**Central Fatigue**

*it’s all in the brain*

**Prof Dr Romain MEEUSEN**

**V R I J E U N I V E R S I T E I T B R U S S E L**

**H U M A N P H Y S I O L O G Y - B L I T S**

**Chaire Francqui**

- Central Fatigue »
  - Exists, but is linked to more than one neurotransmitter system
  - Probably other ‘stressors’ are necessary to disturb this solid homeostatic mechanism
- Thermoregulation – how hot is the Brain ? »
  - The dopaminergic system has an important role in the ‘drive’ to continue during prolonged exercise in the heat
- Neurogenesis and Exercise »
  - Exercise is one of the most important ‘primers’ for neurogenesis
- The Overtraining Syndrome: facts and fiction »
  - The hormonal disturbance due to NFO or OTS can be detected using a ‘double exercise protocol’
- Cryotherapy »
  - Recovery From exercise: should we cool the body ?

**Fatigue**

A failure to maintain the required or expected force or power output

Is there a link with the Brain ?

Animal & Human studies using ‘central manipulation’

**Peripheral Fatigue**

- Substrate availability
- Accumulation metabolites
- Ca^{2+} distribution (release and uptake)
- Neuromuscular function impairment
- ...

**Exogenous carbohydrate intake is limited**

At exercise intensities below 50% to 60% of VO_{max}, exogenous CHO oxidation will increase.

With increasing total CHO oxidation rates, usually above approximately 50% to 60% of VO_{max} oxidation rates will not increase further.
Carbohydrate ingestion

Increases performance
Also during long duration training
Training period

Central Fatigue

Fatigue associated with specific alterations in CNS functioning other than muscular dysfunction

Central mechanisms

✓ Mental factors can affect performance
✓ Perception of effort
✓ Inadequate CNS drive to the working muscles
✓ Motivation, mood, pain tolerance
✓ ...

What happens in the Brain during exercise?

✓ Neurotransmitters
✓ Exercise & NT
✓ Extracellular space
✓ Exercise & Fatigue

Noradrenergic System

✓ Locus coeruleus:
  Attention, arousal, sleep-wake cycles, learning & memory, anxiety, pain, mood, depression

Dopaminergic system

✓ Substantia nigra:
  initiation voluntary movement, Parkinson’s disease
✓ Ventral Tegmental area:
  reward system, addiction, psychiatric disorders
Serotonergic System

- Raphe nuclei:
  - Caudal: spinal cord
  - Pain
  - Rostral: arousal, sleep-wake, attention, mood, addiction, depression, ...

Exercise and Brain NT concentrations

<table>
<thead>
<tr>
<th></th>
<th>Acute Exercise</th>
<th>Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>↑ Striatum, Cortex,</td>
<td></td>
</tr>
<tr>
<td>DA</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
| 5-HT           | ~ (↑)          | ↑[5-HT] & ↑[5-HIAA] Region specific

Exercise and Brain Neurotransmitters

First Neurotransmitter studies
- Whole brain concentrations
- Different brain regions
- Acute Exercise
- Chronic exercise
- Tissue preparations

What happens in the specific brain regions during exercise?

Microdialysis

Microdialysis is a sampling technique for determination of substances from the extracellular space of essentially any tissue of the body. A small hollow needle is introduced in a specific brain area to collect neurotransmitters.

Features of Microdialysis

- extracellular fluid
- every organ
- intact tissue
- living, awake, freely moving animals
- sample continuously
- recovering and/or introducing substances
- minimal damage
Guide implantation
Recovery from surgery
Probe implantation
Experiment

Baseline Neurotransmitter levels in Rat Striatum 6wks of Training

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Trained</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA (fmol/20min)</td>
<td>178.4 ± 32.6</td>
<td>57.1 ± 13.1*</td>
</tr>
<tr>
<td>NA (fmol/20min)</td>
<td>27.7 ± 6.1</td>
<td>8.3 ± 2.6*</td>
</tr>
<tr>
<td>GLU (µmol/20min)</td>
<td>0.86 ± 0.18</td>
<td>0.28 ± 0.03*</td>
</tr>
<tr>
<td>GABA (µmol/20min)</td>
<td>0.018 ± 0.004</td>
<td>0.019 ± 0.006</td>
</tr>
</tbody>
</table>

Monoamines: 20 min of moderate exercise - Striatum

DA release at rest & during 60 min exercise

Percent Increase

Absolute Values

Speed - Duration

Exercise & Brain NT

Exc influences release of neurotransmitters in different brain regions
Speed & duration
Training: « adaptation »
cfr. peripheral mechanisms
The Central Fatigue Hypothesis

During prolonged exercise athletes not only get fatigued because of a decrease in substrates, but there is also fatigue induced by brain mechanisms.


The ‘Central Fatigue Hypothesis’

Is based on the increase in brain [5-HT] during exercise.

Newsholme and colleagues (1987) assumed that during prolonged exercise increased brain serotonergic activity may augment:

- lethargy and loss of drive resulting in a reduction in motor unit recruitment,
- affecting physical and mental efficiency of athletes.

Tryptophan (TRP)

One of the 8 essential amino acids found in the human diet.

Essential amino acids must be gotten from food or supplements;

\[
\text{Tryptophan (TRP)} \rightarrow \text{5-Hydroxytryptophan (5-HTP)} \rightarrow \text{5-Hydroxytryptamine (5-HT)}
\]

TRP → Serotonin (5-HT)

An amino acid becomes an important signal transducer in the human brain!!

Can this small molecule be responsible for fatigue??

5-HT

5-HIAA

BRAIN

REST

BLOOD
Serotonin and its precursor: long duration exercise

- TRP in periphery bound to albumin
- FFA more affinity to albumin
- Long duration exercise
  - more free TRP

BCAA & TRP use the same carrier to cross the BBB
TRP- hydroxylase not saturated
  - no rate limiting step!

What about the “Central Fatigue Hypothesis”? ?

Central Fatigue

Several Animal & Human experiments have been performed,

... BUT DO WE REALLY KNOW WHAT HAPPENS IN THE BRAIN?


Free TRP conc. before and after a marathon

After

Before

Exercise, 5-HT and Hippocampus

Effects of tryptophan and/or acute running on extracellular 5-HT and 5-HIAA levels in the hippocampus of food-deprived rats

Exercise and 5-HT

- food restriction
- precursor availability
- precursor-induced changes in synthesis → release?

Material & Methods

- food-deprived rats
- L-TRP (50mg/kg) or saline
- exercise (60 min 12m/min)
- combination
- microdialysis in hippocampus

<table>
<thead>
<tr>
<th>Group 1: L-TRP &amp; Exc</th>
<th>n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2: Saline &amp; Exc</td>
<td>n=6</td>
</tr>
<tr>
<td>Group 3: Exercise</td>
<td>n=6</td>
</tr>
<tr>
<td>Group 4: L-TRP</td>
<td>n=6</td>
</tr>
<tr>
<td>Group 5: Saline</td>
<td>n=6</td>
</tr>
</tbody>
</table>

Results

Baseline values (n = 30)

5-HT: 7.0 ± 1.2 fmol/20µl
5-HIAA: 5.5 ± 0.7 pmol/20µl

Sign.↑ [5-HT] & [5-HIAA]

Sign.= Saline-Exc / L-TRP-Exc

Hippocampal 5-HT release

Combination L-TRP + Exc

No sign early fatigue

BCAA – 5-HT – central fatigue

✓ Newsholme et al
✓ Animal & human studies: [5-HT] in brain ↑ ???
✓ Drug induced alterations of [5-HT]
✓ Nutritional manipulations
✓ Other neurotransmitter manipulation
✓ ...

Nutritional Manipulations → Brain ??

- Amino Acids
  - BCAA
  - TRP
  - TYR
  - CHO
Long duration exercise – BCAA supplementation

BRAIN

BLOOD

BCAA administration


No positive results in well-controlled studies

Interruption Exc & BCAA

- CHO and CHO + BCAA drinks improved performance
  - co-ingestion of CHO ! (?)

TYROSINE (TYR) ➔ Dopamine

- Several authors failed to show positive effects on exc performance (e.g. Struder et al 1998; Chenevre et al 2002, Sutton et al 2005)
- TYR ingestion might improve stress-induced cognitive and behavioral deficits (working memory, attentional tasks etc.)
  - Soccer ?

Other possible factors responsible for ‘Central Fatigue’

- Other neurotransmitters (GABA, GLU, ...)
- NH₃
- BBB permeability
- Metabolic, thermodynamic, circulatory and humoral responses that can lead to a disturbance of cerebral homeostasis

Pharmacological studies

Agonist: will 'strengthen' the effect of the drug
Antagonist: will decrease or block the effect
Reuptake Blocker: sits in the reuptake transporter and therefore creates more and longer NT interaction in the synapse
Central Fatigue & Serotonin
- Brain neurotransmitters are influenced by exercise.
- Several possible transmitter systems might also be involved.
- In animal studies it was possible to manipulate performance, but, ...
- In Humans no effect was found,

> Until now no straightforward evidence that 5-HT is the only player in the field.

What about Dopamine?
- Intracranial self stimulation
  - VTA

Dose dependent effects
- AMPH injection
  - Run to exhaustion
- Dopaminergic (DA) neurotransmission
  - AMPH inj. ➔ DA release in Striatum

Microdialysis: Striatal Dopamine

Manipulation of Brain Neurotransmitter systems
Pharmacological manipulations of brain neurotransmitter concentrations
Nutritional manipulations
DA agonism & 5-HT antagonism
DA manipulation
NA manipulation
5-HT reuptake inhibition
Combination:
- 5-HT/NA reuptake inhibition
- NA/DA reuptake inhibition
...

Materials & Methods
- Young healthy subjects (n= 5-9)
- well trained cyclists
- age (yrs) = 23 ± 1.7
- weight (kg) = 73.5 ± 8.5
- height (cm) = 182 ± 5.8
- \( \text{VO}_{\text{max}} = 73.5 ± 6.4 \text{ ml/kg/min} \)
- 90 min Time trial à 65% \( \text{Watt}_{\text{max}} \)

Exercise Performance Humans

Performance (90 min Time Trial)

PRL (mIU/L)

Re-uptake inhibition in humans
- No influence on time trial performance
- Hormonal disturbances indicate the “central effect”
- Serotonergic & Catecholaminergic actions differ per hormonal output
- Animal research to confirm “central” action
Catheterisation

Venlafaxine Rats (5-HT/NA)

Hormonal influence
Auto-inhibition GH cfr Humans?

Venlafaxine Rats

Piacentini, Meeusen et al JAP 2003

Bupropion Rats (DA/NA)

Hormonal values
dopaminergic influence

Piacentini, Meeusen et al JAP 2003

Conclusions

Although the theoretical rationale for the “serotonin-fatigue hypothesis” is clear it is mainly supported by results from animal studies or circumstantial evidence:

- changed levels of substrates,
- amino acids,
- neuromodulators,
- or pituitary hormones.
Conclusions

It is likely that the interaction of cerebral metabolic, thermodynamic and hormonal responses during prolonged exercise will determine the delicate communication between the brain and the periphery. Fatigue is therefore likely to be an integrated phenomenon with complex interaction among central and peripheral factors.

Central Fatigue

- Exists
- But it is not as simple as the first hypothesis put forward
- The administration of BCAA has no real influence on endurance performance
- Glucose ingestion has indicating the importance of the peripheral factors

Central Fatigue: It’s All in the Brain?

Both peripheral and central regulatory mechanisms will be stressed
- Disturbance of Cerebral Homeostasis that eventually can lead to Central Fatigue
- Neurotransmitters are involved
- But although brain disturbances occur, fatigue mechanisms seem to need other stressors
- Thermal stress is a good candidate to explore this

Fatigue?