

PREVENTIVE MEASURES OF NEURODEGENERATION.

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ABSTRACT: The present article deals with different measures which will prevent the 'NEURODEGENERATION' in the neurons of the central nervous system. The neurodegenerative diseases are characterized by conformational changes in the proteins that result in misfolding, aggregation and intra or extra-neuronal accumulation of amyloid fibrils. To prevent this pathology, we have different "TOOLS" which are elaborated in the main article below. The goals of Medicine are to promote health, to preserve health, to restore health when it is impaired and to minimize suffering and distress. These goals are embodied in the word "PREVENTION". Successful prevention depends upon a knowledge of causation, dynamics of transmission, identification of risk factors and risk groups, availability of prophylactic or early detection and treatment measures, an organization for applying these measures to appropriate persons or groups and continuous evaluation of and development of procedures applied. Prevention framework includes Primary – true prevention, Secondary – early detection & screening, Tertiary – doing the best possible in established disease. Effective treatment or intervention for people identified through early detection with evidence of early treatment leading to better outcome than late treatment. Neuroprotection is the mechanisms and strategies used to protect against neuronal injury or degeneration in the Central Nervous System. The goal of neuroprotection is to limit neuronal dysfunction/death after CNS injury and attempt to maintain the highest possible integrity of cellular interactions in the brain resulting in an undisturbed neural function.

KEY WORDS: Prevention, Neurodegeneration, Tools.

INTRODUCTION: Neurodegenerative disease has become one of the most exciting and well researched areas of neuroscience in the past few years. This is due to the growing awareness of dementia within our society which is largely caused by diseases such as Alzheimer's. Neurodegeneration itself is basically the progressive loss of neurons via apoptosis, structural abnormalities, or a general failure to function. More than 600 disorders afflict the nervous system. Many neurodegenerative diseases including Parkinson's, Alzheimer's, and Huntington's occur as a result of neurodegenerative processes. As research progresses, many similarities appear which relate these diseases to one another on a sub-cellular level. Discovering these similarities offers hope for therapeutic advances that could ameliorate many diseases simultaneously. There are many parallels between different neurodegenerative disorders including atypical protein assemblies as well as induced cell death. Neurodegeneration can be found in many different levels of neuronal circuitry ranging from molecular to systemic.

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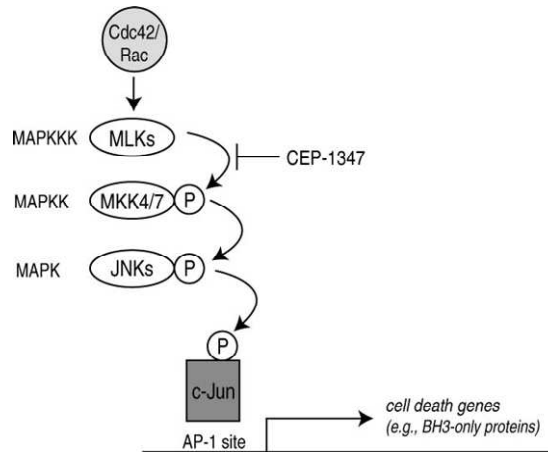
TOOLS:

- **Molecular chaperones :**

Molecular chaperones provide a first line of defense against misfolded, aggregation-prone proteins and are among the most potent suppressors of neuro-degeneration known for animal models of human disease.

Molecular chaperones are neuroprotective because of their ability to modulate the earliest aberrant protein interactions that trigger pathogenic cascades. Eg. CEP-1347 (a semi synthetic derivative of the fermentation product K-252a).

Molecular Chaperones inhibit c-JNK pathway (Jun N terminal kinase pathway)—Inhibition of Neuronal cell death. CEP-1347 has the potential of not only retarding disease progression but also reversing the severity of symptoms by improving the function of surviving neurons. The possible importance of the JNK pathway in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases provides a rationale for the use of CEP-1347 for the treatment of these diseases. Activation of JNK pathway is critical for naturally occurring neuronal cell death during development as well as the pathological neuronal cell death of neurodegenerative diseases. The JNK path way is mitogen-activated-protein kinase (MAPK) pathway that is activated in response to many extracellular stimuli and different forms of environmental stress. The MAPK pathway is organized as a cascade of at least 3 kinases. The JNK pathway can be activated by small G- proteins, such as Cdc42&Rac members of the RHO family GTPases. In the neurons, the MLK family of kinases serves as the major MAPKKs and phosphorylates MKK4 & MKK7, which in turn phosphorylate the JNKs. Activation of JNK pathway induces the expression of BH3-only proteins members of Bcl2-2 family which are critical upstream regulators of neuronal apoptosis. (See the flow chart below).



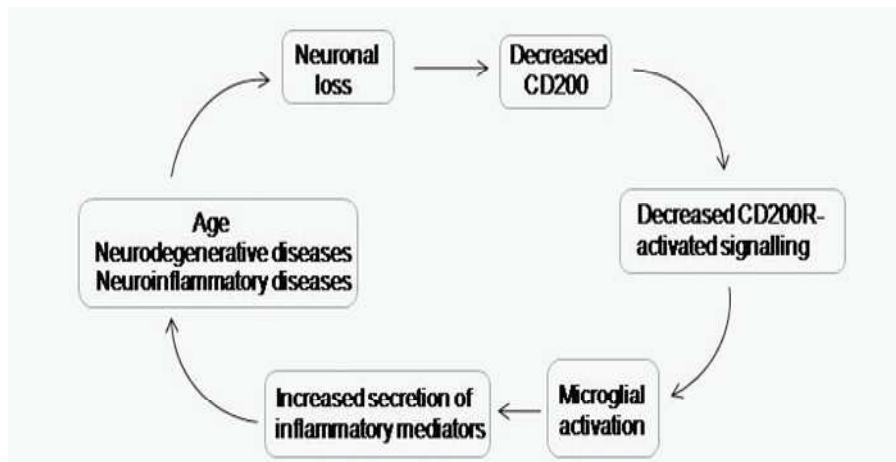
CD200 & CD200R: CD200 is a human protein encoded by the CD200 gene. The protein encoded by this gene is a type 1 membrane glycoprotein, which contains 2 immunoglobulin domains & thus belongs to the immunoglobulin super family. CD200R is an important inhibitory receptor present on microglia, actively maintains microglia in a quiescent state through its interaction with CD200, a trans-membrane glycoprotein expressed on neurons. (See the diagram below). CD200 & CD200R dysfunction exacerbates microglial activation and dopaminergic neurodegeneration in a rat model of Parkinson's disease.

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Based on our recent findings that VEGF-B, is a potent protective/survival factor for both the neuronal and vascular systems, which are two critical components in most neurodegenerative disorders. VEGF mediated signaling could contribute to astroglial activation & inflammatory reactions.

ROLE OF ASTROCYTES IN NEURODEGENERATION: Astrocytes play a critical role in normal function of the mammalian nervous system. Astrocytes regulate K⁺ buffering, glutamate clearance, brain antioxidant defense, close metabolic coupling with neurons, and modulation of neuronal excitability. In numerous pathological states, such as AD (Alzheimer's Disease), PD (Parkinson's disease), ALS (Amyotrophic lateral Sclerosis) and astrocytes are involved in both exacerbation of damage (reactive astrocytes 2% present in the old age tissues) and neuroprotective mechanisms. They support neurons in many ways, all of which are essential for repair and regeneration. Disturbances in astrocytic functions are implicated in neurodegenerative diseases pathogenesis, therefore, modulation of astrocyte functioning may prove to be an efficient therapeutic strategy in many chronic CNS disorders.

ROLE OF CD200-CD200R IN NEURODEGENERATIVE CHANGES.



VEGF: (VASCULAR ENDOTHELIAL GROWTH FACTOR)

ROLE OF CONNEXIN HEMI CHANNELS IN NEURODEGENERATION: Dysfunction of astroglial and microglial hemichannels, as well as gap junction channels, are likely mechanisms commonly elicited in all brain diseases associated with inflammatory responses. Therefore, normalization of connexin- and pannexin-based channel dysfunctions should confer tissue protection, improve quality of life, and extend survival of patients suffering acute or chronic brain inflammatory responses. Thus, it is proposed that chronic or acute processes of neurodegeneration might be prevented by blocking glial and neuronal hemichannels. Prevention might also be accomplished by reducing the effects of soluble factors (i.e., glutamate, ATP, prostaglandins, and cytokines) accumulated in the microenvironment of the inflamed CNS.

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ROLE OF ACID SENSING ION CHANNELS [ASICs] IN NEURODEGENERATION: ASICs represent new biological components in peripheral sensory and CNS neurons. Increasing evidence indicates the involvement of these channels in both physiological and pathological processes of CNS (Grunder & Chen, 2010). Therefore, targeting these channels may provide novel and effective therapeutic interventions for a number of CNS diseases.

ROLE OF DIET IN NEURODEGENERATION

1. DHA: DOCOSA HEXAENOIC ACID.

It is relevant that DHA (Family of n-3 polyunsaturated fatty acids) is the most unsaturated fatty acid in our organism and is found specifically concentrated in the brain, retina and sperms of higher animals (Uauy et al., 2001). DHA, when provided by the diet, comes mainly from marine organisms such as fish (fatty or blue species), shellfish, and algae (Horrocks et al,2004).DHA plays a relevant role in the preservation of both the histology and physiology of the neuronal tissue as the individual ages, by preserving the nervous system functions among which memory and learning are the most remarkable (Lukiw & Bazan, 2008).

2. CALORIE RESTRICTION:

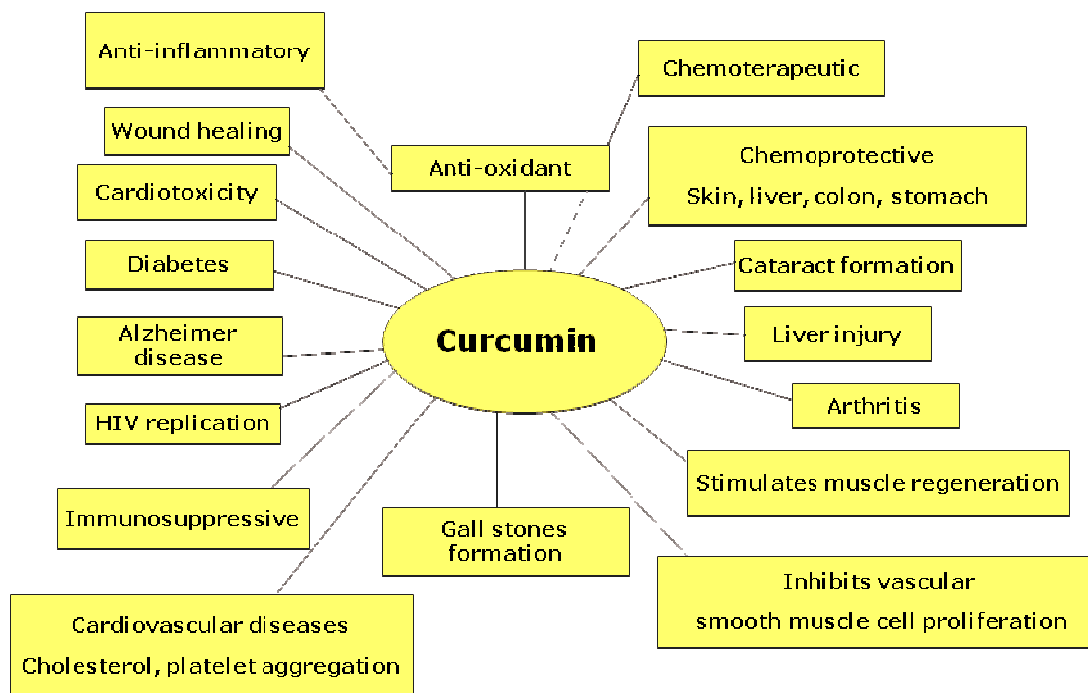
Calorie restriction induces sirtuins, silent information regulator proteins that regulate life span, enable DNA repair, protect DNA, and improve the survival of the most abundant antioxidants found in the diet, polyphenols have shown neuroprotective effects in studies over the past decade neurons.

Researchers believe that coenzyme Q10, a fat-soluble compound primarily synthesized in the body and also consumed in the diet, may have the potential to affect the course of neurological disease in which mitochondrial function is impaired and oxidative stress and damage are present

3. POLYPHENOLS:

The most abundant antioxidants found in the diet, polyphenols have shown neuroprotective effects in studies over the past decade. It appears that the mechanisms of action for dietary polyphenols extend beyond their antioxidant activity. These include activities such as iron chelation, scavenging radicals, activating survival genes and cell signaling pathways, and regulating mitochondrial function and possibly of the ubiquitin-proteasome system.

4. CURCUMIN: Curcumin appears to slow the formation of—and possibly even destroy—accumulated plaque deposits at the root of AD. Curcumin significantly lowered oxidized proteins and interleukin-1beta, a proinflammatory cytokine, in Alzheimer transgenic mice brains, according to a 2001 study in **The Journal of Neuroscience**, Greg Cole, PhD, a professor of medicine and neurology at UCLA, who has studied the effects of curcumin on AD, reports that curcumin is a potent antiamyloid drug with an established safety profile that has reversed cognitive defects in animal models.



5. MEDITERRANEAN DIET:[Balanced diet of low fat, moderate carbohydrate, and good protein.]

Along with a host of disease-prevention benefits, the Mediterranean diet has also been linked with a lower risk of AD. Researchers discovered that higher adherence to the Mediterranean diet was associated with a lower risk of AD, possibly due to the reduction in inflammation and an antioxidant effect.

6. DIETARY DAMAGE: while nutritional strategies that reduce inflammation and oxidative stress appear to hold promise for preventing neurodegenerative disease, it's important to note that some nutritional factors may actually enhance brain inflammation. Obesity seems to be on the top of the list of concerns. Studies have shown that people with higher levels of adiposity are at higher risk for both future PD and AD and that central adiposity is related to cognitive decline and dementia.

"Body fat promotes inflammation. Body fat may store toxins. A fatter person even has a smaller hippocampus," says Perlmutter of links between obesity and neurodegeneration.

7. ACHILLEA FRAGRANTISSIMA [AF]:(LAVENDER COTTON-A DESERT PLANT)

Extract of Achillea fragrantissima Down regulates ROS Production and Protects Astrocytes from Oxidative-Stress-Induced Cell Death. Af extract inhibits H₂O₂- and ZnCl₂-induced ROS (Reactive oxygen species) generation. AF extract reduces 2,2'-azobis(amidinopropane) (ABAP)-mediated peroxy radicals levels in astrocytes (ROS-reactive O₂ species.).

ACHILLEA FRAGRANTISSIMA:



8. WOLF BERRY FRUIT (raw & dry):

WOLFBERRY

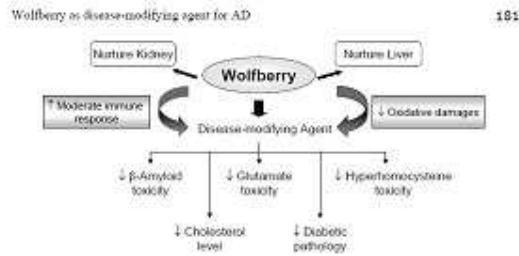


Figure 2. Multifaceted protective effects of wolfberry against neurodegeneration in AD. Wolfberry has a long history for being used as medicinal herb in oriental medicine. It acts as a tonifying herb to nurture the kidney and liver, which may account for its anti-aging properties. It can also modulate body immune response and act as anti-oxidant. These may be responsible for its neuroprotective effects against several conditions related to AD pathogenesis. Wolfberry is able to attenuate Aβ peptide toxicity and glutamate excitotoxicity. It can also reduce pathological changes cause by high cholesterol level and diabetes mellitus. All of these beneficial effects enable wolfberry to become a potential disease-modifying agent for the prevention or treatment of AD.

AD risk factors: 4. management in patients: 4. neurodegeneration

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