes in Alzheimer brains[28]. In addition, the identification of clearly distinguishable patterns of blood flow pathology support the concept of Alzheimer's disease as a heterogeneous disorder[38,39]. Data indicates that Alzheimer disease related changes are not an unavoidable consequence of aging[40].

BRAIN AGING AS INITIATION OF TISSUE CHANGE WITH INCREASED MICROGLIAL EXPRESSION OF MHC CLASS II

Microglial activation might characterize initiation of tissue damage in aging that is analogous to initiated embryologic development[41].

Modes of tissue change would specifically arise as variable forms of activation of pathways including those related to microglia[42]. A heightened level of microglial activation would be reflected in increased expression of MHC Class II in terms of biology of aging as an initiation event. In Alzheimer's disease, microglial dysfunction may be associated with a loss of neuroprotective properties[43].

INTERACTIONS OF VASCULAR HEMODYNAMICS AND NEURONAL NETWORK VIABILITY IN BRAIN AGING AND ATROPHY

Decreased blood flow would evolve as atrophy of cortical grey matter or central white matter arising as dysregulation of hemodynamics[44-48]. Cerebral hypoperfusion constitutes the most accurate predictor of probable Alzheimer disease in a future time[49].

Disturbed insulin transduction may be an early pathobiologic event also[50]. Midlife systolic blood pressure is the strongest blood pressure component predicting incident dementia[51]. Deposition of fibrillar beta amyloid by perivascular cells leads to endothelial cell injury, obliteration of capillaries and reduced length of the vascular network[52].

Modes of interaction of cellular pathways of oxygen consumption and glucose utilization[53] would mark hemodynamic blood flow and neuronal network viability as indices of progression in brain aging. Hyperinsulinism may induce neuroinflammation and also potentiate the risk for development of Alzheimer's disease[54]. Age-related brain atrophy would progress in terms of levels of viability of integral neuronal networks determining cognitive decline with advancing age.

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