Critical illness

A condition whereby a patient, through trauma or disease, becomes dependent on pharmacological and/or mechanical support of his vital functions, without which he/she would die shortly
Thyroid (patho)physiology during critical illness?

**Acute**
- changes in peripheral metabolism and binding

**Prolonged**
- + neuroendocrine dysfunction

Low-T3 syndrome
- or
- non-thyroidal illness (NTI)
- or
- euthyroid sick syndrome
Associations with mortality and morbidity

- T3/rT3 ratio is associated with increased mortality in the ICU (Peeters et al., JCEM, 2005)

- Many symptoms in critically ill patients can be related to the low T3 levels. Signs of hypothyroidism?
  - CNS depression
  - Need for inotropes
  - Hypothermia
  - Diaphragm dysfunction
  - Polyneuropathy
  - Weaning failure
  - Kidney failure
  - Tegumentum dystrophy
  - ....

→ Are the low T3 levels harmful???
Is the low T3 syndrome an adaptive response?

PRO

- Energy sparing mechanism
- Selected by nature
- Do not treat

CON

- Symptoms related to the low T3 levels?
- Correlation between T4 levels and probability of death
- Patients should be treated

Problem: lack of well powered RCT for TH treatment in the ICU

First increase our understanding of the pathophysiology of the low T3 syndrome or NTI
Suppressed D1 and upregulated D3 activity in critical illness

Liver D1

T3 / rT3

Liver D3

Human liver biopsies (N=76)

I cardiovascular collapse
II MOF with sepsis
III MOF with SIRS
IV severe brain damage

Peeters R et al. JCEM 2003
Study 1: The type II iodothyronine deiodinase (D2)

- D2 is expressed in skeletal muscle

- D2 can contribute to circulating TH levels
  (Luiza Maia et al, JCI, 2005)

Is D2 reduced and hereby contributing to the low T3 levels during critical illness?
D2 is increased in skeletal muscle of critically ill patients

Mebis L et al. JCEM, 2007
From patient to rabbit …

D2 is regulated by TH levels during critical illness

Δ AUC T3 (nmol/L over 4 days)

Δ AUC T4 (nmol/L over 4 days)

Relative D2 mRNA

- Saline
- TRH + GHRP-2
- T3 + T4
Adaptive response of D2 during critical illness

- **D1 is reduced**
  - Decreased activation of TH

- **D3 is increased**
  - Increased inactivation of TH

- **D2 is increased**
  - Adaptive response to the low TH levels
Changes in TH transporters cause low T3 levels during prolonged critical illness?
MCT8 – clinical relevance

- Association between mutations in a thyroid hormone transporter (MCT8) and severe X-linked psychomotor retardation (Friesema et al., Lancet, 2004) = Allan-Herndon-Dudley syndrome (AHDS)
  - congenital hypotonia
  - spasticity
  - severe psychomotor delays
  - muscle hypoplasia
  - generalized muscle weakness
  - limited speech
- Changes in serum TH levels:
  - elevated free T3
  - low to below normal free T4
  - normal TSH
Expression of MCT8 and MCT10 in critically ill patients

* P < 0.001 vs. acute ill group, † P = 0.05 vs. acute ill group

Mebis L et al, EJE 2009
Relative TH transporter mRNA expression in rabbit tissues

* P < 0.05

Mebis L et al, EJE 2009
Compensatory changes during prolonged critical illness?
= An argument pro treatment?
Study 3: Changes in the central component of the HPT-axis

Fliers E, et al.

Decreased TRH gene expression in patients with chronic non-thyroidal illness

JCEM 1997; 82: 4032-4036
Central regulation of the HPT axis

- Local hyperthyroidism?

Prolonged neuroendocrine dysfunction

Healthy

Critically ill

T3↑

TRH ↓

PVN

TRH

TRH
Thyroid hormone pathway in the hypothalamus

- Blood vessel
- OATP1C1
- T4
- T3
- D2
- MCT8/10
- Astrocyte/tanycyte
- TRH neuron
- T2
- T3
- D3
- TR's
Thyroid hormone pathway in the hypothalamus

1. TH transporters
2. TH metabolism by D2/D3
3. TH tissue content
4. TR’s
Thyroid hormone pathway in the hypothalamus

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TH transporters in the hypothalamus

MCT8  MCT10  OATP1C1

$P = 0.16$  $P = 0.04$  $P = 0.002$

Mebis et al. Crit Care 2009
D2 and D3 in Rabbit Hypothalamus

Relative D2 mRNA

$P = 0.03$

D2 activity (fmol/min/mg)

$P = NS$

D3 activity (fmol/min/mg)

$P = NS$

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2. TH metabolism by D2/D3
3. TH tissue content
4. TR’s

Mebis et al. Crit Care 2009
TH tissue content of the hypothalamus

1. TH transporters
2. TH metabolism by D2/D3
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Mebis et al. Crit Care 2009
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TR expression in the hypothalamus

Mebis et al. Crit Care 2009
Thyroid hormone pathway in the hypothalamus

1. TH transporters
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General Conclusions (2)

Other mechanisms for TRH repression?

Prolonged
+ neuroendocrine dysfunction

[Diagram showing relationships between T3, T4, TSH, TRH, rT3, T2, and D1, D2, D3, with arrows indicating regulation and repression.]
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