International Journal of Molecular Medicine and Advance Sciences 1 (2): 143-148, 2005

Loss of Synaptically Determined Viability of Neurons in Alzheimer Brain Atrophy

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Abstract: Multiple exogenously derived systems of promotion and of induced progression would perhaps actually participate within contextual frameworks of self-promotion as age-related dementia. Indeed, impaired synaptic connectivity and impaired synaptic integrity might assume pathogenic roles leading to aspects of both induced and self-promotion towards pathways of evolving brain atrophy. Even beyond simple schemes of induced effect or of self-progression, however, synaptic transmission or non-transmission might help characterize the Alzheimer process as systems of disturbance arising from micro-circulatory ischemia to lack of neurotrophic effect to systems of nonviability of neurons and of neuronal non-responsiveness. In simple terms, the specific associations of the Alzheimer process with aging would appear a specific characterization of synaptic pathobiology central to basic dynamics of dementia both as an organic atrophic state and also as persistently active pathways of progression once initiated.

Key words: Synaptically determind, brain athrophy, neuron, alzheimer

INTRODUTION

The synapse and the essential viability of the neuron: Is preserved synaptic function the one main criterion of biologic viability of the neuron? Conceptually, one might even consider the essential physiologic role of a neuron to center on synaptic transmission in terms of both receptivity and of transmission of impulses.

Such a view would convey conceptually the impression that the roles of the various sub-compartments of a neuron and of neuronal networks involve in the contribution towards synaptically mediated viability. In this regard, for example, autophosphorylation of calcium/calmodulin-dependent protein kinase II appears involved in the regulation of multiple neuronal functions including the intrinsic properties of neurons[1].

It would certainly appear, hence, that essential attributes of viability of a neuron, and conversely, the conceptual identity and significance of selective neuronal vulnerability would directly reflect dynamics of synaptic transmission and of synaptic receptivity. .Indeed, Brain-Derived Neurotrophic factor and Neurotrophin-4/5 appear to be anterograde survival factors for post synaptic cells in the developing rat superior colliculus, within an overall scheme of retrograde, anterograde or paracrine trophic support series of viability systems[2].

Perhaps, in a strict sense, receptivity would represent a source of various mechanisms promoting the generation and conduction of impulses in terms of modulated neurotransmission in the first instance. Also, expression of different gap junction types during neurogenesis might define intercellular pathways for transmission of developmentally relevant molecules with subsequent modulation of growth and differentiation of neurons[3].

Hence, perhaps, the one fundamental attribute of synaptic physiology would concern itself mainly with the post-synaptic membrane as a receptive endplate rather than with release of the neurotransmitter from the presynaptic membrane as synaptic vesicles. Hence, in simple terms, the central nervous system might essentially be viewed as a receptive series of mechanisms based on relatively simple but highly modifiable pathways of synaptic interconnectivity beyond any concept of directly linked stimulation or response of neurons. Integrative functionality in the CNS would at times even constitute non-generation of a response in spite of stimulation based on concepts of essential receptivity of the CNS.

Is neurodegeneration simply an increased susceptibility to a stress-inducing agent: It is conceivable to consider an active neurodegenerative process as a fundametnal susceptibility to effects of oxidative stress. Indeed, in terms of an increased neuronal vulnerability to a potentially vast range of stressful injury, primary neurodegenerative disorders would possibly evolve as substrates for the further progressive loss of neuronal viability. In this sense, for example, adaptor protein complexes such as AP-3, if absent in both its ubiquitous and neuronal form, would promote neurologic disorders. Indeed, the neuronal AP-3 can produce synaptic vesicles from endosomes *in vitro*[4].

Neurodegeneration, for example, as a heterogeneous series of inherited defects, would relate to genetic, protein, or even oxidative metabolic pathways of disturbance that assume particular pathobiologic

significance in a setting of predisposed injury as exerted by oxidative stress. Hence, in a general sense, the primary neurodegenerative defect would be considered a suitable medium in terms of possible interactive predisposition leading to progressive neuronal injury as precipitated by various potential agents including oxidative stress.

In a more fundamental sense, it might be valid to consider neurodegeneration as an essentially disturbed oxidative metabolic activity. In fact, one might actually refer to cell/neuronal degeneration as necessarily a pathway of aberrant metabolic activity that is inherently a pathobiologic predisposition to cellular stress injury. Not only this, it might in addition also be valid to consider such an involvement of the oxidative pathways in terms of a primary neurodegenerative defect contributing to self-progression of the disease process.

Within such a scheme, a heightened degenerative state involving the neuron would evolve in a context of the high oxidative metabolic rates developing and maintained in neurons in general, both in health and also under circumstances of stress or active disease. Perhaps, in an important sense, one would distinguish a difference between neuronal stress induced by active disease versus other forms of evolution classically of neurodegenerative type. Is it in fact valid to consider neurodegeneration as a generic pathobiologic phenomenon fundamentally centered on oxidative stress as the nature of evolving neuronal injury rather than as simply specific forms of neuronal injury per se? Is it in fact the very nature of progressive neurodegeneration to be one of stress-induced injury, specifically inherent to oxidative stress rather than as a primary form of disease involvement of such neurons?

Certainly, such conditions might appear to translate such a concept of increased selective vulnerability of neurons in terms of variable vulnerability of individual neurons and of neuronal subsets that are specifically of oxidative type and evolving as patterns of exposure to such oxidative-type stress.

Within such a concept of neurodegeneration, the very nature of disease might actually assume particular significance in terms of the nature and severity of a series of stress-inducing injuries. Such neuronal injury would by definition constitute active pathobiologic integration of attributes of the neuron concerned within a series of stress-inducing events of exposure. Such a view would perhaps implicate the nature of interaction and of degree of recoverability of neurons as a variety of stressful exposures determining parameters of progression of a neurodegenerative process as defined clinically, pathobiologically, morphologically and biochemically. Also, the postsynaptic cell can regulate synaptic strength by changing sensitivity to neurotransmitter and by generating a retrograde signal that regulates presynaptic transmitter release. Diversity of synaptic receptors appears to provide mechanisms for generating synaptic plasticity[5].

Synaptic connectivity as postynaptic determination of neuronal viability and maintenance of such viability: A full spectrum of neuronal and synaptic injury appears to develop in temporal lobe epilepsy. In addition, the bulk of such injury would appear to localize particularly in regions of high synaptic density.

Indeed, neurons with a high degree of synaptic connectivity are rendered susceptible to injury in cases of epilepsy as with spiny interneurons in cases of temporal lobe epilepsy. Within such a framework of selective vulnerability there would appear implicated an essential phenomenon of neuronal viability in terms of maintenance of integrity of synaptic connectivity.

Also, neurons with high synaptic connectivity selectively injured in epilepsy would further contribute to progressive neuronal injury due to loss of such synaptic connections. Hence, within simple conceptual systems of primary synaptic injury and of secondarily impaired viability of these same neurons during periods of epileptic ictus, one would delineate mechanisms of subsequent reactive synaptogenesis and of regeneration (as with mossy fiber regeneration and the formation of thorny dendritic spines) that are initiated, maintained, and finally incorporated within the local neuronal circuitries.

In this regard, in contrast to the early cell proliferation and patterning effects including synapse formation classically ascribed to Wnts, the auditory and cerebellar phenotypes mediated by a targeted deletion of the fuzzled-4 gene in fz4(-/-) mice would implicate Frizzled signaling in maintaining viability and integrity of the nervous system in later life[6].

The above considerations would appear fully consistent with a concept of central synaptic operability in determining both susceptibility to neuronal injury and also in maintaining viability of such neurons under both normal and pathologic conditions. For example, transgenic expression of the alpha 7 Beta1 integrin chain can compensate for absence of dystrophin and induce maintained structural functionality of the neuromuscular junction[7].

Certainly, such considerations might particularly emphasize normal funcitonality states as an essential determinant in maintenance of such normal functionality. Indeed, spontaneous motor activity appears to contribute significantly to neuromuscular and motor development[8]. Indeed, also, normal synaptic transmission and anatomy

would appear fully dependent on a periodically constant maintenance of normal synaptic transmission. For example, skittles, a Drosophila phosphatidyl inositol 4 phosphate-5 kinase is required for cell viability and is implicated in vesicle trafficking[9].

Furthermore, such a concept might be suggestive of the importance of vital postsynaptic stimulation of neurons in ensuring viability of presynaptic neurons and indeed of the integral synapse itself.

Such disorders as epilepsy and also specific pathogenic pathways as with amyotrophic lateral sclerosis would appear centered on synaptic integrity and on maintenance of such synaptic integrity in terms essentially of viability of both post- and pre- synaptic neurons. In this regard, especially, enhanced exocytotic activity supported by a strengthened exocytotic capability might underlie the high viability of rate cerebellar granule neurons cultured under depolarizing conditions p[10].

The actual process of reactive compensation and regeneration as integral components of CNS plasticity would appear to revolve mainly around synaptic phenomena of viability and of reaction to injury as essential schemes of closed neuronal circuitry. Certainly, a dramatic reduction in synaptophytin immunoreactivity together with aberrant plastic changes and loss of synaptic integrity would appear to progress concurrently with fibrillary amyloid Beta deposition in Alzheimer's[11].

It is this peculiar combination of a full integrity of individual neuronal circuits within a single global integrity of a single central nervous system that one would realize postynaptic stimulation as a probable main determinant in CNS disease progression. Also, for example, cannabinoid receptor agonists that act presynaptically to inhibit the release of glutamate would appear to slow the progression of neurodegenerative diseases[12].

Is a primary synaptic pathology as evidenced by lewy bodies one essential primary lesion in alzheimer's disease: It appears reasonable to consider cortical Lewy body deposition an essential characterization of all cases of dementia with any degree of Lewy body formation, irrespective of the presence of or absence of any concomitant Alzheimer-type lesions in cortex or elsewhere in the brain. The bulk of pathologic involvement in the brain as manifested by Lewy bodies implicating synapses would be evidenced by alpha-synuclein immunohistochemical positivity. Such an interpretation would perhaps help shed some light on the nature and roles of Alzheimer-type lesions in patients with dementia, a situation whereby both the neurofibrillary tangle and the neuritic plaque would assume roles as core processes of disease involvement in Alzheimer's.

Within such a framework of the neurofibrillary tangle and of the neuritic plaque evolving as an implicated synaptic lesion, Lewy body deposition would assume specific significance in terms of pathology of both cerebral cortex and amygdala.

But what is the nature of the classic lesions as seen in Alzheimer's? Given a concept of consequential pathology subsequent to neurofibrillary tangle and neuritic plaque deposition there would appear to evolve a concept of essential nonspecificity in terms of an "Alzheimer" process that participates as variable involvement of synaptic lesions in disease progression.

From a pathogenic as well as from an etiologic point of view, it would apear significant to consider the evolution of the dementia in terms of the Lewy body deposition, especially in the cerebral cortex in an added possible context of progressive neurofibrillary tangle and neuritic plaque formation. Certainly, sharp fluctuations in consciousness and hallucinations and sensitivity to neuroleptics that are modified by development and progression of sequential lesions constituted by the neurofibrillary tangles and neuritic plaques would help towards characterization of Lewy body disease in terms also of Alzheimer process-type dynamics.

Hence, in an overall scheme of involvement implicating an essential pathogenic induction of synaptic injury would be manifested as Lewy body deposition throughout often much of the cerebral cortex. Much of the core manifestations of the dementia might actually be attributable to primary synaptic pathology that secondarily progresses.

However, to some extent, consequential formation of neurofibrillary tangles and of neuritic plaques would modify pathologic brain involvement in large part or as a whole in a context of clinical manifestations of dementia.

Within schemes of fluctuations of symptoms as seen classically with relatively pure diffuse cortical Lewy body disease there would evolve a primary state of pathologic involvement predisposing to subsequent formation of neuritic plaques and of widespread neurofibrillary tangle deposition. In terms of pathogenesis, particularly with regard to the neuritic plaque, the primary role of synaptic pathology and of Lewy body formation throughout much of the cerebral cortex would implicate neuritic degeneration based presumably on multifocal disturbance of the micro-circulation and as ischemically induced trophic lack.

In this regard, it would appear significant that neurotrophins might induce formation of functional excitatory and inhibitory synapses as noted experimentally between cultured hippocampal neurons[13]. Also, it is significant to note that synaptic proteolysis

induced by hypoxia would appear to triggered by calcium influx in promoting hippocampal synaptic dysfunction[14].

Is neurotrophic effect one intrinsically combined with effects of synaptic neurotransmission in axonal regeneration: The general approach that associates the administration of a number of neurotrophic factors including fibroblast growth factor with improving viability and particularly with regenerative capabilities of peripheral nerves and their supplying neurons is essentially one not primarily or directly concerned with the actual precipitating cause of the neuropathy[21]. Certainly, the essentially enhanced regenerative effects exerted by neurotrophic factors would enhance axonal regeneration in terms also of associated myelin sheaths.

Indeed, the myelin sheaths as a secondarily superimposed component on the axon in peripheral nerve morphology and physiology, would themselves assume pathologic significance in essential disease progression. Certainly, regeneration would implicate the sustainment of the axon as circumstances of active and intense participation in redirected axonal growth as seen after axotomy.

In this regard, also, a new kinesin (superfamily protein KIF1A) transports a synaptic vesicle precursor; KIF1A-mediated axonal transport would play a central role in viability, maintenance, and function of neurons, particularly mature neurons[16].

But, in a fundamental sense, there must in the first place be the elicitation of an active stimulus with a corresponding receptive signal translation and subsequent messenger transfer, phenomena presumably generated mainly in the neuronal cell body. In this regard, for example, distribution of a low affinity p75 neurotrophin receptor (p75NTR), as revealed by immunohistochemical staining also within astrocyte somata and dendrites, would be suggestive of a controlling neurotrophic effect in modulating viability of local hippocampal cell populations[17].

In a sense, perhaps, therefore, neurotrophic factors are essentially concerned with the DNA transcription, and with protein translation phenomena in the perikaryon, phenomena that would be a rate-enhancing step over an above those required for simple sustainment and maintenance of axon integrity.

However, some other essential series of events would be required for effective regeneration to develop. Indeed, for example, activation of the target muscle would appear to play a critical role in retrograde signaling maturation of a secretory apparatus in target-contacted neuronal processes[18]. It is perhaps the ability for actual utilization of proteins in axonal outgrowth that one would essentially characterize specific attributes of a given neurotrophic effect. How can a neurotrophic factor so effectively direct active incorporation of proteins towards specific regeneration of axons? Indeed, viability of transected axons in cultures devoid of other cells depends on protein pools synthesized prior to transection and on energy stores[19]. Certainly, axonal regeneration would require a pre-existing axonal stump involving also the neuronal perikaryon as components of the injured state-- one possible mechanism of such recognition of the injured state or lesion might in fact involve a synaptic discontinuity.

Also, systems such as those involving chaperones at the synapse as represented by cysteine string protein (a major synaptic vesicle and secretory granule protein) might be implicated in regulated exocytosis. Indeed, cysteine string protein though its membrane targeting functions and its binding and activation of the HSP 70/hsc70 chaperone ATPases would be involved in fulfilling a key role in neurotransmitter release[20].

Hence, perhaps, much of the regenerative ability of neuronal axons would implicate loss of synaptic function at the distal nerve axonal terminals, as a main mechanism of active sustainment and of potential regeneration in the nervous system. It is often believed that synaptic neurotransmission implicates presynaptic to postsynaptic membrane impulse conduction. Indeed, a significant impulse current might constitute an essential disturbance of synaptic neurotransmission influencing basic biologic states of response and implicating also the presynaptic axon. In this regard, especially, aberrant patterns of synaptic activity as induced experimentally between rat hippocampal neurons in culture, would promote neurotoxicity and neuronal death[21].

In this connection, also, synaptogenesis itself apparently often requires glial or astrocytic support for optimal neuronal survival and maturation, particularly also as a late milestone in neuronal differentiation[22].

An essential association of specific morphologic lesions in classic alzheimer's disease within a framework of several promoting and operative factors: Within the whole clinicopathologic syndrome spectrum of Alzheimer type changes there apparently develops a fundamental tendency for neurofibrillary tangle deposition. Neurofibrillary tangles would in fact evolve as pathologic phenomena characterizing in particular a state of dementia with or without motor disturbance. Even the senile dementia with tangles seen in very old subjects, particularly females, would be consistent with the concept of a specific tendency for neurofibrillary tangle formation

with advancing age; perhaps, the principal single form of neuronal pathology as an attribute of advancing age might actually implicate neurofibrillary tangle formation as a progressive lesion with aging.

Certainly, from a purely pathobiologic point of view, a given set of multiple pathogenic agents might contribute in a particular individual to patterns of distribution of constituent lesions as seen morphologically in the brain and also as determined by types of neurodegeneration causing cognitive impairment and dementia in that individual.

As such, for example, classic Alzheimer's disease would implicate pathogenic agents that not only produce neurofibrillary tangles but also promote a predisposition to the operative or active induction of developing neuritic plaque, beta-amyloid deposits, and congophilic angiopathy-- in fact, a concept of classic Alzheimer disease would allow for a degree of variability of a whole series of other lesions ranging from Lewy bodies, to subcortical involvement, apoE type association, the essential process of cerebral atrophy itself, the association of mild to severe ischemic lesions, the development of neuropil threads, argyrophilic grains, Hirano bodies, and granulovacuolar inclusions.

In addition, there would exist within such a concept of classic Alzheimer disease an essential variability in degree of cortical atrophy that would implicate also more circumscribed lobar types of atrophy in this disease as more characteristically found in Pick's disease.

Certainly, in spite of a heterogeneous spectrum of morphologic lesion involvement of the brain, the hippocampus and the allocortex would appear pivotal sites in initiation of the Alzheimer process apparently primarily revolving around neurofibrillary tangle formation.

Also, senile dementia with tangles would appear to outline essential attributes of the aging process in terms of a complex morphology that is related to the classic Alsheimer type implicating for example disuse atrophy[23].

Other factors would appear to operate in leading to a strong association of such diverse morphologic lesions resulting in Classic Alzheimer's such as oxygen delivery[24].A strong association of neurofibrillary tangle formation with developing neuritic plaques, neuropil threads, would relate possibly to ischemic-type changes and Beta-amyloid deposition as virtual pathways of pathogenesis of promotion and of active induction of Alzheimer disease phenotype.

It is perhaps within the strict framework of common associations of the main pathologic lesions as seen in Classic Alzheimer's disease that one might eventually be able to indicate whether neuropil threads and argyrophilic grains are in fact different stages in the development of neurofibrillary tangles themselves, or even whether these three types of lesion represent one pathogenic mechanism affecting different subcellular components of the neuron.

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