Developing and marketing cognitive products: ranging from life style and prevention to medical nutrition

Juliane Hellhammer, PhD

daacro – Full Service CRO – booth 146
Nutrient – biological effects – marketing strategies

**Regulatory framework**
Europe – USA – Canada – Japan …?

**Science**
Known or suspected physiological effects?

**Further steps**
More evidence needed?
Mechanisms of action?
As the life expectancy of the world’s population has increased within the last decades, the number of older adults suffering from age-related health problems, such as cognitive decline, is also expected to rise.

Therefore, testing interventions with the potential to prevent or reduce loss of cognitive function is important for public health.
STRESS as a risk factor

- Stress-induced behavioral and physiological changes modulate brain activity and neurocognitive performance in healthy subjects.

- These negative effects of stress on memory and other cognitive functions have been widely explored in numerous research projects using a wide range of methodologies including alternative medicine.

- Next to a growing ageing population, stress (as one of the most rapidly increasing risk factors for health impairment) calls for action.
The human brain uses about 50% of the body’s overall energy reserves.

Its energy balance is sustained by the release of the hormone cortisol which mobilizes the energy supplier glucose.

In stressful situations cortisol is released to enable the brain and the body to respond to the stressor.

However, very high cortisol levels result in damaging effects on the brain and the immune, metabolic and cardiovascular systems.
The selfish brain - hypothesis

The supply, demand and need of the brain as final consumer under conditions of psychosocial stress → cerebral energy homeostasis has highest priority in human energy metabolism.

Desired treatment effects should normalize the cortisol levels

- Cortisol hypo-reactivity
  - concentration ability
  - arousal
  - mental fatigue, etc.

- Cortisol hyper-reactivity
  - irritability
  - distractability
  - memory consolidation, etc.
Measuring responses to psychosocial stress

The Trier Social Stress Test (TSST)
– a protocol for assessment of individual responses to an acute stressor under controlled laboratory conditions.

<table>
<thead>
<tr>
<th>The classical Trier Social Stress Test - protocol - 15 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intro</td>
</tr>
<tr>
<td>2 min</td>
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</table>

The Trier Social Stress Test protocol

- More than 20 years and many hundred clinical trials have provided a broad database for stress measurements.
- Different versions for children & adolescents, groups, etc. have been established and include a variety of methods, such as cognitive testing, imaging, biomarkers, perceived well-being...
An example: Effect of phospholipid nutrients on brain function

- Phospholipids (PL) are a major component of cell membranes (phospholipid bilayers)
- PL constitute > 60% of total brain lipids
- PLs are characterized by different head units (PC, PE, PI, PS, PG)
- PLs perform vital functions within the body by supporting cognitive function, cardiovascular health, nerve health, liver function and digestion
- Dietary sources: fish, meat, egg, soy and milk
- Dietary PL has a good oral bioavailability and may cross the blood brain barrier
## Phospholipids (PL) and brain function

<table>
<thead>
<tr>
<th>Represents % of the brain PL</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PC</strong> Phosphatidyl choline 33-37%</td>
<td>key building block of membrane bilayers and provides choline for Acetycholine (ACh) synthesis and transmission</td>
</tr>
<tr>
<td><strong>PE</strong> Phosphatidyl ethanolamine 36%</td>
<td>key building block of membrane bilayers</td>
</tr>
<tr>
<td><strong>PS</strong> Phosphatidyl serine 10-20%</td>
<td>plays a key role in biosynthesis and release of neurotransmitters is neurotrophic, increasing total number and size of neurons</td>
</tr>
<tr>
<td><strong>PI</strong> Phosphatidyl Inositol 2-5%</td>
<td>key membrane constituent and a participant in essential metabolic processes</td>
</tr>
<tr>
<td><strong>SM</strong> Sphingomyelin 11%</td>
<td>contributes to myelination of neurons, is required for the activity of a number of membrane-bound proteins and is also a source of choline. SM not found in plants.</td>
</tr>
</tbody>
</table>
Lipogen‘s soy lecithin-derived phosphatidic acid (PA) and phosphatidylserine (PS)

- Since 1992, with very good bioavailability (Shinitzky, 1999)
- Kinetic: soy lecithin-derived PS is absorbed and metabolized, with elevated serum levels 1.5 h after an oral administration
- 1. clinical trial with 72 subjects aged 60-80 yrs: 3 months intake of 300 mg/day vs. placebo with positive effects on memory and mood (Gindin et al., 1995)
- 2. study showed beneficial effects of a 1 month intake of 300 mg/day on perceived stress in a mental arithmetic task (Benton et al., 2001)
I. Efficacy and safety of Lipogen’s PSPA™

Effects on stress?

✓ A 4-week double-blind, placebo-controlled, randomized study conducted with healthy subjects: PSPA™ (400 mg) can reduce the endocrine (ACTH and cortisol) and perceived stress response in a laboratory stress condition (TSST).

II. Efficacy and safety PSPA™

Effects on cognitive function?

1. Study. A 3-months double-blind, placebo-controlled study performed in healthy volunteers: PSPA™ can improve memory, mood and cognitive function in elderly subjects.

2. Study. A 2-months randomized, double-blind, placebo-controlled study performed in patients with Alzheimer’s disease (AD): PSPA™ can stabilize daily functioning, emotional state and self-reported general conditions in AD patients.

III. Efficacy and safety PSPA™

Effects in chronically stressed subjects?
Mechanisms of action?

✓ A 6-week double-blind, placebo-controlled, randomized study performed with healthy males: PSPA™ (400 mg) can normalize the stress hormone response to an acute stress test (TSST) in subjects with high chronic stress levels.

PSPA™ and products on different markets
IV. Efficacy and safety PSPA™

US Patent published July 2013:
Compositions and methods for alleviating symptoms associated with premenstrual syndrome and premenstrual dysphoric disorder
US 20130171269 A1

Ongoing study

Reduction of discomfort for women suffering from premenstrual syndrome (PMS)?

A 4-month double-blind, placebo-controlled, randomized study performed with 40 females: can a 3-month intake of PSPA™ (400 mg) reduce symptoms associated with PMS?
PSPA™ … now it gets interesting

Suspected mechanism of action

Meaning …

• clinical studies in line with regulatory guidelines and company strategies
• and at the same time, including scientifically innovative ideas and methods

➤ This will lead to sustainable results and accelerate product development. New areas for application will become accessible.
Further aspects for development of functional nutrients

- Exploring human brain function remains a challenge, here stress protocols will remain a helpful tool
- Sensitive methods and proper defined study populations (sub-population, age, duration of treatment) are critical
- Personalized nutritional supplementation by endophenotyping subjects
Stratified nutrition: targeting stress endophenotypes

<table>
<thead>
<tr>
<th>Axes</th>
<th>Systems</th>
<th>Function</th>
<th>Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glandotropy</strong></td>
<td>CRF, ACTH, Cortisol</td>
<td>energy supply of the brain</td>
<td>Example: phospholipids</td>
</tr>
<tr>
<td><strong>Ergotropy</strong></td>
<td>norepinephrine, epinephrine</td>
<td>enhancement of cognitive and physical performance</td>
<td>Example: tyrosine</td>
</tr>
<tr>
<td><strong>Trophotropy</strong></td>
<td>serotonin, vagus</td>
<td>regeneration, resilience,</td>
<td>Example: tryptophan</td>
</tr>
</tbody>
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**W.R. Hess**
Swiss Nobel Laureat

Juliane Hellhammer
Other dietary nutrients that may influence cognitive function

Micronutrients: vitamins and trace elements

Secondary metabolites extracted from natural products (plants and medicinal mushrooms)
<table>
<thead>
<tr>
<th>Micronutrients (vitamins)</th>
<th>Function</th>
<th>Effects (based on human clinical trials)</th>
<th>Sources</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B6 (pyridoxine)</td>
<td>is involved in the synthesis of some neurotransmitters;</td>
<td>beneficial effect on premenstrual depression</td>
<td>sunflower seeds, pistachio nuts, fish</td>
<td>Wyatt et al., 1999</td>
</tr>
<tr>
<td>Vitamin B9 (folic acid)</td>
<td>preserves brain during its development and memory during aging</td>
<td>Deficiency of vitamin B9 in elderly population decreases intellectual capacity</td>
<td>liver, eggs, many green vegetables (cress, spinach, leeks, lentils, asparagus, broccoli, cauliflower), maize, chickpeas, almonds, chestnuts</td>
<td>Hassing et al., 1999</td>
</tr>
<tr>
<td>Vitamin B12 (cyanocobalamin)</td>
<td>is involved in the synthesis of some neurotransmitters;</td>
<td>Deficiency of vitamin B12 induces neurological disorders, e.g. adolescents who have a borderline level of vitamin B12 develop signs of cognitive changes; improves cerebral and cognitive functions in older cobalamin-deficient persons</td>
<td>meat, fish, shellfish, soy products, eggs</td>
<td>Louwman et al., 2000; van Asselt et al., 2001</td>
</tr>
<tr>
<td>Vitamin E (alpha-tocopherol)</td>
<td>it is a lipid-soluble antioxidant that can cross the blood-brain-barrier; directly involves in nervous membrane protection</td>
<td>it is used to prevent dementia among healthy adults, e.g. the risk of dementia is significantly increased for the lowest vitamin E concentration compared to highest one</td>
<td>eggs, vegetable oils, cereal germs, salad, cabbage, spinach</td>
<td>Larrieu et al., 2004; Bourre, 2006; Gestuvo &amp; Hung, 2012</td>
</tr>
<tr>
<td>Micronutrients (trace elements)</td>
<td>Function</td>
<td>Effects (based on human clinical trials)</td>
<td>Sources</td>
<td>References</td>
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<td>---------------------------------</td>
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<tr>
<td>Iron</td>
<td>is necessary to ensure oxygenation and to produce energy in the cerebral parenchyma (via cytochrome oxidase), and for the synthesis of neurotransmitters and myelin</td>
<td>Iron deficiency is found in children with attention-deficit/hyperactivity disorder (ADHD)</td>
<td>liver, mussels, oysters, lentils, beans, spinach</td>
<td>Konofal et al., 2004</td>
</tr>
<tr>
<td>Zinc</td>
<td>plays a role in cognitive development</td>
<td>Zinc deficiency impairs whole-body accumulation of polyunsaturated fatty acids and thus brain supplying could be affected e.g., zinc deficit induces behavioral changes</td>
<td>oysters, beef and lamb meat; wheat germs, spinach</td>
<td>Cunnane et al., 1995; Golub et al., 1995</td>
</tr>
</tbody>
</table>

Bourre, 2006; Gestuvo & Hung, 2012
### Secondary Metabolites in Plants

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Function</th>
<th>Effects (based on human clinical trials)</th>
<th>Sources</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGb 761 extract of Ginkgo biloba</strong></td>
<td>it may improve brain function by changing cerebrovascular circulation through cerebral vasodilation, reducing blood viscosity, reducing oxygen free radicals</td>
<td>Can stabilize and, in a substantial number of patients, improve the cognitive performance and the social functioning of demented patients; However, the beneficial effect of G. biloba for people with dementia or cognitive impairment is inconsistent</td>
<td>Ginkgo biloba</td>
<td>Pierre et al., 1997</td>
</tr>
<tr>
<td><strong>Ginseng saponins extracted from Ginseng</strong></td>
<td>it is an adaptogen, a substance that increases resistance to physical, chemical and biological stress</td>
<td>it shows promising results for improving glucose metabolism and moderating the immune response which may have implication for cognitive function</td>
<td>Ginseng</td>
<td>Shergis et al., 2012</td>
</tr>
</tbody>
</table>

*Gestuvo & Hung, 2012*
<table>
<thead>
<tr>
<th>Secondary metabolites in medicinal mushrooms</th>
<th>Function</th>
<th>Effects (based on human clinical trials)</th>
<th>Sources</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysaccharides &amp; triterpenes extracted from medicinal mushrooms</td>
<td>can increase the body's ability to resist the damaging effect of stress via stabilizing the normal physiological processes; anti-aging properties</td>
<td>polysaccharide extract of medicinal mushroom has been showed to improve symptoms of neurasthenia, a condition characterized by nervous exhaustion</td>
<td>Ganoderma lucidum</td>
<td>Tang et al., 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cs-4® obtained from medicinal mushroom can improve well-being and exercise performance in healthy elderly participants</td>
<td>Cordyceps sinensis</td>
<td>Chen et al., 2010</td>
</tr>
</tbody>
</table>
Disease prevention through healthy diet and nutrition

Progression of dementia

Genetic predisposition, Environment, **Lifestyle**

Phase I
(intact brain)

Cognitive tests & MRT for detection of vascular lesions, neurodegeneration, cognitive decline

Phase II
(first changes in the brain function)

Irreversible brain changes

Phase III
(clinically diagnosed dementia)

Nutrients to prevent cognitive decline

Ageing

Disease prevention through healthy diet and nutrition

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Juliane Hellhammer
Summary and future directions in development of functional nutrients

- Nutrients may play a major role in preserving cognition in an aging society
- Though limited, there is evidence for potential interaction with other therapies
- Additional investigations of the responsible mechanisms for nutrient effects on cognitive health are needed including tailored clinical trials
- Big data or N=1 trials?

Mayer et al., 2014 J Neurosci 34 (46): 15490-15496
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