The Modulation of Age-Related Cognitive Decline and Neurodegenerative Disease Via Fruits and Vegetables: The Longevity Dividend

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Aging

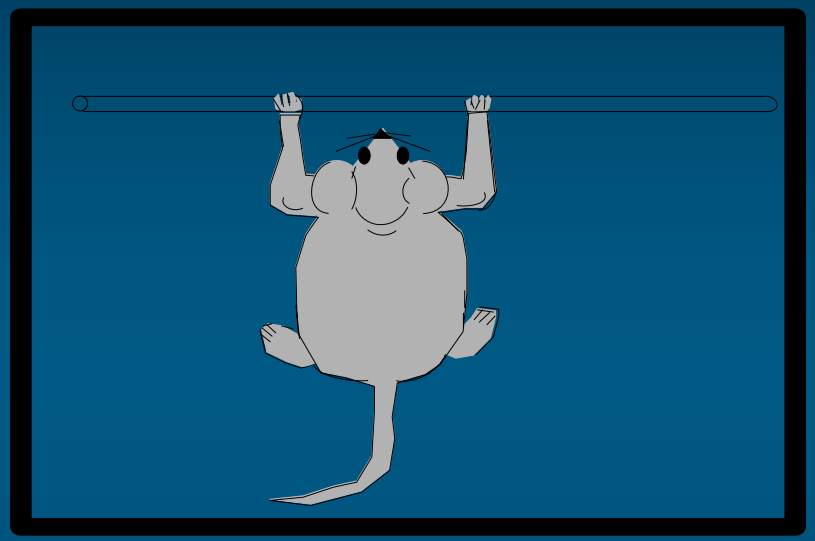
Aging can be defined as a condition where *stressors* are not counteracted by protective functions leading to a dysregulation in development. In the neuroscience world it is characterized by losses in ***neuronal function accompanied by behavioral declines (decreases in motor and cognitive performance)*** in both humans and animals

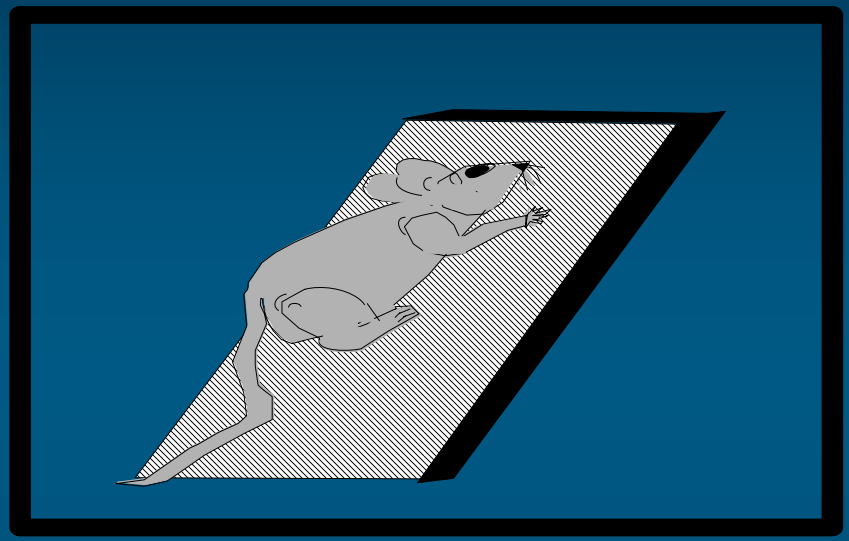
Cognitive and Motor behavior changes in senescence

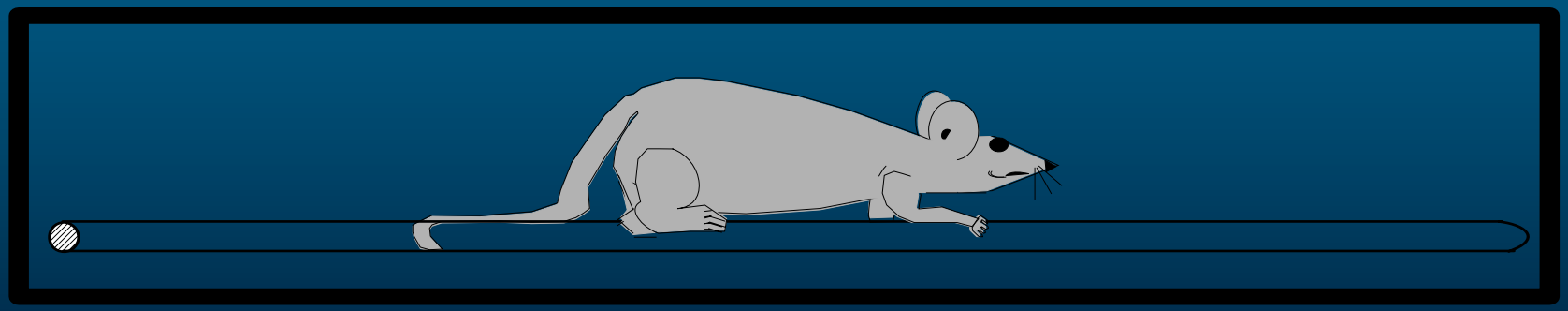
- Motor: inclined screen, rotorod, planks of various widths, wire suspension. These assess balance strength and coordination.

- Cognitive: short term and long term memories as assessed via a Morris water maze

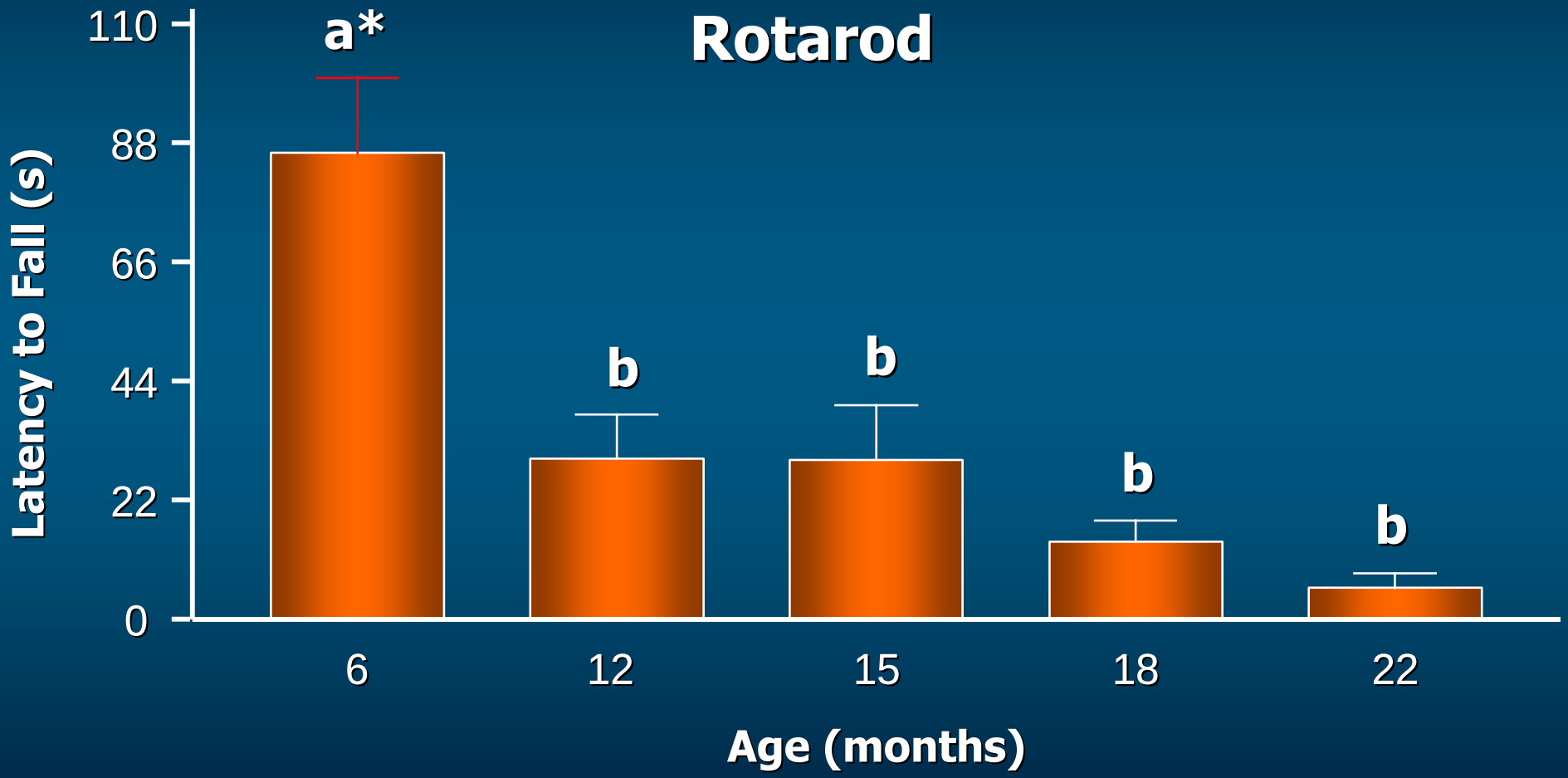
Motor Tasks







Rotarod Test
Rat Age Study



*Means with different letters are significantly different from each other (*P*<.05).

Shukitt-Hale et al. *Exp Gerontol*. 1998;33:615-624.

OXIDATIVE STRESS AND INFLAMMATION THE "EVIL" GEMINI TWINS OF BRAIN AGING I.

THE BRAIN UTILIZES 20% OF THE BODY'S OXYGEN AT REST –HIGHER AMOUNTS DURING PROBLEM SOLVING.

- Decreases in antioxidant protection:
  - 1. Increases in the ratio of oxidized to total glutathione (Olanow, 1992).
  - 2. Alterations in redox active iron (e.g., see Savory, et al., 1999; Gilissen et al., 1999).
  - 3. Significant lipofuscin accumulation (Gilissen et al., 1999).
  - 4. Reduced glutamine synthetase (Carney et al., 1994).

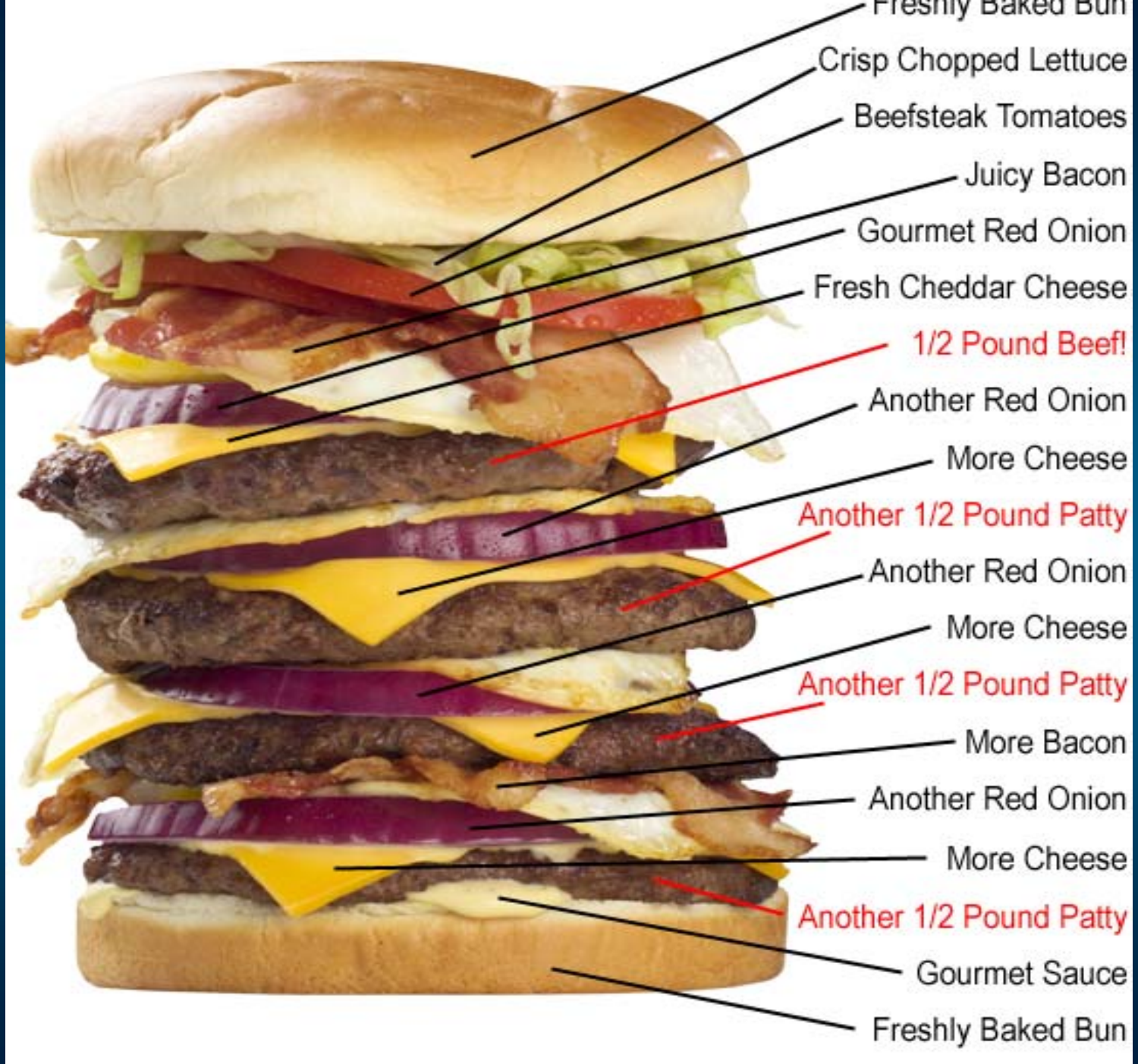
OXIDATIVE STRESS AND INFLAMMATION THE "EVIL" GEMINI TWINS OF BRAIN AGING II.

- **Alterations in markers of inflammation:**
  - 1. Increased cytokines (e.g., TNF alpha, IL-1 beta production has been detected in CNS in brain injury and AD (Rosenman et al., 1995; Woodroofe, 1995).
  - 2. Activation of microglial cells. (DiPatre& Gellman 1997 Hong et al., 2006).
- Changes in the vulnerability of specific muscarinic receptor subtypes to oxidative and inflammatory stressors (Joseph and Fisher 2002; 2003).

Possible Prevention of Alzheimer's Disease: Dietary Considerations

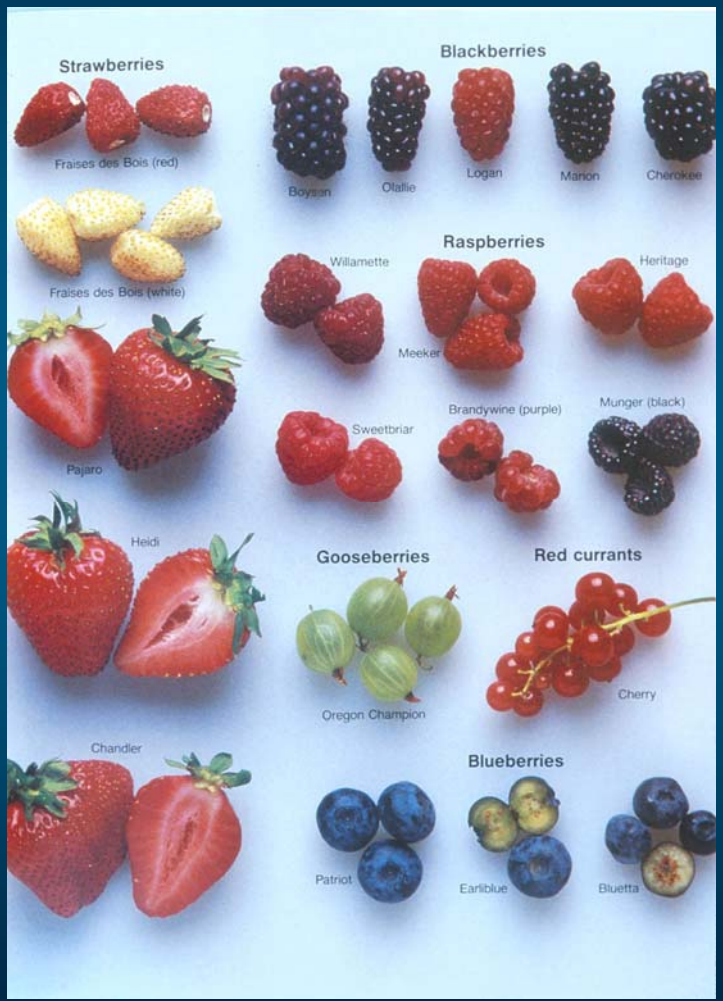
- Consumption of fish, fish oils, etc, containing n3 DHA or EPA[1]
- Curcumin[2,3]
- Melatonin[4]
- Folic acid, vitamin B complex, especially in persons with high homocysteine levels[5]
- Use of vitamin E, and/or vitamin C in enriched foods or supplements[6]
- Alpha lipoic acid and L carnitine supplements[7]
- High antioxidant fruits and vegetables[8]

1. Young et al. *Reprod Nutr Dev*. 2005;45:1-28 (B); 2. Lim et al. *J Neurosci*. 2001;21:8370-8377 (B);
3. Ringman et al. *Curr Alzheimer Res*. 2005;2:131-136 (B); 4. Wu et al. *J Pineal Res*. 2005;38:145-152 (B);
5. Anello et al. *Neuroreport*. 2004;15:859-861 (B); 6. Zandi et al. *Arch Neurol*. 2004;61:82-88 (B);
7. Rogers et al. *Age Ageing*. 1999;28:205-209 (B); 8. Joseph et al. *Am J Clin Nutr*. 2005;81(1 suppl): 313S-316S (B); Adapted from Jansson. *Med Hypotheses*. 2005;64:960-967 (B).


Freshly Baked Bun
Crisp Chopped Lettuce
Beefsteak Tomatoes
Juicy Bacon
Gourmet Red Onion
Fresh Cheddar Cheese
1/2 Pound Beef!
Another Red Onion
More Cheese
Another 1/2 Pound Patty
Another Red Onion
More Cheese
Another 1/2 Pound Patty
More Bacon
Another Red Onion
More Cheese
Another 1/2 Pound Patty
Gourmet Sauce
Freshly Baked Bun

Quenching the Fire! Using Grapes and Berries to Changing the Neuronal Environment to Alter Signaling and Behavior

Fruit Polyphenolics



Courtesy of W. Kalt, Ph.D.

Phenolics

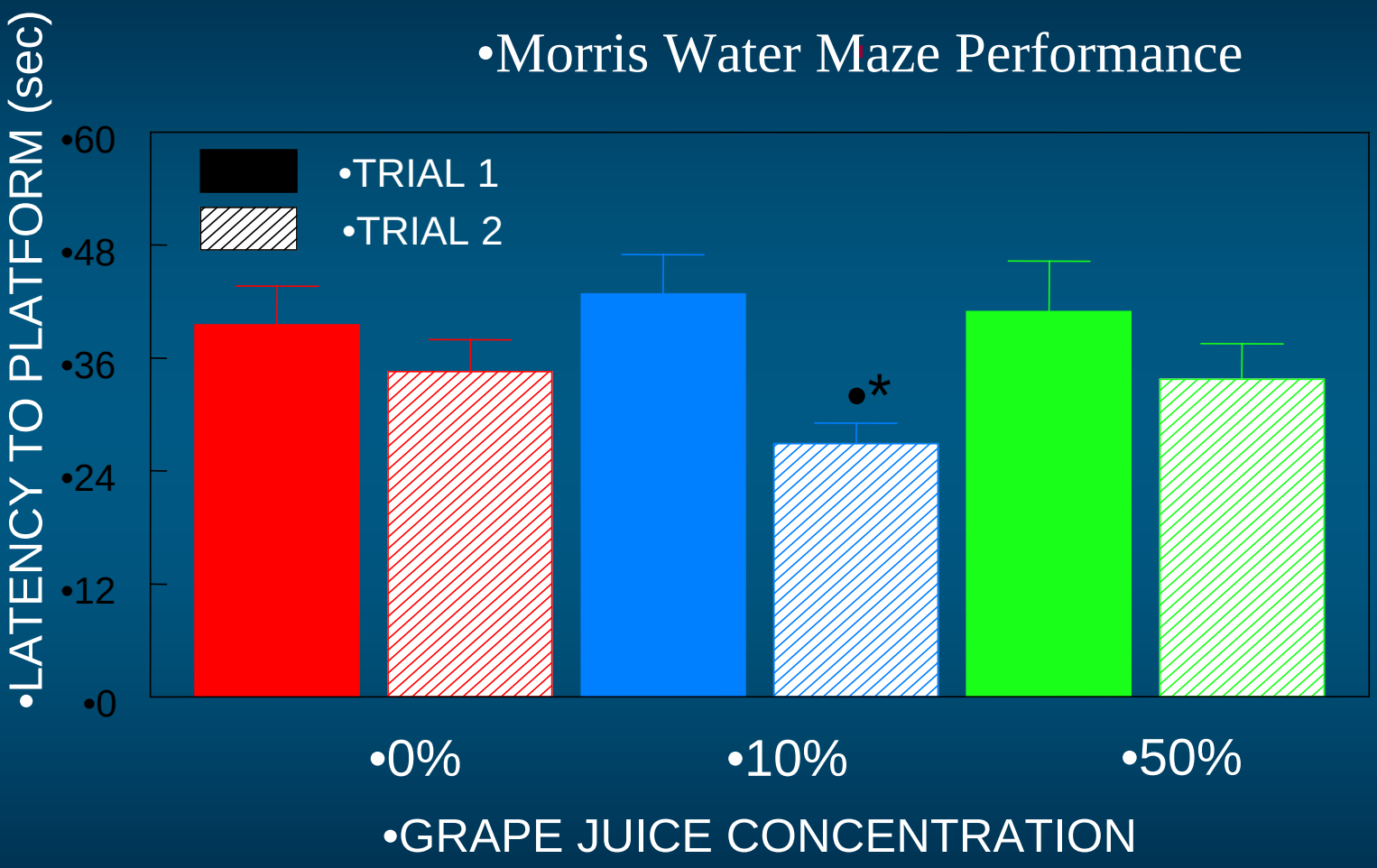
- Simple Phenolics
- Hydroxycinnamates
- **Flavonoids**
  - Anthocyanins
  - Flavonols
  - Proanthocyanidins
  - Catechins

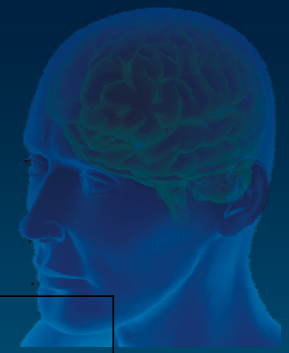
Reversal of Age-Related Changes in Neuronal Function and Behavior Through Dietary Supplementation: Major Findings

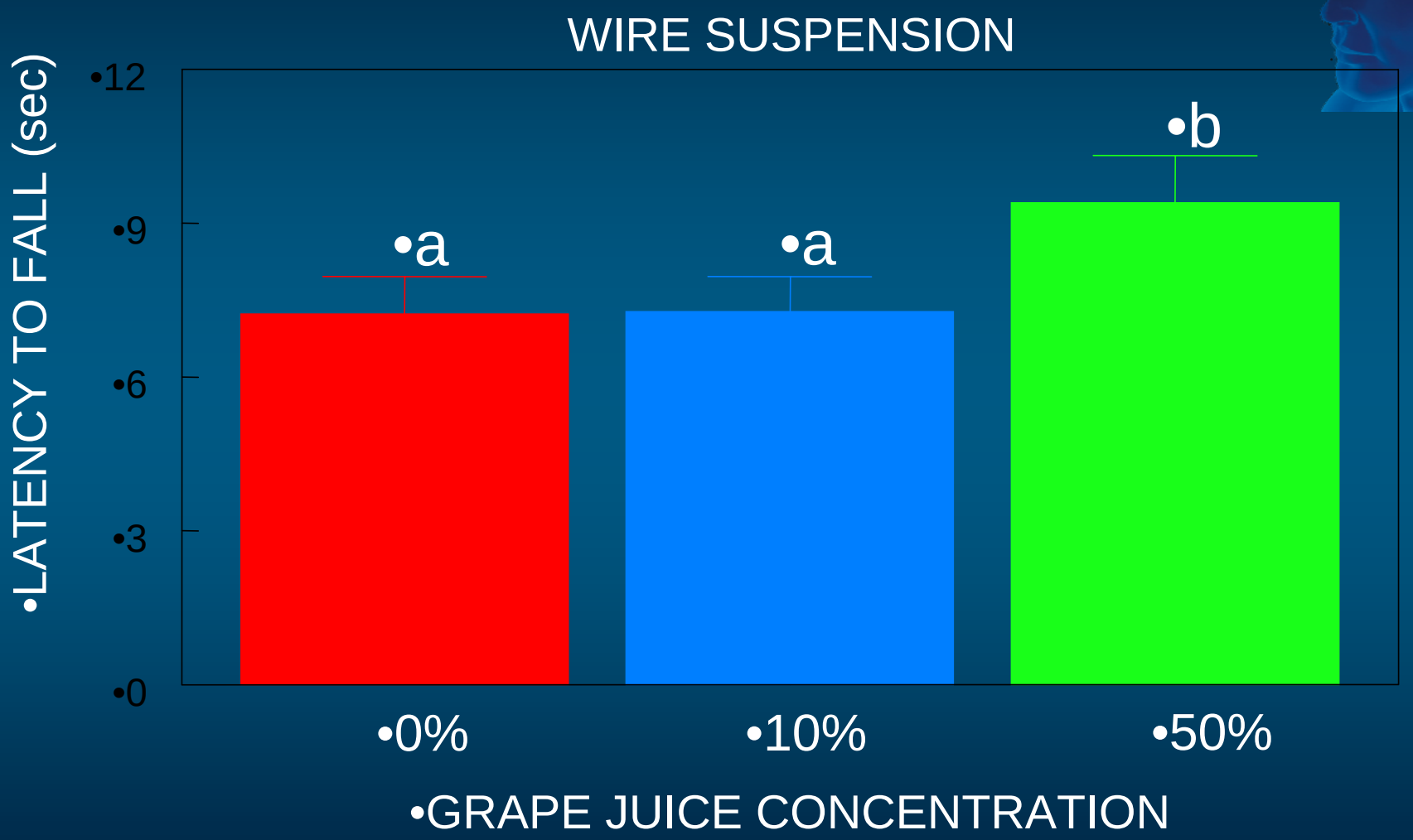
The supplemented diets reversed decrements in

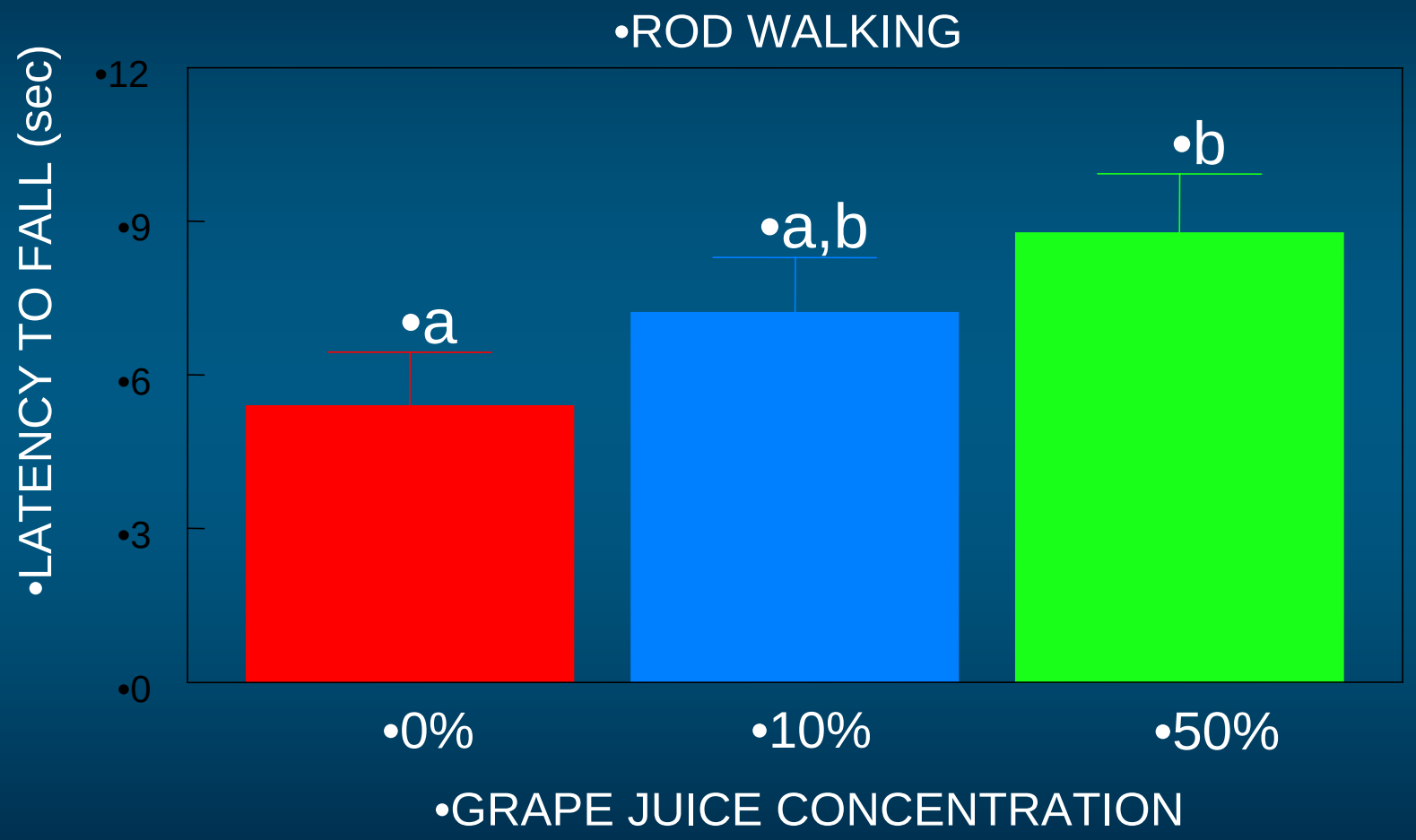
- Neuronal function, eg,
  - Striatal calcium sequestration
  - Cerebellar noradrenergic sensitivity
  - Muscarinic receptor sensitivity
- Behavior
  - Morris water maze performance
  - Motor behavioral performance (rod walking, accelerod)
  - In motor behavioral learning Bickford
  - In exploration of a novel environment Malin

Joseph et al. *Am J Clin Nutr*. 2005;81(1 suppl):313S-316S.


•Morris Water Maze Performance
•LATENCY TO PLATFORM (sec)
•60
•48
•36
•24
•12
•0
•TRIAL 1
•TRIAL 2
•*
•0%
•10%
•50%
•GRAPE JUICE CONCENTRATION




WIRE SUSPENSION
•LATENCY TO FALL (sec)
•12
•9
•6
•3
•0
•a
•a
•b
•0%
•10%
•50%
•GRAPE JUICE CONCENTRATION

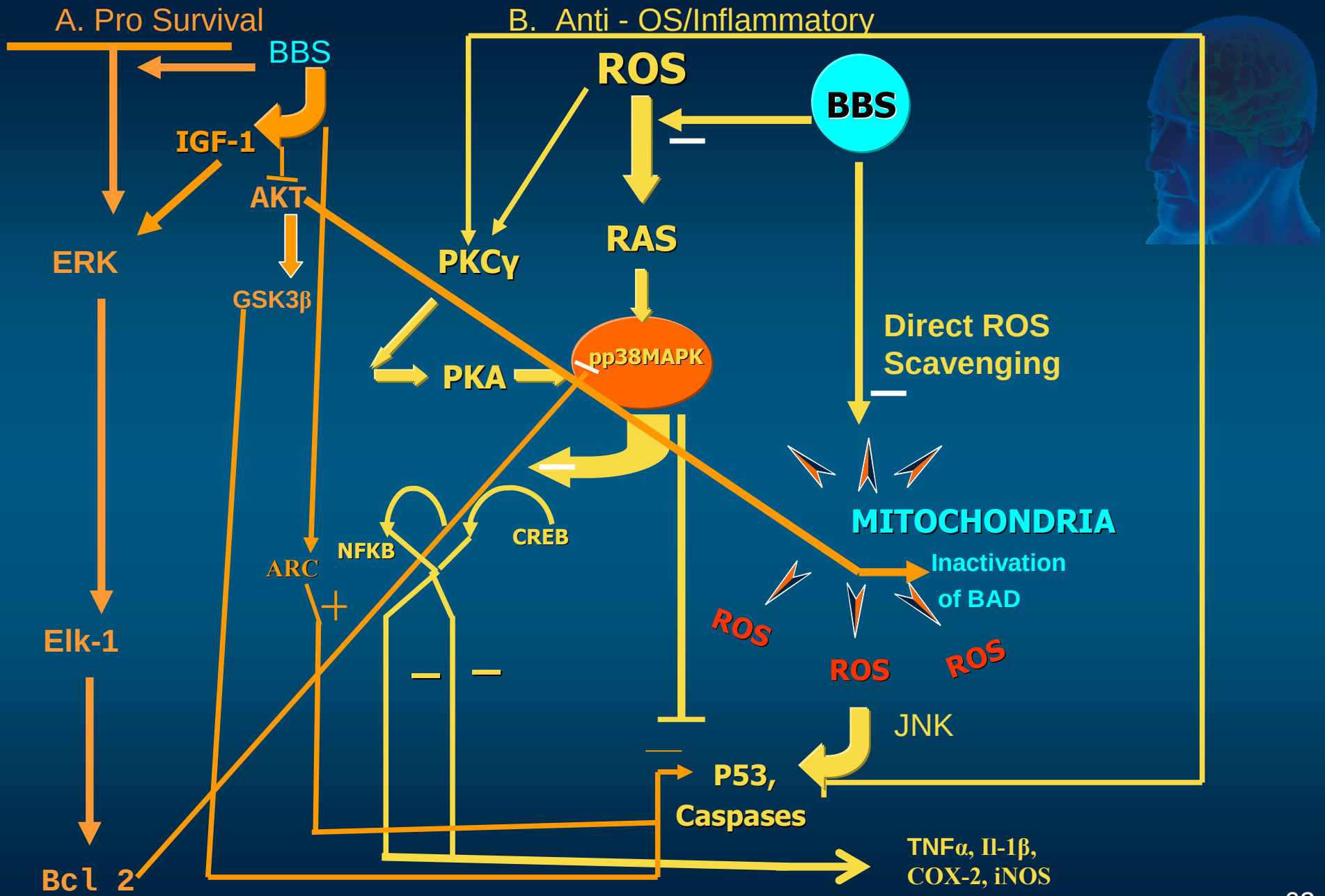

•ROD WALKING
•LATENCY TO FALL (sec)
•12
•9
•6
•3
•0
•a
•a,b
•b
•0%
•10%
•50%
•GRAPE JUICE CONCENTRATION

Other Fruits (nuts) and Veggies That Alter Behavioral Deficits in Aging In Addition to Blueberries

- Memory
  - Spinach
  - Strawberries
  - Cranberries
  - Black currants
  - Concord grape juice
  - Plum juice
  - Blackberries
  - Walnuts
- Motor
  - Cranberries
  - Concord grape juice
  - Strawberries
  - Blackberries
  - Walnuts

Possible Mechanisms in the Beneficial Effects of the Berry and Grape Polyphenolics

- Functional antioxidant effects/anti-inflammatory effects
  - Decreased sensitivity to oxidative stress
  - Decreased sensitivity to neurotoxins and inflammatory agents
  - Increased calcium clearance
  - Membrane effects.
  - Alterations in signaling
    - Decreased inflammatory signaling
    - Decreased oxidative stress signaling
    - Increased protective signaling
    - Signaling in learning and memory


A. Pro Survival
BBS
IGF-1
AKT
ERK
GSK3β
Elk-1
Bcl 2
B. Anti - OS/Inflammatory
ROS
BBS
RAS
PKCγ
PKA
pp38MAPK
Direct ROS
Scavenging
MITOCHONDRIA
Inactivation
of BAD
ROS
ROS
ROS
JNK
P53,
Caspases
NFKB
CREB
ARC
TNFα, Il-1β,
COX-2, iNOS


OPEN
Picante Sauce
Gerber
2ND

God

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