Thyroid hormone metabolism during critical illness

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Critical illness
Critical illness

- Infection
- Trauma
- Burnwounds

Cellular stress

Inflammation

Hypercatabolism

Organ dysfunction

Mortality
Low T3 syndrome
NTI

Peeters R et al. JCEM 2005; 90:4559-4565
TH metabolism is dramatically altered

- TH binding proteins
- TH transporters
- TH receptors

Diagram:

TRH → TSH → T4

T3 ↓ ↓ rT3 ↑
Substitution of T4 in a thyroidectomized critically ill patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before initiating 120 µg T4 IV</th>
<th>4 days after initiating 120 µg T4 IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4 (5-14 µg/dL)</td>
<td>4.1 µg/dL</td>
<td>2.6 µg/dL</td>
</tr>
<tr>
<td>T3 (80-200 ng/dL)</td>
<td>49 ng/dL</td>
<td>49 ng/dl</td>
</tr>
<tr>
<td>TSH (0.27-4.20 mIU/L)</td>
<td>11.5 mIU/L</td>
<td>6.5 mIU/L</td>
</tr>
</tbody>
</table>
Treatment with substitution doses of T4 & T3 demonstrates increased TH metabolism.

**T4 (nmol/l)**
- TRH - 60 µg/kg/h (N=8)
- Healthy controls (N = 4)
- T4 - 3 µg/kg/d (N=8)
- T3 - 1 µg/kg/d (N=8)
- T4 - 3 µg/kg/d + T3 1 µg/kg/d (N=8)

**T3 (nmol/l)**
- TRH - 60 µg/kg/h (N=8)
- Healthy controls (N = 4)
- T4 - 3 µg/kg/d (N=8)
- T3 - 1 µg/kg/d (N=8)
- T4 - 3 µg/kg/d + T3 1 µg/kg/d (N=8)
Decreased TRH expression in chronic CI

Sudden death
Without NTI

Critically ill
patient with NTI

Fliers E, et al. JCEM 1997; 82: 4032-4036
Decreased TRH expression in chronic CI

Healthy control

Chronic illness

Mebis L et al, Crit Care 2009; 13(5):R1-10
Decreased plasma TSH in chronic CI

Healthy control

Acute Critical Illness

Prolonged Critical Illness

Van den Berghe et al, JCEM 1998; 83(6):1827-1834
Biphasic pattern of low T3 syndrome

Acute CI

TRH ➔ TSH =

T4 =

T3 ➔

C

rT3 ↑

Prolonged CI

TRH ➔ TSH ➔

T4 ➔

T3 ➔

rT3 ↑

Additional central suppression

Altered peripheral metabolism
Hepatic Dio1 decreases with increasing severity of illness

Liver Dio1 (pmol/mg/min)

I cardiovascular collapse
II Multiple organ failure with sepsis
III Multiple organ failure with SIRS
IV severe brain damage

Peeters R et al. JCEM 2003; 88: 3202-3211
Positive correlation liver Dio1 activity & TH plasma concentrations

Debaveye Y et al, Endocrinology 2005; 146(12):5604-5611/
Peeters R et al. JCEM 2003; 88:3202-3211
Effect of high doses of T4 & T3 on Dio1 activity

- T4 - 9 µg/kg/d (3 x Substitution dose)
- T3 - 5 µg/kg/d (5 x Substitution dose)

Debaveye Y et al. Endocrinology 2008; 149(8): 4218-4228
Effect of high doses of T4 & T3 on Dio1 activity

Hepatic Dio1 activity
(fmol/ml/min)

P=0.0006

T4 - 9µg/kg/d (3x SD)
T3 - 5 µg/kg/d (5 x SD)

Means ± SEM

Debaveye Y et al. Endocrinology 2008; 149(8): 4218-4228
Hepatic Dio3 activity increases with increasing severity of illness

Liver Dio3 (fmol/mg/min)

I  cardiovascular collapse
II  Multiple organ failure with sepsis
III Multiple organ failure with SIRS
IV  severe brain damage

Peeters R et al. JCEM 2003; 88: 3202-3211
Low GH contributing to high Dio3 activity?

Van den Berghe et al, JCEM 1998; 83(6):1827-1834
Increase in plasma GH normalizes Dio3 activity

Liver D3 (fmol/mg/min)

* NS

Saline GHRP-2 +TRH GH


TRH/GHRP-2 infusion during prolonged CI

placebo vs. TRH

placebo vs. TRH+GHRP-2
TRH/GHRP-2 infusion during prolonged CI

T4 (nmol/L)  

$p < 0.0001$

T3 (nmol/L)  

$p < 0.0001$

GHRP-2 +TRH [1 µg/kg/h for 5 days] / placebo

placebo / GHRP-2 +TRH [1 µg/kg/h each for 5 days]

5 days TRH+GHRP-2 infusion increases anabolism and reduces catabolism

![Graph showing changes in Osteocalcin and urea/creatinine ratio with placebo and GHRP-2 & TRH treatment.]

Increased Dio2 mRNA & activity in muscle of prolonged CI patients

Mebis L et al., J Clin Endocrinol Metab 2007; 92: 3330-3333

DIO2 mRNA

D2 activity (fmol/mg/min)

Healthy controls
Acutely stressed patients (elective surgery)
Prolonged critically ill patients

* NS
Dio2 is also increased in the hypothalamus during prolonged critical illness

Healthy control

Chronic illness

Mebis L et al, Crit Care 2009; 13(5):R1-10
Increased Dio2 in lung tissue in sepsis & ALI

Increased Dio2 in the liver residing macrophages

D2 mRNA in liver
After LPS treatment

Metabolism to 3,3-T2?

Chemical structures and metabolic pathways involving T3, T4, rT3, and 3,3-T2 are illustrated. D1, D2, and D3 pathways are indicated for the metabolic transformations.
But even with high doses of TH: no change in 3,3’ T2....

Debaveye Y et al, Endocrinology 2005; 146(12):5604-5611
If anything, plasma 3,3’-T2 is low during CI

<table>
<thead>
<tr>
<th></th>
<th>Critically ill patients</th>
<th>NON-Critically ill</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,3’-T2</td>
<td>6.4 (4.0-9.1)</td>
<td>14.0 (10.7-18.9)</td>
</tr>
<tr>
<td>T3</td>
<td>33.4 ± 29.4</td>
<td>84.7 ± 25.5</td>
</tr>
<tr>
<td>rT3</td>
<td>25.0 (13.9-56.2)</td>
<td>13.9 (10.9-19.3)</td>
</tr>
<tr>
<td>T4</td>
<td>5.6 ± 2.9</td>
<td>8.8 ± 2.5</td>
</tr>
</tbody>
</table>

Metabolism to 3,5-T2?

T3 → D1? → D2? → 3,5-T2 → T4 → rT3
3,5-T2 is elevated in critically ill patients

Assessed with in house developed monoclonal immunassay (Prof. Kohrle)

Langouche et al, Thyroid 2016; 26(12):1674-1680
3,5-T2 increases with worse outcome

Langouche et al, Thyroid 2016; 26(12):1674-1680
3,5-T2 inversely correlates with T3

Langouche et al, Thyroid 2016; 26(12):1674-1680
Pathways of TH metabolism

- Glucuronidation
- Sulfation
- Deiodination
- Decarboxylation & deamination

Van der Spek et al, Mol Cel Endo 2017; 458:29-38
T3-S is increased in patients with NTI

Chopra et al, JCEM 1992; 75: 189-194
T4-S is increased in prolonged critically ill patients

1 cardiovascular collapse
2 MOF with sepsis
3 MOF with SIRS
4 severe brain damage

Peeters RP et al, JCEM 2005; 90(12):6460-6465
Sulfotransferase activity is not increased during prolonged critical illness

Peeters RP et al, JCEM 2005; 90(12):6460-6465
T4-S correlates with liver D1 activity during prolonged critical illness

Peeters RP et al, JCEM 2005; 90(12):6460-6465
3-T1AM is decreased in critical illness

Assessed with in house developed monoclonal immunassay (Prof. Kohrle)

Langouche et al, Thyroid 2016; 26(12):1674-1680
3-T1AM is not related to outcome

Langouche et al, Thyroid 2016; 26(12):1674-1680
3-T1AM is independently and positively correlated with T3, not with T4 or rT3

Langouche et al, Thyroid 2016; 26(12):1674-1680
TH metabolism during critical illness:

- **T1**: 
  - **D1, D2** (↑)
  - **T4** (↓)
  - **D3** (↑)
  - **3,3'-T2** (↓)
  - **3,5-T2** (↑)
  - **rT3** (↑)
  - **3-T₁AM** (↓)

- **T4S**, **T3S**: Sulfation? Decarboxylation?
Impact of reduced nutritional intake on NTI and TH metabolism?

FASTING DURING HEALTH

TRH → TSH ≈ T4 ≈ T3, rT3

Boelen A et al. Thyroid 2012; 22:192-199
Impact of reduced nutritional intake on NTI and TH metabolism?

Total enteral energy intake (% of target)

ICU day
Partial reversal of NTI with feeding during critical illness

Mebis L, ..., Langouche L. Endocrinology 2012;153:973-984
The effect of feeding on D1 and D3 during CI

**Dio1 activity**
(pmol/mg/min)

**Dio3 activity**
(fmol/mg/min)

Control  Fed  Fasted

Mebis L, ..., Langouche L. Endocrinology 2012;153:973-984
The impact of fasting on the low T3 syndrome in human patients

EPaNIC RCT
Incomplete enteral nutrition

Early supplementary parenteral nutrition (within 24h)

Late supplementary parenteral nutrition (beyond 1 week)

N = 2312
N = 2328

Casaer M et al, NEJM 2011; 365:506-517
Fasting during human CI

Total Energy (kcal/kg/day)

- Early PN - fed
- Late PN – fasted

Casaer M et al, NEJM 2011; 365:506-517
Fasting during human CI affects NTI

Early PN – fed (n=129)

Late PN – fasted (n=123)

Langouche L et al. JCEM 2013;98:1006-1013
Changes in TH related to outcome benefit of late PN/fasting?

<table>
<thead>
<tr>
<th>Randomization to late PN</th>
<th>Likelihood for earlier alive ICU discharge [hazard ratio (95% CI)]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ $T_4$ (per nmol/L added)</td>
<td>1.417 (1.087-1.849)</td>
<td>0.01</td>
</tr>
<tr>
<td>Δ $T_3$/$rT_3$ (per unit added)</td>
<td>0.874 (0.772-0.988)</td>
<td>0.03</td>
</tr>
<tr>
<td>Δ $T_3$/$rT_3$ (per unit added)</td>
<td>1.010 (1.002-1.019)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Langouche L et al. JCEM 2013;98:1006-1013
The effect of fasting during human ICU stay

- Altered peripheral metabolism
- Infections
- Organ dysfunction
- NTI

- T3/rT3
- TRH
- TSH
- T4
- T3
- rT3

Additional central suppression

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