Future nutrition: can stress models help to achieve personalized nutrition?

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daacro – Full Service CRO

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Why focus on stress in clinical studies with nutrients?

Stress is considered one of the most rapidly increasing risk factors for health problems.

Stress hormones impair brain function.

Stress promotes a variety of physical and mental disorders.

Stress enhances the risk of conditions like obesity, heart disease, Alzheimer's disease, diabetes, depression, gastrointestinal problems, and asthma.

Stress leads to poor health behavior (e.g. eating habits).
Thus, stressed people seek help from nutrients to improve their health conditions and to increase their individual ability to succeed.

- EFSA claim on food: enhanced function claim, or
- EFSA claim on food: reduction of disease risk claim.

Particularly in subthreshold disorders, stress symptoms are still mild and can be managed with herbal medicine and nutritional supplements.

- High standards for the quality of scientific evidence are required!

But how can we characterize people with deficits and still not enter the pharmaceutical drug law?

Choosing the right study population & study methods!

Subjects can be characterized by:
- gender
- age
- complaints or symptoms
- baseline characteristics
- norm sample
- standardized testing

The Trier Social Stress Test

Methods can be characterized by:
- field – laboratory
- self report – external assessment
- choice of biomarkers
- computer-assisted tests, …
But choosing is not enough: we need models

**Acute and chronic stress affect brain function**

- Two pathways: fast acting catecholamines and the slower acting hormones, with the release of cortisol as the endpoint.
- Acute stress activates both physical and mental resources. After an acute stressful situation the biological activity returns back to baseline.
- Chronic stress does not allow the system to recover and regenerate resources. Stress hormones like cortisol get dysregulated and impair both health and cognitive functions.
Methods: measuring effects of *acute stress*

The Trier Social Stress Test (TSST): A valid and reliable method to induce acute stress under laboratory conditions

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

This standardized protocol is novel, unpredictable and uncontrollable for a subject and causes anticipation and ego-involvement.
Methods: measuring effects of **acute stress**

Depending on a variety of factors (e.g. compound, questions, budget) the TSST-protocol will be designed.

A protocol developed 1993 in Trier. Today, the international Gold Standard in clinical trials.
Over 20 years of research delivered many results.

- **Psychometric measures:** anxiety, mood, cognitive functions, attention, well being, etc.
- **Autonomic nervous system:** blood pressure, heart rate, heart rate variability, temperature, respiration, skin resistance, norepinephrine, epinephrine
- **Endocrine system:** ACTH, free and total cortisol, prolactin, growth hormone
- **Metabolism:** glucose, insulin
- **Immune system:** pro- and anti-inflammatory cytokines, leukocyte subsets, etc.
- **Gene expression:** repression and induction of gene-expression
- **Psychomotoric:** physical activity, mimic, pantomimic, phonetic analyses
- **CNS:** EEG
How do reactions from the TSST look like?

**Salivary cortisol**

**Heart rate**

Salivary cortisol and heart rate measurements over time with regard to the TSST.
Example: Cognitive testing and acute stress

The timing is important!

Methods: measuring effects of chronic stress

Assessment of:

- Perceived psychological stress
- Perceived stress effects on health, mood, cognition
- Biomarkers (cortisol, heart rate variability) at baseline and in response to awakening.
Chronic stress and cognitive testing

**Chronic Stress**

- Chronic stress generally impairs cognitive functions, such as declarative memory performance.

**Measures**

- Stress effects on cognitive function can be assessed by various test batteries, such as the Cambridge Cognition System CANTAB®.
  
  22 Tests by function - main types of task:
  - screening tests - visual memory tests - executive function,
  - working memory and planning tests - attention tests - semantic/verbal memory tests - decision-making and response control tests.
The stress hormone cortisol mobilizes glucose and serves the energy supply of the brain, particularly under stressful conditions ("selfish brain hypothesis")

- Saliva cortisol is the unbound and biological active hormone fraction
- A dysregulation is associated with a broad array of stress symptoms
- Saliva sampling is easy, non-invasive, and stress free.
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: phospolipids</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>
</table>
How to approach a clinical study with nutrients?

Sponsor: What is the intention of the study?

- Regulatory framework requirements!
- Where shall claim cover: USA (FDA) or Europe (EFSA)?
- Quality of study design!
- Choice of (cognitive) tests!
- Baseline performance – important predictor of response to nutrient!
- Appropriate analyses!
- Demonstration of causality!
Example I:
a first clinical study with a phospholipid enriched milk product

Study performed for Arla, Denmark: a milk phospholipid (13.5 g/day; rich in Phosphatidylserine, Sphingomyelin) with a intake period of 3 weeks.

Subjects showed a slightly improved working memory and a shorter reaction time in an item recognition test. The effects were most pronounced subjects reporting a higher stress load.
Followed by a 2nd clinical study for Arla in a subpopulation with chronically stressed subjects

**Question:** Can a milk PL improve cognitive functioning in chronically stressed?
# Study outline

<table>
<thead>
<tr>
<th>Study title</th>
<th>Effects of two doses of LACPRODAN® PL-20 in a highly stressed population on acute stress reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>75</td>
</tr>
<tr>
<td>Number of groups</td>
<td>3</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Healthy, but chronically stressed males, age 30 – 50 yrs</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Not chronically stressed (TICS &lt; 15); smoking or alcohol abuse; illness or medication</td>
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</tbody>
</table>
| Treatment      | Group I: Placebo  
Group II: 150 mg - 0.06% phosphatidylserine (PS 1)  
Group III: 300 mg - 0.12% phosphatidylserine (PS 2)      |
| Treatment duration | 6 weeks                                                                                                           |
| Outcome objectives | Normalization of stress response measures, improvement of memory |

Answer: Chronically stressed do better in an acute stressful situation
Our data suggest that LACPRODAN improves the ability of the organism to adapt to chronic stress.

LACPRODAN may be protective in persons who are persistently exposed to chronic stress, thus stabilizing both physical and mental health.

LACPRODAN supplementation buffers stress induced memory deficits.

Our results are in line with previous studies highlighting a beneficial influence of PL on memory functions.
Example II: a clinical study with a soy lecithin phosphatidic acid and phosphatidylserine complex (PAS)

In 2004 a four week intake of 400 mg PAS per day showed a dampened endocrine (ACTH and cortisol) and perceived stress response in the TSST.

Example II:
In 2013 a second clinical study with male subjects and the same product replicated these results for chronically stressed

Memree™ contains high-quality soy phosphatidylserine and is a trademark of Lonza Ltd, Switzerland.
Summary and future directions for clinical studies with nutrients

- Stress protocols are helpful tools by providing a „window into the brain“

- Integrating scientific expertise — understanding underlying mechanisms to improve nutraceutical development

- Selecting sensitive methods and well defined study populations (sub-population, age) fitting the study objectives

Future directions:

- elderly population with minor cognitive impairment
- stratified nutrition
- learning more and more about the brain and underlying pathways.
daacro – contract research

all services from one source – making sponsor’s needs ours

- Clinical study site and laboratory with a background of 30 years of expertise in psychobiological stress research
- Services: study planning > study conduct > study statistics > study publication
- Sponsors: pharmacological - , nutritional - , and health care companies
Thank you for your attention!

Contact us at the Food Matters Live Event : Stand RP 29

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