Cognitive Function & Brain Health

Explore the Possibilities of Synapsin®

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Synapsin® - PCCA Part #30-4969

• Innovative powder blend for use in dietary supplement formulations for cognitive support and neurological health
• Developed with Jim LaValle, RPh, CCN, ND and his company Natural Formulations—Patients with TBI, executive burnout, neurodegenerative conditions, cognitive improvement in aging, etc.

Synapsin® - PCCA Part #30-4969 (cont’d)

• Synapsin® contains blend of:
  – Ginsenoside RG3 (from Panax Ginseng)
  – Nicotinamide Riboside
  – Ingredients to aid in solubilization / dispersing
• Used at a concentration of 10% in SL and nasal spray formulations, along with methylcobalamin or hydroxocobalamin as the active.

Synapsin® - PCCA Part #30-4969

• Common formulation example:
  – Methylcobalamin 2mg/ml with Synapsin® 10%
    • Ginsenoside RG3 2mg/mL, nicotinamide riboside 50mg/mL in final formula
    • Refrigerate, protect from light, glass spray bottle, 15 to 30mL common dispensing volume of final formulations.
    • Ongoing stability study of formulations to expand BUD
    • 1-2 sprays EN up to 3 times per day. For normal cognitive support, once daily.
Neuroinflammation

- Inflammation of central nervous system (CNS) tissue
- Mild inflammation - beneficial; CNS' natural defense
- Chronic inflammation - a BIG problem
- Leads eventually to:
  - Neuronal dysfunction
  - Neuronal injury
  - Neuronal death
Causes of Neuroinflammation - Way for CNS to Cope With:

- **Pathogens**
  - Viral
  - Bacterial
  - Fungal
  - Protozoal
- **Toxins**
  - Environmental - pollution, chemicals, heavy metals
  - Foods - preservatives, dyes, artificial colors / flavors
  - By-products of disease - proteins

Causes of Neuroinflammation

- **Traumatic brain injury (TBI)**
  - Sports and recreational injuries
  - Military
  - Motor vehicle accidents
  - Electric shock / lightening strikes
  - Violence
- **Immune / autoimmune conditions**
- **Neuronal degradation**
  - Aging
  - Chronic stress

Neuroinflammation Orchestration

- **Led by microglial cell activation**
- **Other cells involved include:**
  - Astrocytes
  - Macrophages
  - Inflammasomes
  - Mast cells
  - Toll-like receptors
Neuroinflammation Orchestration (cont’d)

- Led by microglial cell activation (cont’d)
- Other cells involved include:
  - Inflammatory mediators
    - Proinflammatory cytokines (including IL-1 family, TNF-alpha, INF-gamma)
    - Prostaglandins
    - Chemokines
    - Adhesion molecules
  - Oligodendrocytes
  - Vascular cells - pericytes
  - Neurons

Microglia

- Glial cell
- Innate immune cells of CNS
- Key component in neuroinflammation
- Activate in response to neural injury
- Acute inflammation of brain = rapid action of microglia
- Generates reactive oxygen species (ROS)

Chronic Microglial Activation

- Sustained release of inflammatory mediators
- Blood brain barrier (BBB) becomes permeable to:
  - Circulating blood components
  - Peripheral immune cells - macrophages, T cells, B cells
- Enter brain space and encounter neurons and glial cells
- Glial cells = express major histocompatibility complex II molecules II (MHC II)
Chronic Microglial Activation

• Results in chronic inflammation
• Chronic up-regulation of microglial cells
• Leading to:
  – Neuronal damage / death
  – Neurobehavioral impairment
  – Chronic neurodegenerative conditions


Microglial Cell Activation - Plays Role In:

• Traumatic brain injuries (TBI)
• Transient ischemic attack (TIA) / stroke
• Aging
• Memory impairment (chronic stress)
• Alzheimer’s disease and dementia
• Learning difficulties
• Seizures
• Parkinson’s disease
• Huntington’s disease
• Amyotrophic lateral sclerosis (ALS)
• Autism
• Psychiatric conditions - depression, OCD, panic attacks, schizophrenia, bipolar
• Multiple sclerosis (MS)
• Diabetes

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Adult Neurogenesis

- Production of new neurons in an adult brain
- Follows a similar complex multi-step process
  - Proliferation of progenitor cells, followed by morphological and physiological maturation
  - Ends with a fully functional neuron integrated into pre-existing hippocampal network

Mediators of Adult Neurogenesis

- Stress / sleep disruption suppress adult neurogenesis
- Stress interferes with all stages of neuronal renewal & inhibits both proliferation and survival.
- Glucocorticoid and NMDA receptors have been identified on progenitor cells
- Lasting inhibition of AN occurs after an initial stressor, despite later normalization of cortisol.
**Rg3**

- Manufactured from Panax ginseng (Asian ginseng) root
- Rg3 is a ginsenosides
  - Group of major pharmacologically active components in ginsengs
- Rg3 Formed by steaming Asian ginseng root
- 20(R) Rg3 isomer
  - (R) isomer reported improved absorption
  - Improved blood brain barrier penetration

*Bae, et al. Pharmacokinetics and tissue distribution of ginsenoside Rh2 and Rg3 epimers after oral administration of BST204, a purified ginseng dry extract, in rats. Xenobiotica. 2014;44(12):1099-1107.

**Rg3 NeuroPharmacology**

- Helps attenuate microglial activation
- Decreases neuroinflammation
  - COX-2 inhibition
  - Inhibition of matrix metalloproteinase-9 (MMP-9)
  - Improves NO and ROS (reactive oxygen species) levels
  - Decreased inflammatory mediators - TNF-alpha, IL-1Beta


**Rg3 NeuroPharmacology**

- Neuroprotective
- Decreases excitotoxicity
- Decreases oxidative stress-induced inflammation
- Improves neuroinflammation outcomes

**Rg3 NeuroPharmacology**

- Attenuates NMDA (glutamate) receptor-mediated currents
- Decreases NMDA-induced neurotoxicity
- Inhibits L-type Ca(2+) channels
  - Counters increased levels seen in microglial activation


**Nicotinamide Riboside (NR)**

- Form of vitamin B3 (niacin) found mainly in Cow’s milk / yeast
- Improves NAD⁺ levels in conjunction with nicotinic acid and tryptophan
- Incorporated into cellular NAD⁺ pool via Nrk pathway or Nam salvage after conversion to Nam by phosphorylation
- Neuroprotective activity


**NR**

- Supports neuronal NAD⁺ synthesis without inhibiting sirtuins
- Sirtuins - important regulators of metabolism and longevity
- NAD⁺ is a rate-limiting co-substrate for sirtuin enzymes
- NR regulates sirtuin function and subsequent regulation of oxidative metabolism

* Suva AA. Nicotinamide and vitamin B3: from metabolism to therapies. J Pharmacol Exp Ther. 2008;324(3):883-93
Lab animal studies - NR improves sirtuin pathway in obesity and type 2 diabetes
Mice in the study also reported to have:
- Improved endurance
- Improved oxidative profile
- Improved respiratory capacity
- Increased muscle mass


Activation of NAD+ expression linked with a decrease in beta-amyloid (Aβ) toxicity in Alzheimer’s
PGC-1α - a crucial regulator of Aβ generation
Affects β-secretase (BACE1) degradation
Helps promote peroxisome proliferator-activated receptor-y coactivator 1 (PGC-1α)-mediated BACE1 ubiquitination and degradation


Orally available commercial product containing nicotinamide riboside is patented
Oral dose 250-500mg daily
May also be used intranasally and / or sublingually
Methylcobalamin

- Coenzyme form of vitamin B12
- Neuroprotective
- More absorbable and bioavailable than cyanocobalamin


Methylcobalamin

- Helps improve methylation processes
- Improved homocysteine, methylmalonic acid
- Helps improve cognitive function


Methylcobalamin Compounded Nasal Spray with Synapsin®

- Rx John D. Rockerman
  1329 Berry Ln
- Compounded Medication:
  Methylcobalamin 2mg/ml
  With Synapsin® 10%
  Intranasal Spray
  Dispense 30ml
- Compounded Dose: One to two sprays intra-nasally, up to three times a day
Potential Uses of MB12 Compounded Nasal Spray with Synapsin®

- Chronic stress management
- Cognitive support
- Traumatic brain injury (TBI) cognitive recovery
- Neurodegenerative disease cognitive support
  - Alzheimer’s
  - Parkinson’s
  - Amyotrophic lateral sclerosis (ALS)
- Stroke / TIA cognitive recovery
- Cognitive improvement in aging patients

RG3 Case Study - 58 y/o Male

- 58 y/o white male, PhD
- Clinical diagnosis - cortico-adrenal insufficiency
- Discharged from 3 major medical centers
- Disabled x 4 years
- Started RG3 nasal spray spring 2015
  - 2 sprays tid
- Also nicotinamide riboside 50mg/ml sublingual drops
  - 1ml, initially QD, then TID

RG3 Case Study - 58 y/o Male

- Patient able to return to work 3 weeks after starting therapy with both agents
- Disruption in ability to obtain RG3 and NR, June 2016
- Patient relapsed and in short period of time, unable to function / work again
- Therapy resumed, clinical symptoms improved
  - Patient has continued therapy since
Survey of RG3 Patients

- 2016 patient survey
- 24 patients prescribed RG3 surveyed on perceived effects

Question: Since Taking RG3, have your symptoms...
23 Patients Responded

Question: Has your overall cognitive functions...

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Question: Would you recommend this medication to your friends and family? 23 Responded

Keep in Mind…..

Life is the only game where the object of the game is to learn the rules

Thank you

Questions?