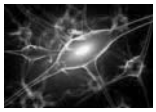
Cognitive Function & Brain Health

Explore the Possibilities of Synapsin®

James B. LaValle, RPh, DHM, MS, CCN, ND (trad)
Gus Bassani, PharmD

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.



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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.

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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.

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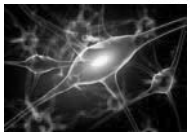
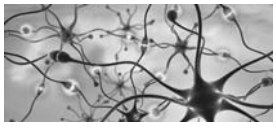
Synapsin®: Advances in NeuroInflammation

James B. LaValle, RPh, DHM, MS, CCN, ND (trad)
Founder: Progressive Medical of California
Chairman of the Board: Metabolic Intelligence

Neuroinflammation

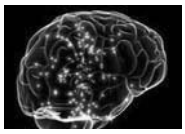
- Inflammation of central nervous system (CNS) tissue
- Mild inflammation - beneficial; CNS' natural defense
- Chronic inflammation - a BIG problem
- Leads eventually to:
  - Neuronal dysfunction
  - Neuronal injury
  - Neuronal death





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

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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

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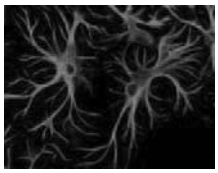
Neuroinflammation Orchestration

- Led by microglial cell activation
- Other cells involved include:
  - Astrocytes
  - Macrophages
  - Inflammasomes
  - Mast cells
  - Toll-like receptors



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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

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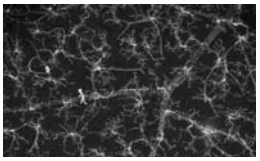
Microglia

- 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)



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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)

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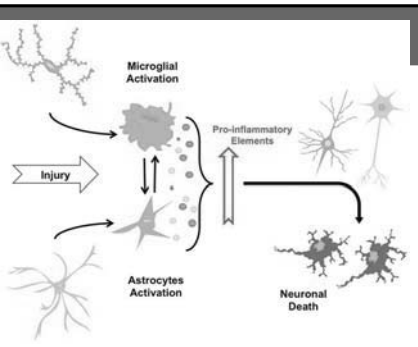
Chronic Microglial Activation

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

* Hart B, et al. Commentary on special issue: CNS diseases and the immune system. J Neuroimmune Pharmacol. 2013;8(4):757-9.



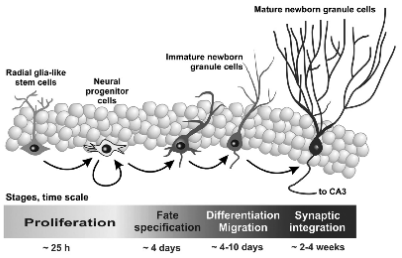
Microglial Cell Activation - Plays Role In:

- 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

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

Adult Neurogenesis



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.

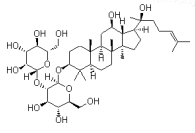
Rg3 NeuroPharmacology

- 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

* Joo SS et al.Prevention of inflammation-mediated neurotoxicity by Rg3 and its role in microglial activation. Biol Pharm Bull. 2008 Jul;31(7):1392-6.
* Bao HY, Zhang J, Yeo SJ, et al. Memory enhancing and neuroprotective effects of selected ginsenosides. Arch Pharm Res. 2005 Mar;28(3):335-42.

Rg3 NeuroPharmacology

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



* Joo SS et al.Prevention of inflammation-mediated neurotoxicity by Rg3 and its role in microglial activation. Biol Pharm Bull. 2008 Jul;31(7):1392-6.
* Bao HY, Zhang J, Yeo SJ, et al. Memory enhancing and neuroprotective effects of selected ginsenosides. Arch Pharm Res. 2005 Mar;28(3):335-42.

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
    - Joo SS of inflammation-mediated neurotoxicity by Rg3 and its role in microglial activation. Biol Pharm Bull. 2008 Jul;31(7):1392-6.
    - Kim YC, et al. Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration. J Neurosci Res. 1990;53 (4):426-32.

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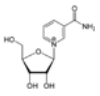
Nicotinamide Riboside (NR)

- 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
  - Yang SJ, L, et al. Nicotinamide improves glucose metabolism and affects the hepatic NAD-sirtuin pathway in a rodent model of obesity and type 2 diabetes. J Nutr Biochem. 2014;25(1):66-72.
  - Bieganowski P, et al. Discoveries of nicotinamide riboside as a nutrient and conserved NRK genes establish a Preiss-Handler independent route to NAD+ in fungi and humans. Cells. 117;495-502.

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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
  - Canto C, et al. The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high fat diet-induced obesity. Cell Metab. 2012;15(6):838-47.
  - Suave AA. Nicotinamide and vitamin B3: from metabolism to therapies. J Pharmacol Exp Ther. 2008;324(3):883-93

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NR

- 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
  - * Canto C, et al. The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high fat diet-induced obesity. Cell Metab. 2012;15(6):838-47.
  - * Yang SJ, et al. Nicotinamide improves glucose metabolism and affects the hepatic NAD-sirtuin pathway in a rodent model of obesity and type 2 diabetes. J Nutr Biochem. 2014;25(1):66-72.

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NR

- 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-γ coactivator 1 (PGC-1α)-mediated BACE1 ubiquitination and degradation
  - * Belenky P, Bogan KL, Brenner C. NAD+ metabolism in health and disease. Trends Biochem Sci. 2007;32(1):12-9.
  - * Bogan KL, Brenner C. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD+ precursor vitamins in human nutrition. Annu Rev Nutr. 2008;115-30.

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NR

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

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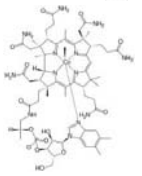
Methylcobalamin

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



* Sun Y, Lai MS, Lu CJ. Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials.Acta Neurol Taiwan 2005 Jun;14(2):48-54.

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Methylcobalamin

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

* Sun Y, Lai MS, Lu CJ. Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials.Acta Neurol Taiwan 2005 Jun;14(2):48-54.

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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

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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

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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

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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

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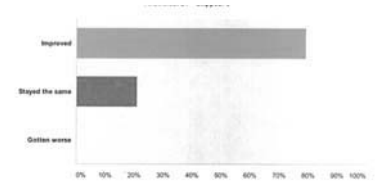
Survey of RG3 Patients

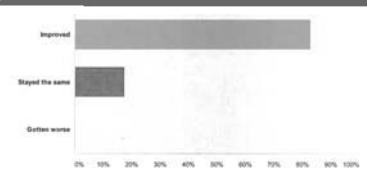
- 2016 patient survey
- 24 patients prescribed RG3 surveyed on perceived effects

Question: Since Taking Rg3, have your symptoms..? 23 Patients Responded



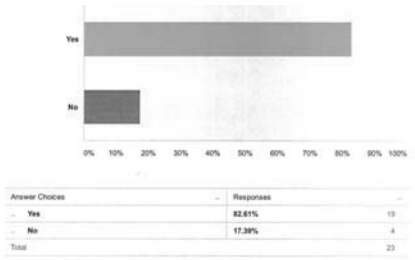
Answer Choices	Responses	
Improved	79.17%	19
Stayed the same	20.83%	5
Gotten worse	0.00%	0

Question: Has your overall cognitive functions…



Answer Choices	Responses	
Improved	82.61%	19
Stayed the same	17.39%	4
Gotten worse	0.00%	0
Total		23

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



Answer Choices	Responses	
Yes	82.61%	19
No	17.39%	4
Total		23

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Keep in Mind…..

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

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Thank you

Questions?

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