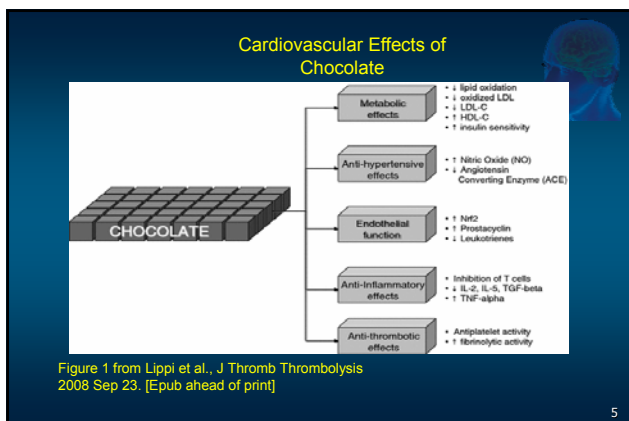


IGF and AD

- A recent paper by Steen et al., (*JAD* 7, 2005, 63-80) shows that there are extensive abnormalities in insulin and IGF-1 and II, as well as insulin and IGF-1 receptors. Leading to a cascade of reduced:
 - insulin receptor substrate
 - tau mRNA
 - phospho AKT
 and increased:
 - APP mRNA expression etc.
 Suggesting that AD may actually represent a neuroendocrine disorder and a "Type 3 Diabetes"



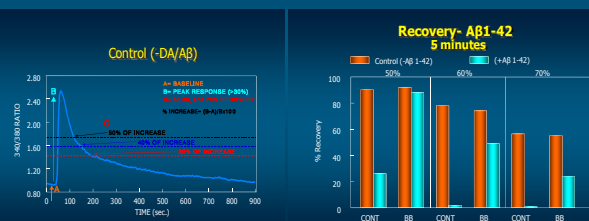
Possible Mechanisms in the Beneficial Effects of the Polyphenolics

- 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

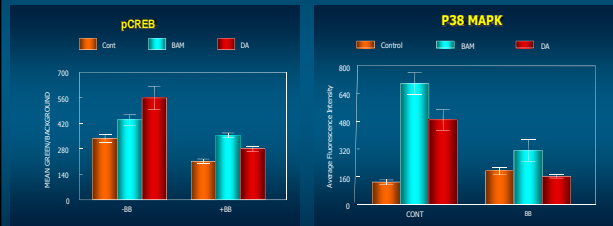
Primary Hippocampal Cultures

Recovery was determined by assessing the time (at 5, 10 or 15 min post depolarization) for the Ca²⁺ levels to return to 50, 60, or 70% of the increase for each time point following depolarization in the cells that responded. Only those cells that showed a [Ca²⁺]_i to 30 mM KCl by > 30% were considered for further analysis.

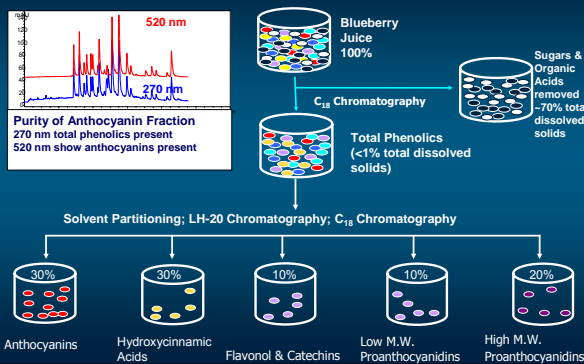
RECOVERY IN PRIMARY HIPPOCAMPAL CELLS WAS DETERMINED BY ASSESSING THE TIME POST KCL-INDUCED DEPOLARIZATION FOR Ca²⁺ LEVELS TO RETURN TO 50, 60, or 70% OF THE INCREASE



INHIBITION OF Aβ₄₂-INDUCED STRESS SIGNALS BY BB APPLICATION



Fractionation of Blueberry Phenolics



CONCENTRATIONS OF COMPOUNDS USED IN HIPPOCAMPAL CELLS

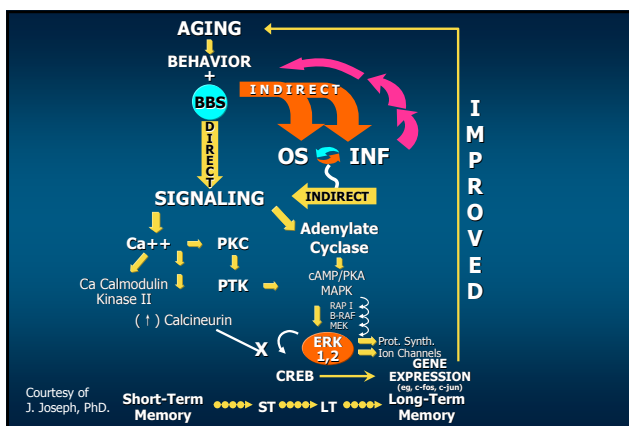
COMPOUND	PHENOLIC LEVEL	CONCENTRATION
BB whole extract	10.15 mg/g	500 ug/ml
Pre-C18	22.70 mg/g	250 ug/ml
Post-C18	329.37 mg/g	17.5 ug/ml
Anthocyanins	363.50 mg/g	15 ug/ml
PACs	414.79 mg/g	14 ug/ml
LMW PACs	1043.37 mg/g	5.5 ug/ml
HWM PACs	492.96 mg/g	11.5 ug/ml
Chlorogenic acid	364.0 mg/g	15 ug/ml

Summary of BB Effects in Primary Hippocampal Cells

- ◆ The effects of BB were dependent upon the stressor (DA or A β) but overall BB increased pMAPK (to DA) and decreased the DA or A β -enhanced PKC γ , p38MAPK, JNK, ARC, and pCREB. All markers of OS/INF.
- ◆ The effects of BB were relatively unchanged as a function of age of the rat at which the primary hippocampal cells were obtained with respect to CREB but was less effective for pMapK, and PKC's as a function of age.
- ◆ The fraction effects were dependent upon the stressor and the parameter assessed, but generally the whole berry was more effective than most of the fractions.

Possible Mechanisms in the Beneficial Effects of the 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



ERK Signaling in Learning and Memory

- ◆ ERK signaling is required in many different forms of memory, among them
 - Fear conditioning¹
 - Reversal learning²
 - Place memory³

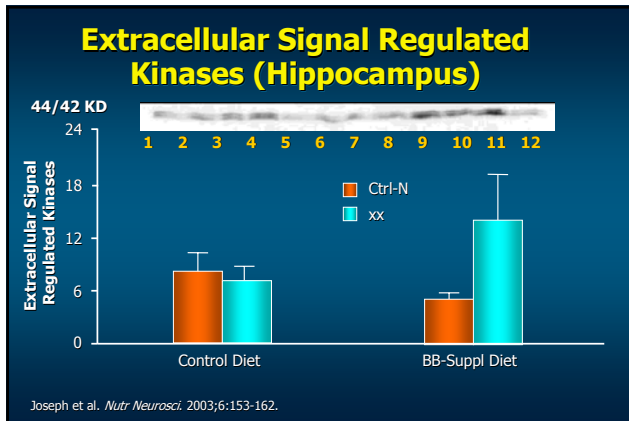
1. English et al. *J Biol Chem.* 1996;271:24329-24332; 2. Mazzucchelli et al. *Neuron.* 2002;34:807-820; 3. Selcher et al. *Learn Mem.* 1999;6:478-490.

We used App/PS1 mice and fed them the 2% diet for 8 months (from 4-12 months of age.

Y-Maze % Alternations Among Supplemented and Controls

Controls	59.4 ± 3.9
Controls + BB	59.5 ± 1.9
[†] Double transg.	45.2 ± 3.8
*Double transg. + BB	61.4 ± 4.0

*Double transgenic For PS-1 and amyloid β . [†]Differs from all other GPS ($P < .03$). Joseph et al. *Nutr Neurosci.* 2003;6:153-162.



Modifying Hippocampal Neurogenesis in the Adult Brain

- ◆ Exercise: presumably by enhancing BDNF expression¹ (even in aged rats)²
- ◆ Environmental enrichment: adult hippocampal neurogenesis was increased 5-fold in mice maintained in an enriched environment from 10-20 mo of age^{3,4}
- ◆ Caloric restriction: also by enhancing BDNF expression
- ◆ Dietary supplementation with blueberries⁵

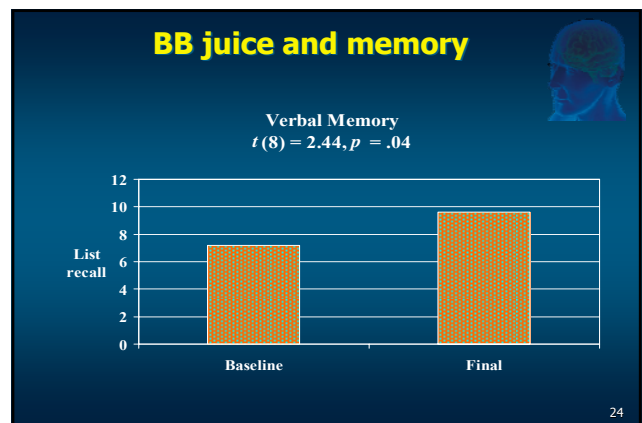
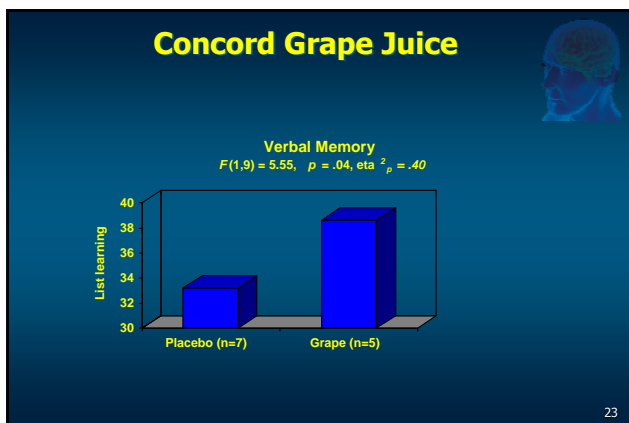
BDNF=brain-derived neurotrophic factor. 1. Cotman et al. *Trends Neurosci.* 2002;25:295-301 (B); 2. Churchill et al. *Neurobiol. Aging.* 2002;23:941-955 (B); 3. Gage et al. *J. Neurosci.* 2002;22:612-613 (B); 4. Lee et al. *J. Neurochem.* 2002;80:539-547 (B); 5. Casadesus et al. *Nutr. Neurosci.* 2004;7:309-316.

HUMAN LEARNING AND MEMORY (MEMORY IMPAIRED)

21

- ◆ Older adults with early memory decline (but no dementia) were recruited from the community, chiefly via advertising in the daily newspaper. There was no difference between the groups with respect to age, education, Clinical Dementia Rating, or waist circumference before the intervention.
- ◆ The list learning task is a verbal memory procedure in which subjects are given repeated exposures to a list of 16 items and asked to recall as many items as possible after each list exposure. The scores represent the total number of recalled items summed across the five testing trials.

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"Strengthening the brain through high antioxidant fruit supplementation"

- ◆ Increases neuronal communication and neurogenesis enabling the brain to take advantage of its redundancy. This would have important implications for use in conventional therapies in conjunction with nutritional protocols in disorders such as Alzheimer or Parkinson diseases.

God

Neuroscience Lab

- ◆ B. Shukitt-Hale
- ◆ D. Bielinski
- ◆ D. Fisher
- ◆ L. Willis
- ◆ Kate Luskin
- ◆ Collaborators
- ◆ W. Kalt Agri, Canada
- ◆ M. Smith, PhD, CWRU, Cleveland, OH
- ◆ G. Casadesus, CWRU, Cleveland, OH
- ◆ B. Rabin, UMBC

- ◆ A. Reznick, Bruce Rapp Med. Sch, Haifa, Israel
- ◆ D. Morgan USF, Tampa, FL
- ◆ D. Malin Univ. Houston, TX
- ◆ D. Ingram, PBRC, Baton Rouge, LA
- ◆ C. Wolkow, NIH/NIA
- ◆ M. Wilson, NIH/NIA
- ◆ Rob Krikorian U. Cin.

