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Towards a Unified Scheme of Progression in Neurodegeneration

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Abstract: A schematic outline of progression of Alzheimer's disease would implicate a neurodegenerative process arising from and sustained by various pathways of possible reactivity to neuronal injury. An etiologically operative system of pathogenic progression might simply evolve in terms of dysfunctionally variable trafficking systems, as phosphorylated Tau isoforms and of interactivity between the endoplasmic reticulum and Golgi subcompartments. Presenilins 1 and 2 might constitute a generic process of homology in molecular protein synthesis that primarily characterizes dysfunctionality of neurons in Alzheimer's disease. A variability of response on the part of neuronal networks might help account for subsequent progression of a clinically demented state characterized by microscopic parameters of accumulation of neurofibrillary tangles and neuritic plaques and of amyloidogenesis. Lewy body accumulation as an inclusion body disease affecting extrapyramidal system and cortical neurons might participate in such neuronal network involvement.

Key words: Neurodegeneration, Alzheimer's disease, unified scheme

INTRODUCTION

THE FINAL NEURODEGENERATIVE INVOLVEMENT PATTERN IN ALZHEIMER'S AS A MULTIGENIC ETIOLOGY AND PATHOGENESIS

Non-Mendelian inheritance, a phenomenon that refers not simply to a strict pattern of inheritance, but to an essential multi-gene involvement, would illustrate dynamics of interaction between individual genes[1].

A multiallelic involvement in the pathogenesis of neurodegenerative disease, as stereotyped disorders of Alzheimer, Parkinson, and amyotrophic lateral sclerosis type, would implicate familial versus sporadic development of closely corresponding features. Activated microglia and reactive astrocytes may release proinflammatory prostaglandins or cytokines that mediate neuroprotective effects via trophic factors or uptake of glutamate[2].

Human presenilin gene missense mutations induce an autosomal dominant, early onset form of Alzheimer's disease that is influenced by trophic and differentiation attributes of neurons as revealed in PC12 cells[3].

Alzheimer's might co-occur with Parkinson's disease within an integrally progressive system involving a neurodegenerative process with possibly inherited attributes. Indeed, such association of Alzheimer's with Parkinson's might assume progression as a neurodegeneration ranging from the temporal lobe dementia with Parkinsonism associated with chromosome 17 to the development of cortical Lewy bodies in patients with cognitive disorder. Alterations in neuronal amyloid precursor protein and glutamate receptor 2/3 subunits expression may mark neuronal susceptibility in the entorhinal cortex[4].

A full resolution of pathogenic aspects of Alzheimer's would necessarily take into account specific foci of involvement in the central nervous system that manifest intrinsic biology of a neurodegenerative disorder as combined neuronal body and axonal involvement.

Oxidative stress in particular appears to modulate cell cycle regulation in postmitotic neurons and affect mitochondrial membrane permeability via Bcl2, trophic factors and energy resources[5]. Other pathogenic effects may include mitochondrial dysfunction, inflammation, excitotoxicity, altered protein degradation and apoptosis[6].

In different ways, dendritic dysfunctionality would implicate ongoing neurodegeneration (as possibly reflected in neurofibrillary tangles and dystrophic neurites) in Alzheimer's within an active system of attempted neuronal recovery[7]. Nerve Growth Factor is the most potent trophic factor affecting cholinergic neuronal survival as seen with neurons of the basal nucleus of Meynert[8].

Etiopathogenesis of the disorder would be modified in terms of a disease process that is influenced by apolipoprotein profile, estrogen/menopausal status, vascular/ischemic events and by amyloid deposition. Such pathogenic factors would fluctuate not only with degree of dementia in an individual patient but also with

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changing dynamics of the essential nature of the ongoing neurodegenerative process in that particular patient, including mixed lineage kinases such as c-Jun N terminal kinase[9]. Relative brain resistance to insulin and Insulin-like Growth Factor I (IGF-1) may implicate amyloid deposition at the blood brain barrier, neuronal atrophy and neurofibrillary tangle formation and phosphorylation[10]. IGF-1 exerts effects on cholinergic dysfunction, neuronal amyloid toxicity, Tau phosphorylation and glucose metabolism[11].

A multigenic etiopathogenesis in Alzheimer's would imply potentially variable and multi-etiology and pathogenesis as progressive neurodegeneration with both focal and global dimensions. Mutations in the amyloid precursor protein is implicated in early onset familial Alzheimer's disease; it induces neuronal apoptosis particularly in cases of reduced trophic effect and as reflected also in oxidative stress[12]. Beta- amyloid solubility and its hydrogen peroxide production are affected particularly by transition metal ion binding[13]. *In vitro* apoptotic neurons produce membrane blebbings that are amyloidogenic and released extracellularly[14]. Caspase 12 mediates apoptosis via endoplasmic reticulum stress affecting Ca2+ or excess protein; this may contribute to beta-amyloid neurotoxicity[15].

A SPECIFIC OR GENERIC-TYPE NEURONAL TRANSPORT DYSFUNCTION IN PARKINSON'S DISEASE PATHOGENESIS

A primary neurotoxic mode of action in the genesis of a neurodegenerative process that promotes extrapyramidal involvement might contrast with a recoverability of cells that have been initially injured.

Modified levels of Nerve Growth Factor in Alzheimer's and Parkinson's would vary according to degree of disease progression in terms particularly of differentiation, growth and survival of neuronal subsets[16], particularly cholinergic neurons[17]. The stress activated protein kinases c-Jun-activated kinase and p38 are implicated in neuronal apoptosis induced by withdrawal of Nerve Growth Factor[18].

The high levels of beta-carboline-9N-methyltransferase activity in cerebral frontal cortex in patients with Parkinson's disease might in particular constitute a neurotoxicity encompassing attempts at recovery of neuronal populations in the central nervous system[19]. This may implicate the expression of trophic cytokines and neurotrophins, glial growth factor receptors such as Erb B-2 and PASK, the mammalian homologue of the fray gene involved in axonal ensheathment[20].

Dendritic branches are a major site of synapse formation and are a likely target in cognitive decline or neurodegeneration, in terms particularly of regional changes in trophic support and in neuronal activity[21]. Protein kinase C plays a role in preventing neuronal apoptosis under trophic factor deprivation[22].

Projection fibers of substantia nigra compacta neurons to the striatum and various other neuronal subsets in brain stem and locus ceruleus might evolve as synaptic connections along axonal pathways. A generic mode of development of neuronal injury would implicate transporter system involvement as neurodegenerative progression and apoptosis involving a decrease in mitochondrial membrane potential[23]. Beta-amyloid production, synaptic malfunction and trophic factor lack may link amyloid cascade pathways with cholinergic neuronal cell loss[24]. In particular, sublethal amyloidogenesis may interfere with critical neuronal signaling pathways, rendering cells more susceptible to DNA damage and trophic deprivation-induced apoptosis[25].

A primary injury in Parkinson's disease as a defective transport mechanism might imply damage to midbrain substantia nigra, striatum, locus ceruleus and brain stem as eventual possible progression of involvement in frontal and cerebral cortical neurodegeneration. Interactions between S100 beta and Fibroblast Growth Factor-2 may be relevant to neuronal survival after partial injury to ascending dopamine pathways, with increased immunoreactivities in reactive astrocytes[26].

LEWY BODIES POSSIBLY RESULT FROM PATHOLOGICALLY RELATED NEURITE AND SYNAPTIC INTERACTION

Insolubility of presynaptic neuritic alpha-synuclein as a phenomenon central to ubiquination is a pathognomonic feature for both Lewy body Dementia and Parkinson's disease. Impaired connectivity in the cerebral cortex or substantia nigra would constitute a biologic expression of impaired synaptophysin synthesis in these disorders[27]. Insulin-like Growth Factor exerts trophic and neuromodulatory effects in the brain via the activation of pathways implicating phosphatidylinosiditide 3/Akt kinase, winged helix family of transcription factor FKHRL1 phosphorylation or production of free radicals[28].

Lewy bodies do not simply reflect impaired inter-neurite or inter-neuronal connectivity but an axonal/neurite transport that participates in synaptically disturbed connectivity between neurons.

Estrogen in particular appears to potentially protect neuronal networks, influencing postischemic survival of neurons and might regulate apoptotic mechanisms[8]. Retinoic acid plays a role in differentiation of the

cholinergic phenotype and would promote neuronal repair and survival following injury[29].

Impaired synaptic transmission affects neurite/axonal transport and involves insoluble aggregation of alpha-synuclein and intracellular ubiquination. A signal process of neurodegeneration and of progressive synaptic pathology would involve neuronal cell death in cerebral cortex of patients with Lewy body Dementia, or in substantia nigra in Parkinson's disease. Neural stem cells appear to inherently secrete neurotrophic factors beneficial to injured neurons[30].

Categorical distinction between neurite/axonal transport and synaptic transmission would not account for essential Lewy body deposition as a pathognomonic phenomenon in neurodegeneration. Disaggregation of beta-amyloid as mediated by metallomethionein III appears to abolish toxicity of cerebral cortical neurons[31].

Diversity of behavior-driven structural changes in the brain affect post-lesion plasticity events and expression of trophic factors[32]. Brain-derived Growth Factor, in addition to its trophic effects in target neurons, involves activity-dependent modification of synapses in the developing and adult nervous system[33].

ASTROGLIOSIS AS CENTRAL TO EFFECTIVE SUSTAINMENT OF NEURONAL VIABILITY IN HEALTH AND DISEASE

An association between neurotrophic action and astrogliosis[34, 35] as seen with Ciliary Neurotrophic Factor might reflect a series of changes whereby astrocytes constitute a reactive sustainment of axonal sprouting and of neuronal body in terms of protein synthesis and subsequent utilization of such proteins[36]. Estradiol elicits developmentally regulated differentiative effects on neurons, and activation of MAPK/ERK may be particularly relevant for neuroprotection during aging and Alzheimer's disease[37].

Astrocytes, more than just supporting cells, would enable effective utilization of protein by neuronal bodies and axons in an overall integral process of progression of attempted neuronal regeneration and of axonal resprouting, including increased expression of 5-Hydroxytryptamine 2a receptors[38].

A neuron would actively sustain itself synthetically and also maintain efforts of attempted recoverability in the face of pathologic insults to either the cell body or axon. Beta-amyloid possesses a number of trophic properties and binds Cu, Fe and Zn, thus preventing these from participating in redox cycling with other ligands. Oxidative stress-induced beta-amyloid generation contrasts with such anti-oxidant action[39].

Even the oligodendrocyte as a possibly specialized astrocytic cell form would contribute significantly not only to axonal transport of the impulse and to trophic sustainment of this same axon, but also contribute in terms of an astrogliosis affecting viability of neuronal networks. Serotonin in particular appears to function not only as a neurotransmitter and neuromodulator but also as a trophic factor in dentate gyrus neurogenesis and active incorporation of new neurons into hippocampal circuits[2].

THE NEURONAL CYTOSKELETON POSSIBLY DETERMINES TRAFFICKING SYSTEM DYNAMICS AS REFLECTED IN PSI/PS2 ACCUMULATIVE AGGREGATION

The essential membrane anchorage of PS1 and PS2 might induce molecular aggregating attributes that account possibly for interconversion between PS1 and PS2 protein forms[40]. Failed axonal transport and early Tau protein aggregation elicit an early synaptic response to partial de-afferentiation that may be mediated by trophic factors[42]. Presenilins (PS1 and PS2) are highly homologous proteins and might implicate membrane-related events that determine biology of presenilin-1 and presenilin-2 especially as abnormal transport of molecular aggregates in Alzheimer's disease. Neurons overexpressing mutated presenilin 1 are more susceptible to degeneration[14, 43, 44].

Early amyloid deposition in mice expressing mutant amyloid precursor protein and presenilin-1 is associated with a progressive loss of serotonin and norepinephrine neurotransmitter levels in the hippocampus later in life[45].

Prostate apoptosis response-4 expression was enhanced and mitochondrial dysfunction and apoptosis exacerbated in cells with presenilin mutations in early onset inherited Alzheimer disease[46].

The membrane-associated accumulative aggregation of PS1 and PS2 would constitute a phenomenon relating to endoplasmic reticulum subcomponents and the Golgi apparatus. An interaction of the endoplasmic reticulum with the cytoskeleton of the cell might also involve PS1 and PS2.

A complex regulatory neurotrophin network would in addition control expression of other neurotrophins, especially affecting cortical transcription pathways[47, 48]. There is selectively profound loss of the high-affinity tyrosine kinase receptor TrkB of brain-derived neurotrophic factor[48].

The association of PS1 with accumulation of beta-

amyloid precursor-like protein 1 and TrkB (as affected by loss of PS1 activity) might implicate intracellular trafficking that dynamically affects accumulative aggregation of PS1 and PS2 in the neuronal cell body.

Primary function of the cytoskeleton of the neuronal cell body would be affected. In addition, protein aggregation has been implicated in neurodegeneration as mediated by transglutaminase-induced protein crosslinking. Switching from trophic signaling to apoptosis may be implicated[49]. The endoplasmic reticulum is increasingly being recognized as a key regulator in neuronal survival and plasticity[50].

TAU ISOFORM REFLECTS INTERACTIVE MEMBRANE-ANCHORED PRESENILIN IN NEURONAL TRAFFICKING AND REGENERATION

Shifts in Tau isoforms would operate as functions of neurofilament trafficking linked to presenilin membrane anchorage permitting dynamic accumulation, aggregation and hyperphosphorylation of Tau[51]. Increased Tau phosphorylation possibly follows consequent to apoptosis of neurons affected by cyclin-dependent kinase activity[52]. Neurons expressing phosphorylated Tau are more resistant to experimental apoptosis than neurons positively labeled for dephosphorylated Tau protein[14].

The strict subcompartmentalizaton of different isoforms of Tau within axons and neurites as normally noted, or within the neuronal somas as seen particularly in Alzheimer's disease, might reflect dynamism of accumulation and of regeneration of new Tau.

The generation of longer isoforms of Tau would associate with Tau spheroids in spinal cord axons as noted also in a hindlimb abnormality and might constitute self-amplified production of more of the same Tau isoform. An integral process with biologic acquisition of functional generation might reflect isoform identity of the Tau filament as an expression of specific regenerative processes linked directly to neurofilament trafficking and to membrane-anchored presenilins.

Altered cytokine and neurotrophin interactions appear to potentially contribute to progression of such neurodegenerative events[53]. A dysregulated cholinergic system would correlate in terms of reciprocal interactions with age-related neuronal and vascular processes leading to senile dementia[54]. Estrogen acts as a trophic factor for cholinergic neurons, modulates expression of apolipoprotein E, decreases oxidative stress and promotes non-amyloidogenic processing of amyloid precursor protein[55].

Brain-derived neurotrophic factor is implicated in neural development and cell survival and also particularly in molecular mechanisms of synaptic plasticity[56]. Vascular endothelial growth factor appears to act as a trophic factor for neural stem cells and for sustained neurogenesis in the adult nervous system[57].

MULTIPLE ORDERS OF OPERABILITY OF NEURONS AS METABOLIC AND PHYSIOLOGIC PATHWAYS IN NEURONAL VIABILITY AND NEUROPROTECTION

Neurotrophic/neuroprotective effect might establish functionality within a system of evolving progression involving neurons[58]. Plasmalogens (glycerophospholipids) are decreased in Alzheimer's disease and this would affect membrane structure and also ion transport, cholesterol efflux and membrane fusion and also expose neurons to oxidative stress[59]. The stability of neuronal networks would depend on synaptic transmission with activity-dependent maintenance signals for both synapses and neurons[60].

Neuroprotection might imply an operative series of mechanisms that permits the re-assumption of certain metabolic and physiologic processes especially in terms of developmental pathways. Neuroprotection involves systems of integral maintenance of cell operability that actively initiate sustained upregulation of trafficking and synthetic pathways. Disrupted cholesterol uptake and metabolism would lead to abnormal trafficking of membrane proteins involved in synapse loss in Alzheimer's disease[61].

Homeostasis as a system of operation would reflect persistence of endpathways that involve upregulation of metabolic and physiologic activity. Neuronal viability and conversely selective vulnerability of neurons would constitute a hierarchical system of effective operability. Neural stem cells in particular appear to constitute inborn programs of homeostatic control and of plasticity in response to the developing and injured brain. Proliferation, migration, cell genesis, trophic effect, guidance and detoxification may feature as mechanisms of neural stem cell programming[62]. Indeed, neurodegeneration might reflect defects in such operatively selective systems of vulnerability of neurons as a generic system of progression.

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