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Accelerated Systems of Neuronal Injury Inamplified Neuronal Agingin Alzheimer's Disease

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Abstract: Selective vulnerability of neurons and selective resistance to neuronal injury appear to operate as pathways inducing functional or dysfunctional recovery in terms of both constitutive and acquired cellular attributes. Normal brain aging may transform to an Alzheimer type progression that induces acceleration of brain atrophy and also the emergence of specific lesions that range from neurofibrillary tangles to neuritic plaques. Neuronal cell loss may be apoptotic in terms of developmental origin of the cells or else involve neurodegenerative atrophy that culminates in variably expressed neuronal cell loss. Defining a distinction between successful brain aging and an Alzheimer disease process might specifically call into focus a series of neurodegenerative pathway effects that range from developmental to pathologic cell loss in determining transformation of cell atrophy to either programmed cell death or necrosis of neurons. A concept of increased susceptibility of select groups of neurons to neurofibrillary tangle formation and evolving neuritic plaques would call into question any reference to Alzheimer's disease as a basic neurodegenerative event in the depletion of both hippocampal and cortical neuronal networks. There might arise a strictly determined focus of evolving change in neuronal homeostatic systems related primarily to how neurons deal with injurious events such as hypoxia or ischemia or even to varying systems of reactive recovery to hypoglycemia or deprived trophic effect. Alzheimer's disease would progress as apoptosis beyond simple realized pathways of involved participation in cell injury. A role for apoptotic neuronal cell death might specifically implicate cell death pathways as a resolved means of compensatory recovery of neuronal networks that integrally are operatively functional or dysfunctional. In terms of such variability in cell response to injury, Alzheimer's disease might prove a means of attempted recovery from injury inherent to an interaction of ischemic hypoxia and variable trophic factor deficit.

Key words: Amplified neuronal aging, neuronal injury Alzahimier's

INTRODUCTION

Apoptosis as a natural abortive mechanism of biologically defective cells: Apoptosis appears to be a fundamental cell biologic phenomenon that is involved in innumerable mechanisms leading to cell death through the operation of primarily developing nuclear events, including in the aged[1].

The involvement of apoptosis in developmental stages of embryogenesis may be suggestive of a role in abortive termination of the life span of those cells in terms of basic cell attributes.

An essential difference between apoptosis and cell degeneration would consist of mechanisms of injury on the part of a cell showing both morphologic and biologic distinctions in evolution of the injury. In an important sense, both apoptosis and cell degeneration can be properly considered only as ongoing processes with a final common endpoint leading to cell death.

Cell degeneration can be recognized in terms of unsuccessful attempts at compensation for an injury inflicted on that cell, thus modifying lesion progression. The injury often tends to be persistent in spite of such compensatory reactions, and may extend transcortically and affect highly localized neocortical neurons during aging[2].

Apoptosis, on the other hand, may actually have developed basically as a programmed cell death pathway directed primarily in eliminating specifically defective cell forms. Hence, in a broad sense, apoptosis may be a stereotyped series of mechanisms leading to cell death and arising primarily in terms of mode of origin, and of the intrinsic nature of homeostatic dynamics of cell viability. The strict occurrence of apoptosis would directly indicate a fundamental biologic defect arising from that cell often if not generally related to developmental origin of the cell. Apoptosis as a physiologic mechanism would develop during the evolution of life forms as a basic mechanism to abort cells that are seriously damaged in a number of possible different ways. Indeed, brain imaging of normal

aging may include cortical atrophy, central atrophy, deep white matter hyperintensities, and periventricular hyperintensities[3].

Apoptosis versus neurodegeneration: It may very well be true that the use of the term neurodegeneration is justifiable mainly as a distinctly outlined mechanism of variably modified apoptosis invoking a multitude or series of different cell death pathways.

On the other hand, "neurodegeneration" would comprise all other forms of cell death as distinct from a primarily progressive cell death pathway centrally directed by nuclear injury and recoverability events.

Neurodegeneration would constitute a heterogeneous group of disorders in terms of specific primary site of origin of the lesion, ultimately progressing through the stage of homeostatically defective viability of the neuron in inducing cell death[4,5].

Also, many causes that precipitate apoptosis may very well be intimately related to defective developmental origin of that particular cell, whereas neurodegeneration would essentially represent a heterogeneous group of primary disorders often incorporating also acquired pathobiologic attributes.

It may be valid to contrast apoptosis and neurodegeneration as two sharply distinct modes or mechanisms of cell death. Apoptosis may constitute a biologically instituted series of pathways that is operative once a basically developmental lesion is in place, whereas neurodegeneration would arise as a postdevelopmental lesion potentially involving many organelles of the cell once that cell has acquired determined systems of possible recoverability. Whereas apoptosis is a developmentally operative system, neurodegeneration may perhaps be best characterized as an unresolved outcome of attempted recovery from various forms of cell injury.

In terms of mechanisms of cell death, apoptosis would induce cell death as a series of mechanisms that were biologically instituted during cell development. Neurodegeneration, on the other hand, would constitute compensatory attempts in preventing further progressive injury to the cell.

In a sense, apoptosis is an all-or-none phenomenon whereby a threshold value in terms of both magnitude and type of injury to the cell would activate a stereotyped series of mechanisms initiated by the nucleus. Such a concept in the context of a relatively fixed cell life-span may actually implicate biologically instituted mechanisms in the origin and development of that cell. This may help explain the finite life-span of cells in terms of particular forms of potential injury inherent to the aging process. Types of aging may best be characterized in terms of specific diseases or lesions inflicted on the cells of the body over the years.

In the same way that carcinogenesis is linked to certain constitutional and also extrinsic carcinogenetic agents, aging might be an integral product of constitutional and other events contributing to occurrence and progression of specific lesions.

In fact, carcinogenesis and aging might be comparable as a series of events involving either renewal in an essentially aberrant manner or else a failure at renewal of damaged cells and tissues in the first instance.

In such a sense, aging and carcinogenesis might represent fundamentally different aberrations of an essential process of normal renewal of cells that are continually being injured and lost.

Neurodegeneration would constitute an expression of an overall effect of cell damage on the part of neurons that are incapable of self-renewal. The relation of Alzheimer's disease with increasing patient age might represent a common underlying set of conditions surrounding neurons that are increasingly incapable of self-maintaining normal homeostasis with increasing age. Thus, the aging process itself as a normal aged brain would constitute a series of processes that initially start out as mechanisms of normal processing and subsequently evolve to a second stage of degeneration and ultimately to a third stage of cell death[6].

Neurodegeneration as an essential interaction result of constitutional and acquired factors in lesion genesis and distribution: The amyotrophic lateral sclerosis and Parkinsonism/Dementia complex groups of patients seen in Guam are intimately related entities. Both groups of disorders appear basically to involve tau as a main focus of involvement. In fact, their close concurrent incidence in siblings and cousins would be suggestive of a basic variability factor in the essential distribution of an identical lesion in both groups of familial disorders.

A basic set of constitutional factors that is prevalent in certain Guam families may possibly predispose to either Amyotrophic Lateral Sclerosis or to the Parkinsonism/Dementia Complex. Such a concept would be suggestive of the possibly important role played by constitutional factors affected in a critical way by environmental factors in determining specific spectra of disease involvement in a particular patient.

Particularly with regard to neurodegeneration as a strictly definable pathogenetic process[7], basic constitutional attributes of the patient would critically interact with certain environmental or other acquired forms of neuronal injury in determining the specific character and distribution of lesions as a

neurodegenerative process. In this manner, aging-associated cognitive decline would represent a preclinical stage of Alzheimer's disease[8].

An innate susceptibility as a specific determinant in lesion production and distribution in neurodegeneration: Parkinson's disease appears to encompass several cases as a much larger group of clinicopathologic disorders rather than simply as a defined extrapyramidal system involvement with specific substantia nigra pathology.

The combination of Parkinson's disease with Progressive Supranuclear Palsy, with Corticobasal Degeneration, with Motor Neuron Disease, even with the presence of significant cortical atrophy and dementia, would apparently necessitate the recognition of Parkinson's disease as only a system pattern of involvement of the central nervous system. As such, it would seem that Classic Parkinson's disease simply constitutes an expression of the distribution of lesions based largely on susceptibility factors. In fact, the etiologic factors involved would intrinsically affect multiple different sites in the nervous system based largely on the presence or absence of involvement of different specific regional mechanisms.

In a sense, a universal or near-universal susceptibility attribute of an individual patient affecting different regions of the central nervous system would largely determine lesion distribution patterns, and hence secondarily specify clinico-pathologic features of patient involvement.

The hippocampus as intrinsically susceptible to the aging process: Several distinctly recognized forms of organic dementia affect the temporal lobe in terms both of an overall degree of atrophy[9] and also in terms of its concentration of specific focal lesions such as senile plaques or Pick bodies.

The temporal lobe would account for the clinical occurrence of dementia in terms of actual development of such focal lesions.

In addition, temporal lobe atrophy leads to the development of distinctly characterized groups of organic dementia that integrally evolve as specifically expressed morphologic entities of disease[10].

Temporal lobe involvement would reflect in a real manner the true nature of origin and progression of pathology involving many states of organic dementia[11]. Indeed, the hippocampus appears to especially constitute a core of structural and physiologic mechanisms that are pathologically implicated in the evolution of the Alzheimer disease process.

Perhaps the hippocampus is a phylogenetically primitive part of the brain in a manner that would predispose to an enhanced progression of the aging process leading to the development of lesions such as neurofibrillary tangles and plaques[12].

In general terms, Alzheimer's disease might implicate a constellation of pathophysiologic lesions that develop and progress largely as a pathologic predisposition to progressive brain aging. On the other hand, hippocampal volumes on magnetic resonance imaging are selectively correlated with memory functioning in successful aging[13].

Selective resistance to neuronal injury in successful brain aging: The Alzheimer disease process would constitute an interruption of the normal brain aging process with acceleration of the atrophy-inducing involvement of the cerebral cortex, as in the region of the lateral prefrontal cortex[14]. The normal aging brain process is by definition a result of multiple safeguard measures that tend to ensure the preservation of a substantial population of cerebral cortical neurons and networks.

The normal brain aging process appears one related to a satisfactory outcome ensuring successful survival of neurons in contrast to a central concept of injury as represented by selective vulnerability to various agents ranging from hypoxia to hypoglycemia. Resting state glucose metabolism in the brain is not reduced in normotensive healthy men during aging after correction for brain atrophy[15].

The nonapplicability of a selective vulnerability concept to successful brain aging would perhaps indicate survival of neurons beyond simple considerations of whether neurons are fields of applied injury or not. It appears true to regard cerebral cortical neurons as themselves chief determinants that start out as potentially vulnerable to various injuries but that finish up as a system relatively resistant to such agents as hypoxia and hypoglycemia in the case of successful brain aging.

Such a concept of acquired relative resistance to injury on the part of aging neurons would help account for various processes of progression that define normal aging as a phenomenon of recoverability beyond simple applied insult.

Analogous to a concept of selective vulnerability there would appear to develop a series of pathways of relative resistance that evolve with increasing age of the individual. In the same manner that neurons are selectively vulnerable to hypoxia, it is also possible to envisage a series of acquired pathways that potentiate the protection of neurons to relative hypoxia as the neuron ages. Selective vulnerability and selective resistance would go hand in hand in the promotion or inhibition of onset of various injuries that progress and transform

neurons as regional groups of highly differentiated nonreplicating cells.

Genetic and acquired systems of influence determining selective vulnerability or selective resistance to neuronal injury with subsequent loss would perhaps evolve as pathways that would or would not set in motion mechanistic events of progression ranging from metabolic to ionic to cytoskeletal lesions.

The correlation of a neuronal state of functionality with morphogenetic events in development and of subsequent evolving responsiveness to injury might perhaps relate specifically to a vulnerability that contradistinctively redefines basic concepts of selective injury.

Successful brain aging would involve maintained constancy of neuronal functional attributes that further define any injury as dysfunctionality affecting whole regional subgroups of neurons. The variability of regional neuronal loss that develops with increasing patient age appears one related to a selective vulnerability or selective resistance to injury of various pathways as neuronal homeostatic mechanisms.

Dysfunctional attributes of neuronal subsets appear an insufficient basis for a centrally operative selective vulnerability such as hypoxic injury to cerebral cortical or hippocampal neurons. Such selective vulnerability may be a simple expression of possible interaction with agents other than hypoxia in developing neuronal cell death.

Dysfunctionality might help account for a transforming attribute due to neuronal injury ranging from deprivation of oxygen to that of glucose.

Indeed, transforming neuronal injury may constitute the acquisition of dysfunctional and attempted recoverability attributes on the part of cells that progress or transform in terms of such injury.

Transformation in disease as a dysfunctional acquisition of neuronal attributes: Oxidative stress affects neurons as integral cellular units and operates in terms of a distinct responsiveness of the cell as a whole. It might be valid to consider satisfactory progression of oxidative stress injury as largely an expression of neuronal dysfunctionality. Even various forms of oxidative stress that affect the neuron as a whole would involve the existence of multiple pathways of convergence that either tend to promote or prevent evolving oxidative stress injury.

In terms of a whole series of injuries that potentially render the whole neuron a possible target for oxidative stress, dysfunctional attempts at cell recovery may themselves act as an active source for such oxidative stress.

Neuroprotection would operatively prevent both onset and progression of neuronal injury. The actual onset of injury to neurons would constitute an actively acquired form of progression relative to potentially neuroprotective mechanisms.

Oxidative injury as a stressful phenomenon inducing neuronal damage transforming various modes of response in terms of dysfunctionality might account for abnormal phenomena such as reperfusion injury after neuronal ischemia. It is perhaps in terms of a recurring series of attempts at recovery of neurons that there would develop attributes of an oxidative stress that participates in neuronal cell death.

An age-related expression of a neuronal cell loss might be suggestive of acquired systems of induced modification of pathways of susceptibility (Rusinek et al, 2003) that transform or do not transform profiles of induced reactivity as seen in oxidative stress injury. A series of phenomena that both arise and progress as systemic representations of various transformed pathways of injury would in addition implicate neuronal recovery as either functional or dysfunctional, including that due to subclinical ischemia (Meguro et al., 2003).

Indeed, oxidative stress may be redefined as injury that transforms to neuronal dysfunctionality as a result of susceptibility to further potentially progressing injury.

Synaptic integrity is determined by neuronal susceptibility traits that integrally transform cellular recoverability: Synaptic dysfunction might account for a convergence of multiple acquired lesions affecting neuronal viability ranging from apoptotic cell death to mitochondrial accumulation of mutations to oxidative stress injury and also to hyperexicitatory injury that damage membranes and subcellular organelles. Also, impaired glucose tolerance may affect hippocampal structure and function[18].

Synapses would appear a focal convergence point of disease involvement that progresses largely in terms of how neurons react to dysfunctional transformation of metabolic and ionic pathways. Indeed, a schematic outline of neuronal reactivities might help account for modes of participation of injury that largely culminate in synaptic loss[19].

Synaptic integrity as a measure of neuronal viability might functionally promote a neuronal system of resistance to or recoverability from various forms of injury such as oxidative stress based on reactive cellular responsiveness.

Neurons may be both susceptible to specific forms of injury such as toxins and hypoxia and yet be capable of utilizing various pathways of response as transforming

attempts in cellular recoverability.

Pathologic effects of presenile dementia are roughly equivalent to the total of the effects of both the disease and aging processes in senile dementia[20].

Neuronal cell loss appears a mixed phenomenon of cell death and of subinvoluting pathways that culminate in injury to mitochondria and cell membranes affecting particularly synaptic transmission of impulses. Glial cell line-derived neurotrophic factor may be involved in hippocampal dysfunction as related to accelerated senescence[21].

Successful brain aging appears primarily a result of functional recoverability that operatively maintains, paradoxically, the constancy of evolving pathways of influence in further enhancing neuronal viability.

Neuronal viability is of itself a constant parametric consideration that transcends functional or dysfunctional cellular attributes and one that would help account for successful aging of the brain in the effective absence of the Alzheimer disease process as accelerated senile atrophy of the cerebral cortex.

Effective distinction of normal brain aging from Alzheimer brain atrophy[21] might constitute a realized series of attempts demarcating the Alzheimer process that not only interrupts and transforms dynamics of preservation of neuronal viability but participates in the ongoing consequences of neuronal cell loss.

This may be individually cellular and also integrally regional in effective progression.

It is in the realization of variable response that one might best characterize neuronal viability both as a concept and as a parametric function in delineating resistance to or recoverability from progressive neuronal atrophy that develops in successful brain aging.

Susceptibility of neurons as genetic and acquired systems of dysfunctional recoverability: A normal brain life span would conceptually appear compatible with a developmental series of determinants in subsequent evolving responses to potential injury that help preserve neuronal viability. This is inducible as a whole series of events determining overall viability of neurons. A normal brain life span of cells would exclude the onset of progressive Alzheimer's disease. Amount and pattern of excess cerebral atrophy may help predict the underlying pathologic process as assessed by MRI brain imaging[23]. Progressiveness in Alzheimer disease pathogenesis might invariably implicate possible forms of neuronal injury that prove irreversible.

Blood flow dynamics and perfusion pressure variability might accompany hypoglycemia and hypoxic events that possibly culminate as integrally operative injury of whole subsets of neurons with increasing age of the patient[24].

The actual accumulative phenomenon that results in pathologic transformation would integrally redefine dysfunctional attributes of a neuronal injury as a measure of difference between the normal brain aging process and the variable atrophy of the brain in disease.

This integrally constitutive brain atrophy would account for progressiveness of the Alzheimer brain process that is genetically inherited and also acquired as attributes of recoverability and of potential dysfunctionality of neurons.

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