Flavanols in Health and Disease

Pre-Meeting workshop II, 3:00-5:00 p.m., November 14, 2012

SFRBM, San Diego, CA

Chairs

Helmut Sies, Düsseldorf, Germany
Alan Crozier, Glasgow, U.K.
Carl L. Keen, UC Davis
Blueberry  
Cocoa  
Cranberry  
Grapes  
Pomegranate  
Tea (Green/Black)
Chocolate consumption in kg/year/capita

Messerli, F. (2012) *NEJM* *367*, 1562-1564
Chocolate and the Nobel Prize

- Chocolate consumption in kg/year/capita
- Nobel Laureates Per 10 Million
- $r = 0.791$, $p < 0.0001$
Flavanols in Health and Disease

EU 7th Framework Programme:

‘Flaviola’

“Targeted delivery of dietary flavanols for optimal human cell function: Effect on cardiovascular health”

www.flaviola.org
A summary of the potential health benefits of dietary (poly)phenols

- **Brain**
  - Memory and learning
  - Cognitive performance
  - Cerebral blood flow
  - Psychomotor activity
  - Inhibition of Neurodegeneration
  - Neurogenesis

- **Vascular function**
  - Reduction of Hypertension
  - Increased blood perfusion
  - Endothelial homeostasis
  - Beneficial lipid profile
  - Inhibition of Platelet activation

- **Cancer**
  - Inhibition of tumor development
  - Detoxification of cancer precursors
  - Cancer cell apoptosis
  - Inhibition of DNA oxidation

- **Inflammation**
  - Inhibition of cytokine/chemokine production mediators
  - Reduced of adhesion molecule expression
  - Inhibition of Neuroinflammation

Chemical structure of flavanol stereoisomers

(-)-Epicatechin

(-)-Catechin

(+)-Epicatechin

(+)-Catechin
“Total antioxidant capacity” of flavanol stereoisomers in rat plasma spiked \textit{ex vivo}

Ottaviani JI \textit{et al} (2011) \textit{Free Rad Biol Med} 50, 237-244
Vasodilatory effect of (−)-epicatechin, (+)-epicatechin, (−)-catechin, and (+)-catechin on femoral artery (FA) in living rats. FA diameter was measured before and 60 s after the iv injection of each flavanol stereoisomer.

NTG, nitroglycerin, (positive control)

Conclusion from these simple observations:

- Polyphenols exert their biological effects NOT by their capacity as 'antioxidants' sensu strictu,

- Their bioactivity is largely mediated through other molecular effects,

- e.g. binding to proteins and modifying their function (inhibiting prooxidant enzymes, activating antioxidant enzymes)

- In vivo: Flavanols act as 'Bioactives' rather than only as 'Antioxidants'
Profile of (−)-epicatechin metabolites in plasma

Very low, if any, free (−)-epicatechin detected in plasma

(−)-Epicatechin metabolism in humans

Sum of flavanol metabolites in plasma after the consumption of vehicle (control) or vehicle containing 1.5 mg/kg bw of (−)-epicatechin, (+)-epicatechin, (−)-catechin, or (+)-catechin

Study with human volunteers

Postprandial plasma antioxidant capacity

Plasma samples were spiked with a mixture of flavanol metabolites

Result: No detectable change in ORAC or FRAP up to 100 μM flavanol metabolites in plasma (unpubl.)
May 16, 2012:

USDA’s Nutrient Data Laboratory (NDL) removed the USDA ORAC Database for Selected Foods from the NDL website

due to mounting evidence that the values indicating antioxidant capacity have no relevance to the effects of specific bioactive compounds, including polyphenols on human health
The data for antioxidant capacity of foods generated by \textit{in vitro} (test-tube) methods cannot be extrapolated to \textit{in vivo} (human) effects and the clinical trials to test benefits of dietary antioxidants have produced mixed results.

We know now that antioxidant molecules in food have a wide range of functions, many of which are unrelated to the ability to absorb free radicals.

For these reasons the ORAC table, previously available on this web site has been withdrawn."

http://www.ars.usda.gov/services/docs.htm?docid=15866
Upshot on Flavanols

• **Keywords**: *Bioactives* rather than (only) *Antioxidants*

• **Active Compounds**: Flavanol *Metabolites*

• **Health and Disease Parameters**: measure chemical compounds involved (not ORAC, *Kit-ology*); *Nitric Oxide, Nitrite*, functional biomarkers (e.g. *Flow-Mediated Dilation (FMD), blood pressure*)

• **Mechanism of Action**: targeted control of prooxidant enzymes in inflammation and cardiovascular biology (specificity); master switches: *Nrf2, NFkappaB*

• **Cardiovascular Health**: Short-term/Long-term; Young/Old
Take-home Message: *Flavanols Session*

- *Bioactives* rather than (only) *Antioxidants*

- **Active Compounds**: Flavanol *Metabolites from Monomer; (−)-Epicatechin; Oligomers (Procyanidins) do NOT contribute*

- **Epidemiology**: blood pressure lowering in human intervention studies at >50 mg flavanol (monomer)/day
• **Mechanism of Action**: prooxidant enzymes, reactive oxygen species (*in vitro*, cell culture expts); inflammatory markers; master switches: Nrf2, NFκB

• **Cardiovascular Health**: Short-term (2 hr)/Long-term (>30 days); *Adaptive* Response

• **Young/Old**: acute (2 hr) response restricted in elderly after longer-term intake