Brain Health with Cerebrolysin and Other Peptides

Cerebrolysin

- A combination of nerve growth factors which aid in the repair and recovery of nerve cells within the brain and PNS.
  - Neuro-protective/Neuro-regenerative: neurotrophic repair properties similar to NGF (nerve growth factors, BDNF)
- Neuropeptide; synthetic nootropic
- LMW can cross BBB/B-CSF

Cerebrolysin: Therapeutic Uses

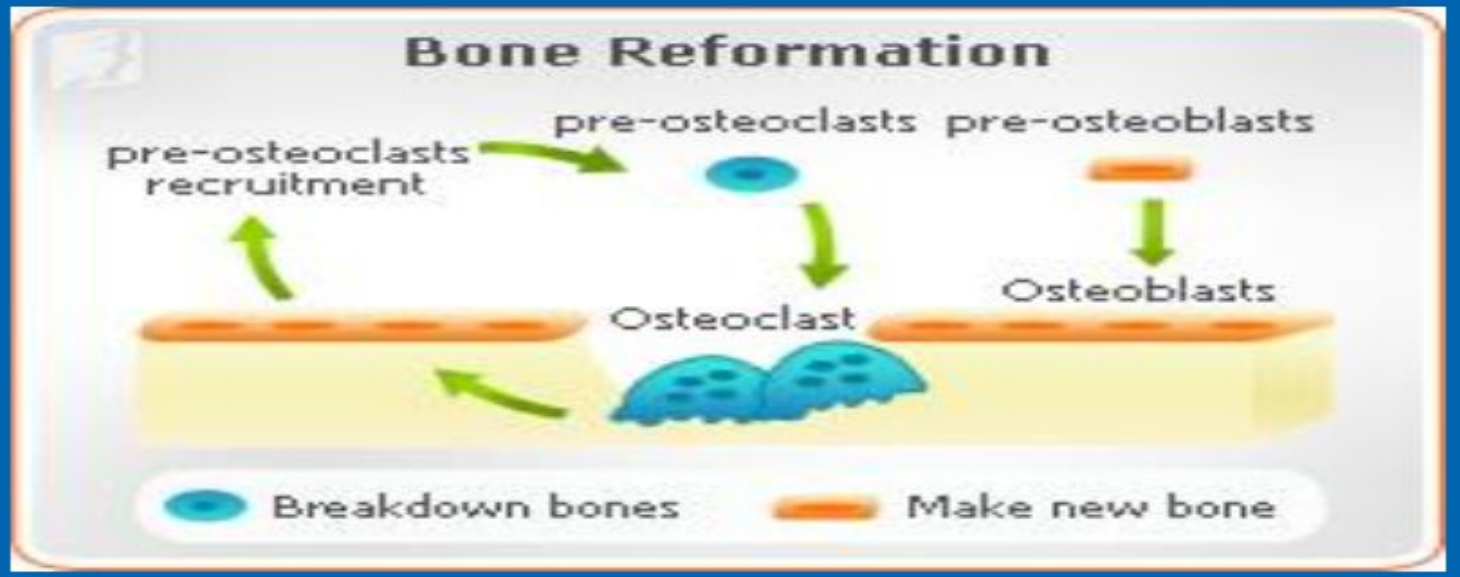
- Concussion/CTE, TBI
- Alzheimer’s Dementia, MCI
- CVA, TIA
- Mood Dysregulation

Cerebrolysin in Dementia

- Decreases Beta Amyloid deposition
- Decreases Tau protein phosphorylation
- Increases synaptic density

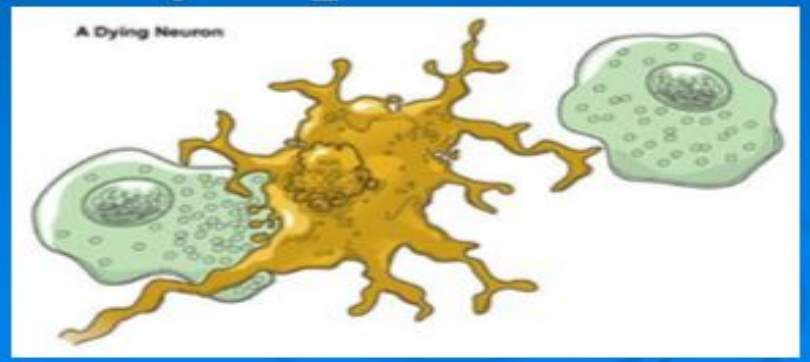
Alzheimer's as a signaling imbalance

Osteoporosis:



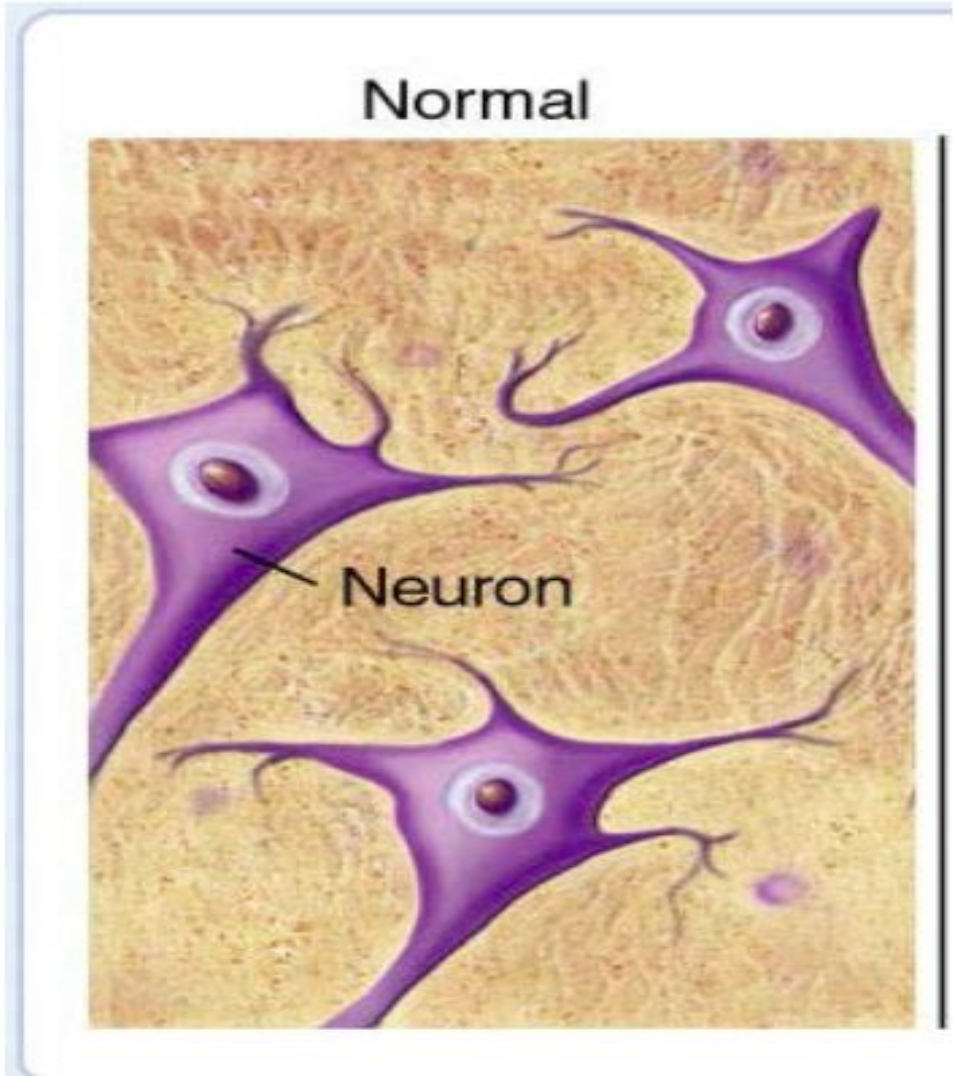
Alzheimer's:

Synaptoclastic



Synaptoblastic

Dementia and Brain Aging: Something Is Interfering With Brain Cell Communication



The perfect Alzheimer's drug would:

Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage, reduce caspase-6 cleavage, reduce caspase-3 cleavage, prevent oligomerization, increase neprilysin, increase IDE, increase microglial clearance of Aβ, increase autophagy, increase BDNF, increase NGF, increase netrin-1, increase ADNP, reduce homocysteine, increase PP2A activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransmission, increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvins, enhance detoxification, improve vascularization, increase cAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase SirT1, reduce NFkB, increase telomere length, reduce glial scarring, enhance repair, etc.

Dale Bredesen 2014

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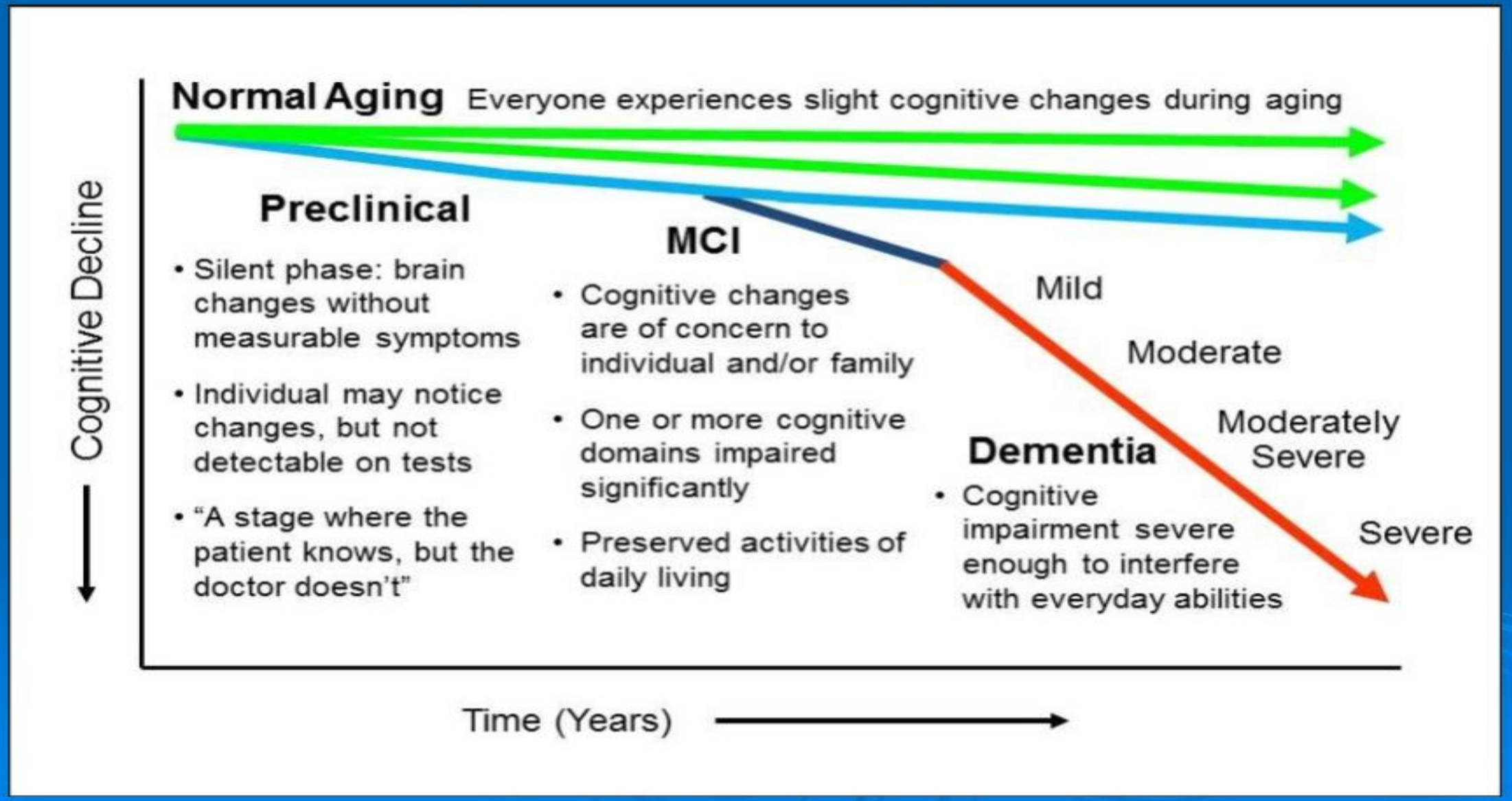
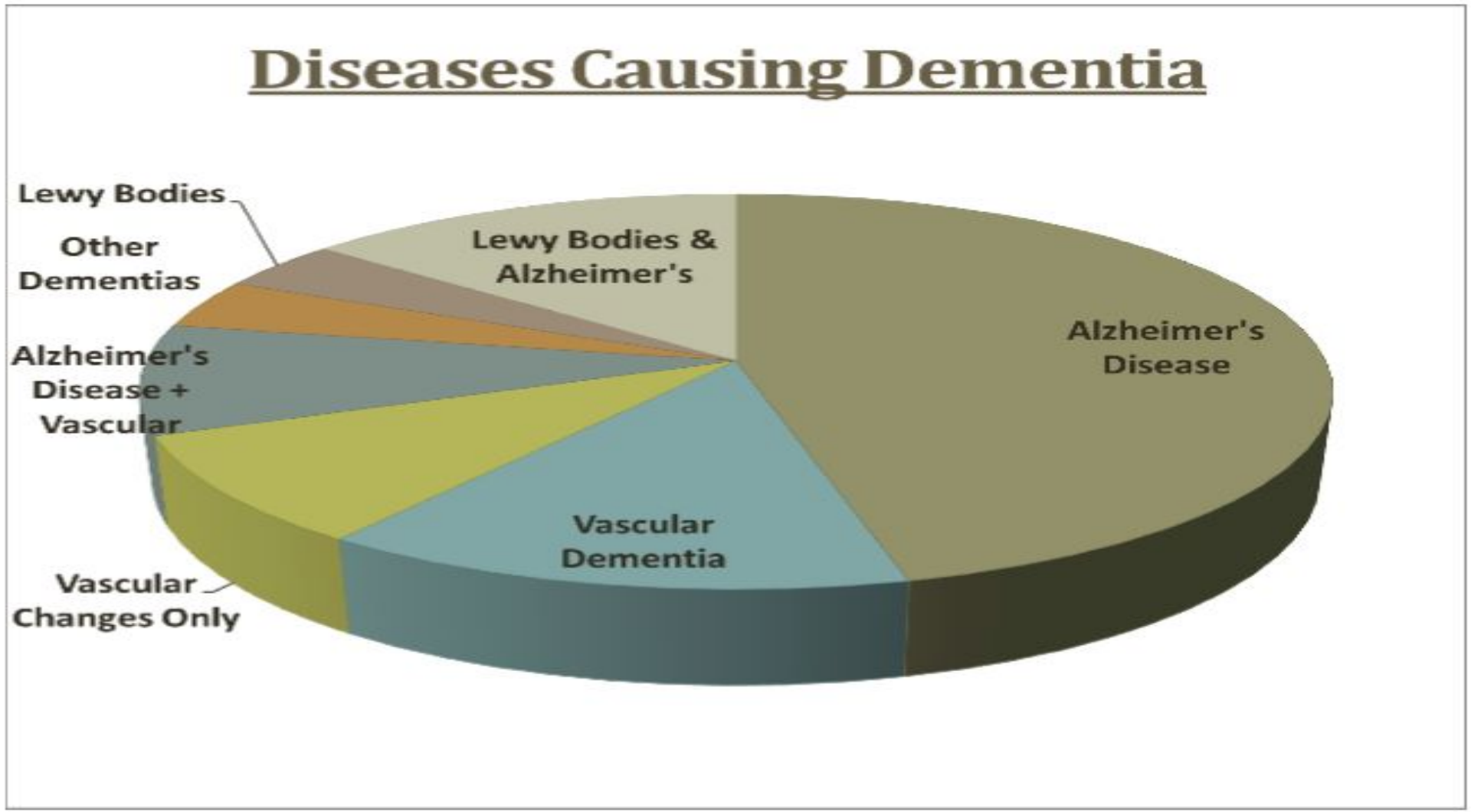
Dale Bredesen 2014

The Progression of Cognitive Impairment



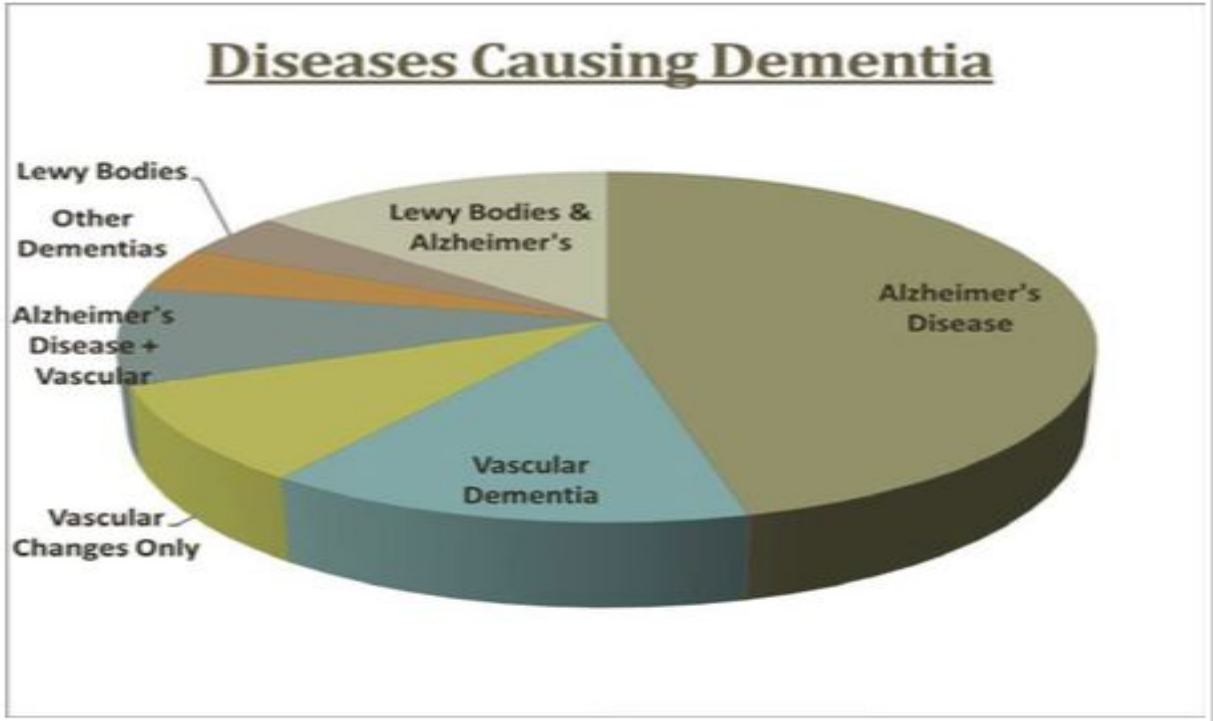
What Can Cause Dementia?



There are as many as 200 known causes of dementia, but most of these causes are very rare.

Approximately 20% Of Dementia Is Quickly Treatable

- If dementia is caused by vitamin or hormone deficiencies, the symptoms may resolve once the problem has been corrected.
- Which vitamins?
- Therefore, dementia symptoms require comprehensive evaluation.



Cerebrolysin in Dementia

- Restores neuronal cyto-architecture
- Results in improved cognitive and behavioral performance
- To consider if ApoE→ E3/E4 or E4/E4

Meta-analysis: the efficacy of nootropic agent Cerebrolysin in the treatment of Alzheimer's disease.
Z.H. Wei, et al.

- An infusion with Cerebrolysin for 4 weeks (30 ml Cerebrolysin daily on five consecutive days of each week) led to a significant improvement of the clinical global impression.
- Compared with placebo, log(OR) was 1.1799, and 95% confident interval was 0.7463–1.6135 ($P < 0.05$), indicating that Cerebrolysin could significantly improve the clinical global impression in patients with mild to moderate AD.
- Cerebrolysin consists of 25% LMW peptides and free amino acids that easily penetrate the BBB and allow for rapid efficacy.

Amelioration of the cerebrovascular amyloidosis in a transgenic model of Alzheimer's disease with the neurotrophic compound Cerebrolysin™

E. Rockenstein, et al.

- Cerebrolysin has the ability of improving synaptic functioning and reducing amyloid deposition.
- Cbl decreased amyloid deposition; these effects accompanied by a reduction in perivascular microgliosis and astrogliosis and increased expression of markers of vascular fitness such as CD31 and ZO-1.
- Cerebrolysin reduced the levels of phosphorylated amyloid precursor protein (APP) and the accumulation of APP in the neuritic processes.

Efficacy of the peptidergic nootropic drug cerebrolysin in patients with senile dementia of the Alzheimer type (SDAT).
E. Rüther, et al.

- Cerebrolysin has a regulatory effect on energy metabolism, a positive influence on behavior through neuromodulation due to its peptide fraction, and most important, a neurotrophic stimulation.
- NO adverse effects were recorded and beneficial effects persisted even 12 weeks after discontinuing treatment.

World Journal of Diabetes

Case Control Study

Brain-derived neurotrophic factor plasma levels and premature cognitive impairment/dementia in type 2 diabetes

Blanca Murillo Ortiz, Joel Ramírez Emiliano, Edna Ramos-Rodríguez, Sandra Martínez-Garza, Hilda Macías-Cervantes, Sergio Solorio-Meza, Texar Alfonso Pereyra-Nobara

Abstract

Trophic Factors

Low levels of BDNF are associated with cognitive impairment in patients with DM2

The decrease of BDNF occurs early and progressively in patients in AD

Murillo Ortíz, B., Ramírez Emiliano, J., & Et al. (2016). Brain-derived neurotrophic factor plasma levels and premature cognitive impairment/dementia in type 2 diabetes. *World Journal of Diabetes*, *7*(20), 615. doi:10.4239/wjd.v7.i20.615

Amplification of blood-brain barrier GLUT1 glucose transporter gene expression by brain-derived peptides. R.J. Boardo

- Cerebrolysin Increases the expression of the BBB-GLUT1 via mRNA stabilization.
  - Cl markedly increased the expression of reporter genes containing GLUT1 translational control elements and cis-acting elements involved in the stabilization of the GLUT1 mRNA transcript.
  - increased levels of the BBB-GLUT1 reporter genes in Cl-treated ECL cells are associated with an increase in the glucose uptake and in the expression of the GLUT1 protein.
- Cl markedly increased the uptake of 3H-2-deoxy-d-glucose (essential brain nutrient) and the levels of the GLUT1 protein.

Increased Density of Glutamate Receptor Subunit 1 Due to Cerebrolysin Treatment: An Immunohistochemical Study on Aged Rats.
P. Eder, et al.

- Glutamate receptor subunit 1 (GluR1) is one of the four possible subunits of the AMPA-type glutamate receptor. The integrity of this receptor is crucial for learning processes.
- Cerebrolysin increased GluR1 density in most measured regions of the hippocampal formation in a highly significant way. These results correlate with the behavioral outcome, revealing an improvement in learning and memory.
- Reductions of GluR1 are noticeable in the hippocampal formation of patients suffering from Alzheimer's disease. Such degradations presumably result in an impaired synaptic communication and might be causally linked to the neurodegenerative process in this cognitive disorder.

50 y.o. male – PPI-Induced MCI

- 50 yo M heartburn, diff breathing→ scope→ “incompetent valve”→ Omeprazole + strict diet-→ sx resolution in 1 month → continued PPI
- 6 months later “memory problems began”; d/c’d PPI x 4 wks→ memory problems continued

50 y.o. male – PPI-Induced MCI

- CYP2C19 variant→ poor metabolizer of PPI
- Cerebrolysin 2cc IM x 1 → complete symptom resolution, with restored memory (per patient and wife)
- Periodic Cerebrolysin 2cc IM prn

TBI
Case Study

20 y.o. male – Severe TBI

- College student: assault to head w/ 5 IC bleeds on CT, B/L frontal and temporal with edema; multiple skull and facial fractures, BIBA to ER unconscious
- PMH: Dermatitis Herpetiformis, ApoE 3/4
- Started on Keppra

20 y.o. male – Severe TBI

- S/P jaw surgery 2 weeks later @ MGH
- Spaulding Rehab: watchful waiting approach; to consider being part of a Huperizine A study

20 y.o. male – Severe TBI

- Cerebrolysin IV drip 5cc 2x/wk x 4 wks
- TB4 IVP 2cc 2x/wk x 4 wks
- TA1 IVP 2cc 2x/wk x 4 wks

20 y.o. male – Severe TBI

- Whole Foods, Sleep
- Omega 3, 6, 9, Inositol, D3, UltraNutient, Pregnenolone, DHEA, B5/B6, UltraB Complex w/ PQQ, Cognitive AA, Adrenal Support, Secretropin
- Discontinued Keppra 6 weeks post assault

20 y.o. male – Severe TBI

- Return to spring semester after 2 months recovery

- During the next 5 months:
  - Cerebrolysin IV drip 3 cc 2x/mo
  - TB4 0.25cc qd x 20d
  - TA1 0.25cc qd x 20d

20 y.o. male – Severe TBI

- During subsequent summer, IVP qowk x 8 wks → alternating Cerebrolysin, TA1 and TB4
- Neurofeedback x 20 sessions
- 8 months later, 80 % improved
- 2 years later, no cognitive impairment

Semax

- Pentapeptide: (Met-Glu-His-Phe-Pro-Gly-Pro)
- Fragment of Adrenocorticotropic Hormone ACTH, ACTH4-10
- Available as intranasal mist or sub-q injection

Semax: Clinical Effects

- Elevates Expression of BDNF and the TrKb receptor
- Activate Dopaminergic and Serotonergic stems
- Anti-depressant / Anxiolytic
- Attenuate chronic Stress effects
- Potential Melanocortin Antagonist MC3R, MC4R

Semax:
Therapeutic Applications

- Stroke / TIA
- Memory / Cognitive disorders
- Boost immune system
- Peptic Ulcers
- Optic nerve

Semax

- Semax counteracts the inhibition of learning and memory induced by neurotoxic heavy metals
- Neurodegeneration 2nd to Dopamine oxidation to 6-OH-dopamine and Dopamine-Quinone
- Studies have shown that Semax promotes the survival of neurons during hypoxia and glutamate neurotoxicity

Semax:
Potential MOA

- Semax increases the quantity and mobility of immune cells and enhances the expression of chemokine and immunoglobulin genes.

- Semax influences the expression of genes that promote the formation and functioning of the vascular system.

- Semax has neuroprotective properties that contribute to mitochondrial stability under stress induced by the deregulation of Ca^{2+} ion flow

Semax:
Proper Dosing

- 300 µg – 1,000 µg SubQ, 2x/week
  - Depending on patient response, more can lead to desensitization
- Can alternate with Selank
- Intranasal administration also available

Selanck

- Pentapeptide: (Thr-Lys-Pro-Arg-Pro-Gly-Pro)
- Nootropic, Anxiolytic
- Synthetic analogue of human peptide tuftsin.

Selanck: Clinical Effects

- Analogue of Tuftsin (IgG antibody) and mimics some of its effects
- Modulates Interlukin 6 and balances T-helper cell cytokines
- Elevates BDNF in hippocampus
- Influence on Monoamine Neurotransmitters
- Diminishes the break down of enkephalins

Selanck: Therapeutic Applications

- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)
  - Non-sedating
  - Non-addictive
  - No cognitive impairment

Selanck: anxiolytic MOA

- Allosteric modifier of the GABA receptor– altering/amplifying the affinity of the receptor for GABA
- Benzodiazepines are allosteric modulators of the type-A γ-aminobutyric acid receptor ($GABA_AR$)
- Increases the inhibitory action of GABA

Selank - Gene Hcrt3

- Sleep Balance - sleep vs. wakefulness
- mRNA level of Hcrt3 after single dose influences balance in anxiety disorder
- Lack of sedative activity like typical benzodiazepine

Selanck– Immunological Effects

- Anti-viral Activity
- Regulation of inflammatory response
- BCL6 protein serves as an important transcriptional regulator of the immune system
- BCL6 plays a pivotal role in the regulation of B- and T-cell development by functioning as a potent transcriptional silencer of various developmental signals

Selanck and Metabolic Syndrome

- Prevents weight gain
- Anticoagulant, fibrinolytic, and anti-platelet
- Decreases blood glucose levels
- Semax and Selank have anticoagulant and hypoglycemic effects– same sequence: Pro-Gly-Pro

Selanck and Gastric Ulcers

- Accelerates the healing of gastric ulcers (ethanol, stress induced)
- Improves blood supply and lymphatic circulation to the gastric mucosa

Selanck:
Proper Dosing

- Combines synergistically with (N-acetyl) Semax
- Dose 300 – 1,000 µg SubQ once a day, 2x/week
- Alternate with Semax
- Intranasal administration available

Thank you!!

Kathleen ONeil Smith, MD, FAARM

Treat Wellness, LLC

Newton, MA

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