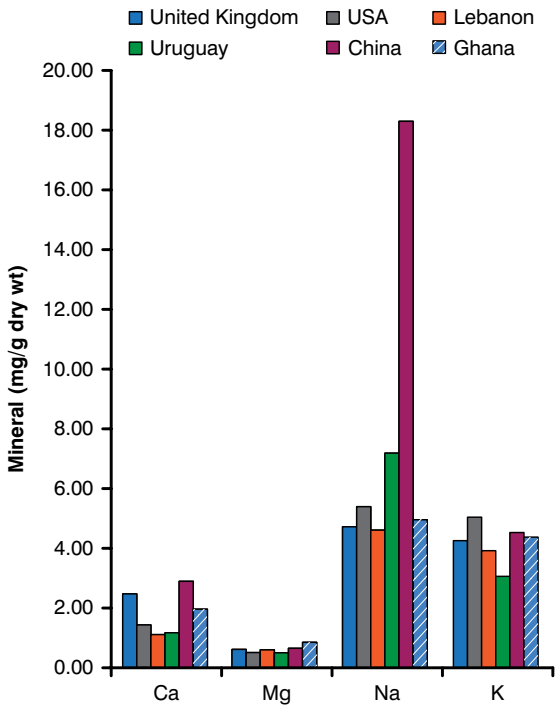
Figure 1. Mineral Intake in the Phase 1 Study in 6 Countries



Ca=calcium; K=potassium; Mg=magnesium; Na=sodium.
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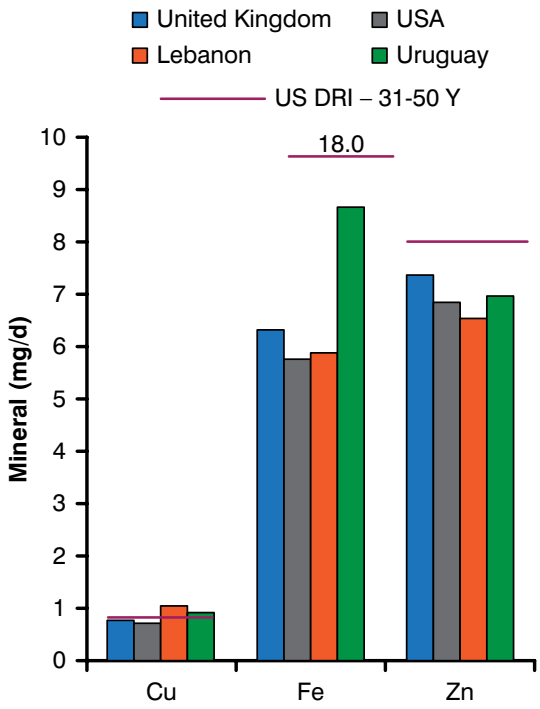
Figure 2. Intake of Copper, Iron, and Zinc in the Phase 1 Study



Cu=copper; DRI=daily recommended intake; Fe=Iron, Zn=zinc.
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A Phase 1 proof-of-principle study in IBCN has demonstrated that the project is feasible, said Prof. Welch. The objective of Phase 1 was to test the process to collect international samples. It also included designing one or two dietary patterns that represented common eating patterns in the research region that are representative of national data and reflect the appropriate energy intake for a woman between 18 and 45 years old.

The intake of calcium, magnesium, sodium, and potassium in six countries based on dietary patterns submitted in Phase 1 is shown in Figure 1, and the intake of copper, iron, and zinc is shown in Figure 2.

The Phase 2 proof-of-principle study is currently underway. Lessons learned from Phase 1 have presented opportunities to refine the processes for Phase 2 and subsequent research by the IBCN. Phase 1 of the study highlighted the need for adequate protocol training, because simply providing a protocol to investigators was insufficient because of differences in cultures and disciplines among countries. Improvements must be made in the documents and instructions to reduce variation in the types of information (eg, weights and menus) received with the diet shipments. Finally, the requirements for ethics approval varied greatly among countries, with some requiring a proposal for the entire project and a literature review, which resulted in a process that was slow and complicated.

Extensive progress has been made in establishing the IBCN project, stated Prof. Welch, providing a foundation to move on to the next research stages and expand the number of participating countries and researchers.

Beneficial Effects of Cocoa Polyphenols in AD: Insights From Basic Science Research

Written Mary Mosley

Research to prevent and treat Alzheimer's disease (AD) is now focused on the development of novel therapeutic approaches that target multiple mechanisms simultaneously. Polyphenols, comprising multiple bioavailable, active metabolites, are now being studied as novel therapeutics for strategies targeting the primary and secondary prevention of AD. Giulio Maria Pasinetti,

MD, PhD, Saunders Family Chair and Professor of Neurology, Icahn School of Medicine, Mount Sinai, New York, New York, USA, presented work from his group examining the effects of cocoa polyphenols in AD.

Select cocoa polyphenol metabolites promote synaptic plasticity through mechanisms that include a reduction in amyloid-β (Aβ) production. At the secondary prevention level, cocoa polyphenols may decrease the burden associated with the accumulation of Aβ plaques and delay the onset of cognitive impairment in individuals with AD [Sperling RA et al. *Sci Transl Med* 2011].

The primary dietary flavan-3'-ol derivatives found in cocoa, as well as in grapes, are catechin, epicatechin, catechin gallate, and epicatechin gallate. In experimental studies using a transgenic mouse model of AD, the group of investigators led by Prof. Pasinetti found that grape seed-derived polyphenols are associated with improved Aβ neuropathology, which, in turn, led to improved synaptic plasticity and slowed cognitive deterioration in these mice [Wang J et al. *Front Aging Neurosci* 2014].

The effect of cocoa polyphenols on mood disorders and depression—the most common psychiatric comorbidities associated with the onset and progression of AD [Pellegrino et al. *Curr Psychiatry Rep* 2013]—is currently being examined. Data from animal studies has been encouraging, and has shown that the reduction in depression-related immobility [Messaoudi M et al. *Nutr Neurosci* 2008] may be attributable to the monoamine oxidase inhibition properties of cocoa flavanols [Xu Y et al. *Pharmacol Biochem Behav* 2010]. Prof. Pasinetti stated that more experimental studies into AD are required to determine the role of cocoa extracts in preserving synaptic plasticity, perhaps through the attenuation of Aβ conformational changes and prevention Aβ neurotoxicity, to determine whether this may change the relationship between depression and AD.

The polyphenol compositions of cocoa extracts vary due to the different methods used to obtain the extracts. Natural, Dutched, and Lavado cocoa extracts have different levels of total polyphenol gallic acid equivalents and oxygen radical absorbance capacity. Prof. Pasinetti reports that Lavado cocoa was shown to prevent globin transcription factor-1 (GATA1) -mediated repression of presynaptic genes in three independent experiments (Pasinetti, data not yet published). Furthermore, Lavado cocoa extract better attenuates Ab oligomerization, followed by Natural and Dutch cocoa extracts (Wang et al. 2014 in press). In *ex vivo* hippocampal slices from wild-type mice, Lavado, but not Dutch, cocoa extract prevented the impairment of long-term potentiation induced by oligomeric-Ab. Long-term potentiation is a key cellular mechanism underlying synaptic plasticity and is essential to learning and memory (Wang et al. 2014 in press).

The hypothetical role of cocoa flavan-3'-ol metabolites in synaptic plasticity has been reviewed elsewhere [Spencer JP. *Chem Soc Rev* 2009]. In brief, synapse growth and increased receptor density, resulting from the activation of the CREB (cyclic adenosine monophosphate (cAMP) response element-binding protein) pathway, leads to an increase in the expression of brain-derived neurotrophic factor (BDNF), which binds to pre- and postsynaptic tyrosine kinase B (TrkB) receptors, thereby triggering glutamate release, phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) signaling, and synthesis of Arc, an immediate-early gene (IEG). PI3K and mTOR are important cellular regulatory pathways. Ongoing studies in Prof. Pasinetti's laboratory recently identified a novel role for cocoa polyphenols in influencing CREB pathways and the activation of IEGs, which are two independent but complementary molecular mechanisms influencing memory consolidation and synaptic plasticity.

Based on the neuroprotective effects of dietary cocoa polyphenols, Prof. Pasinetti and colleagues have undertaken a multi-faceted research strategy, with the ultimate goal to accelerate translational applications in the clinical setting for the primary and secondary prevention of AD. This includes the isolation of cocoa-derived bioactive polyphenol metabolites, their structural characterization and biosynthesis, the testing of bioactive polyphenols for AD disease-modifying activity *in vivo*, and elucidation of the mechanisms of this bioactivity, including the role of molecular pathways involved in Aβ generation, conformational changes, and clearance from the brain.