New insights in the pathophysiology of CRPS

Frank Huygen MD, PhD, FIPP, FFPMCAI (hon)
Department of Anesthesiology Pain Medicine
University Hospital Rotterdam
The Netherlands
Disclosure

- Member Chronic Pain executive advisory board ABBOT
- Member Change Pain Program Grunenthal EFIC (Grunenthal)
- Member RAND project (Medtronic)
- Member Editorial board "Painpractice" (Wiley Blackwell)
- Member Editorial board "Praktische richtlijnen anesthesiologische pijnbestrijding" (Tijdstroom)
- Member Editorial board "Evidence based interventional painmedicine" (Wiley Blackwell)
- Member Editorial board “Handboek pijngeneeskunde” (Tijdstroom)
- Chairman WIP Benelux section
- Vice Chair WIP examination board FIPP
- Chairman Dutch Society of Neuromodulation
- Member scientific committee EFIC Copenhagen 2017 (Chair EFIC Valencia 2019)
- Member central disciplinary tribunal for healthcare
- Financial support research programs Bsik, Zonmw, STW, Stichting Erasmusmc pijnfonds, Spinal Modulation, ABBOT, Medtronic (investigator initiated studies)
Debate pathophysiology

Central nervous system

Spinal cord

Efferent mechanisms

Bloodvessel

Afferent mechanisms

Nerve damage

Tissue damage
Inflammation

- Rubor
- Calor
- Dolor
- Tumor
- Functio laesa

Higher centers

Central nervous system

Spinal cord

Afferent mechanisms

Bloodvessel

- Nerve damage
- Tissue damage
Inflammation

Sudeck introduced the idea of inflammation

Pro

- Prospective study 829 patients
- Metabolic changes in $^{32}$P NMR spectroscopy
- Scintigraphic study: vascular leakage macromolecules
- O$_2$ radicals
- CGRP $\uparrow$

Contra

- No activation immune system
- Blood plasma levels IL-1$\beta$, IL-6, IL-8, IL-10 and TNF-$\alpha$ normal

Conflicting and only indirect evidence for inflammation

Sudeck, 1900; Veldman et al 1993; Heerschap, 1993; Oyen, 1993; Goris et al 1998; Birklein et al 2001; Ribbers, 1998; van Beek, 2001
Inflammation

- Are we looking locally enough?
Mediators of inflammation

• Artificial skin blisters in CRPS involved and contralateral extremity in patients with acute CRPS
Possible Mediators of Inflammation in CRPS

- **Cytokines:** pain, oedema, temperature
- **Neuropeptides:** pain, oedema, temperature
- **Eicosanoids:** pain, temperature

Huygen et al 2004
Ratio IL-6 and TNFα in blister fluid
N=60


Wilcoxon Signed Ranks test: P< 0.001
Cellular immune response

Which cells are involved in this inflammatory process?

- TNFα can be produced by T lymphocytes, monocytes, macrophages and mast cells
- Tryptase is a specific marker for mast cells

Deleuran et al. 1991
Mediators of inflammation released by mast cells

Huygen et al. 2004
Ratio Tryptase in blisterfluid

N=32

Huygen et al. 2004
Inflammation – confirmation in other studies

- Exaggerated expression of pro inflammatory cytokines in liquor and venous blood

- Enhanced migration injected radiolabelled leucocytes and non specific immunoglobulines towards CRPS affected locations

Autonomic disturbance

Higher centers

Central nervous system

Spinal cord

-Efferent mechanisms

-vaso/sudomotor signs and symptoms

Bloodvessel

Nerve damage

Tissue damage
Acute “warm” versus chronic “cold” CRPS

Physiological condition

Acute CRPS

Chronic CRPS

Normal efferent output

Reduced efferent output

Decreased release Norepinephrine

Denervation supersensitivity

Increased α-adrenoreceptor binding affinity

Wasner et al, 2001
Denervation supersensitivity

- Alpha receptors in biopsies of hyperalgesic skin of CRPS patients
- Systematic catecholamine levels in CRPS patients
- Injection of noradrenaline or phenylephrine (alpha adrenergic receptor agonists) increases the hyperalgesia

Drummond et al 2004; Wasner et al 1999;
Blockade of the sympathetic nerve plexus

• Blockade of the sympathetic nerve plexus proximal to the affected activity diminishes the sympathetic outflow
• However just successful in 20-30%
Endothelial dysfunction

Central nervous system

Spinal cord

Higher centers

- vasomotor/thropic signs and symptoms

Afferent mechanisms

Bloodvessel

Nerve damage

Tissue damage
Endothelial vasomotor control

• Endothelial derived vasodilators
  – Nitric oxide
  – Bradykinin
  – Endothelium derived hyperpolarizing factor

• Endothelial derived vasoconstrictors
  – Endotholine-1
  – Angiotensine-2
Endothelial vasomotor control

Endothelial cells

L-arginine $\xrightarrow{\text{ENOS}}$ NO

ppET-1 gene $\xrightarrow{\text{ppET-1mRNA}}$ ppET-1

ppET-1 $\xrightarrow{\text{FL protease}}$ Big ET1 $\xrightarrow{\text{ECE-1/-2}}$ ET1

Smooth muscle cells

sGC $\xrightarrow{\text{cGMP}}$ Vasodilatation

ET$_A$ ET$_B$ Vasoconstriction

Alonso and Radomski 2003
Endothelial vasomotor control

Endothelial cells

- L-arginine
- ENOS
- NO

Inhibition

- ppET-1 gene
- ppET-1 mRNA
- FL protease
- ECE-1/-2
- ppET-1
- Big ET1
- ET1

Stimulation

- sGC
- cGMP

Vasodilatation

Smooth muscle cells

- ET_A
- ET_B

Vasoconstriction

Alonso and Radomski 2003
Endothelial derived vascular tone modulators

- Artificial skin blisters in CRPS involved and contralateral extremity in patients with **chronic cold** CRPS
Ratio Endotholine 1 and NO in blisterfluid

N=22 Wilcoxon signed ranks test: p=0.002

N=17 Wilcoxon signed ranks test: p=0.044

Groeneweg et al. 2006
Endothelial vasomotor control

Cytokines

Endothelial cells

Stimulation

L-arginine → ENOS → NO → sGC → cGMP → Vasodilatation

Inhibition

Endothelial cells

ppET-1 gene → ppET-1mRNA → ppET-1 → FL protease → Big ET1 → ET1

Smooth muscle cells

Vasoconstriction

ET_A → ET_B
Endothelial vasomotor control

Endothelial vasomotor control involves the interaction of L-arginine and NO with endothelial cells. L-arginine is converted to NO by the enzyme NO synthase (NOS), which leads to vasodilatation through the production of cyclic GMP (cGMP). Cytokines derived from endothelial cells can also induce the expression of NOS, leading to increased NO production.

Vasoconstriction is mediated by the release of endothelin-1 (ET-1), which binds to receptors on smooth muscle cells. ET-1 is produced from ppET-1 gene, ppET-1 mRNA, and FL protease. The conversion of ET-1 to Big ET-1 is catalyzed by ECE-1/2.

Alonso and Radomski 2003
Inflammation in cold CRPS

N=15

Dirckx et al 2015
Debate pathophysiology

Central mechanisms

Central nervous system

Spinal cord

Bloodvessel

Nerve damage

Tissue damage
Central reorganisation somatosensory cortex in CRPS1

Pleger et al. 2005
Psychologic determinants

Systematic review, article search from 1980, selected 31

24 have a weak or low methodologic quality

5 prospective studies rapport no relation between CRPS1 and depression, fear, neuroticism and anger

The restrospective studies are inconclusive about the role of psychologic factors

Studies with high methodologic quality do not show any association

Life events is only factor which is possibly associated with CRPS 1

Beerthuizen et al 2009
Psychologic determinants

- Prospective study n= 585

No relation between psychologic factors and development of CRPS

Possible relation between continuing CRPS and catastrophizing

Cause  Consequence

Beerthuizen et al 2011
Genetics CRPS

- Genetic disorders (HLA-DR2) in MHC region short part chromosome 6 more often in chronic CRPS
- HLA-DQ1 significantly higher in CRPS
- Association HLA-DR13 in CRPS
- Significant association TNF2 allele in warm CRPS, homozygote in CRPS \( \geq \) 2 extremities
- Single nucleotide polymorphism within the a\(_{1a}\)-adrenoreceptor is a risk factor for development of CRPS1

Mailis et al., 1994; Kemler et al., 1999; Beek van de et al., 2000; Vaneker et al., 2002; Herleyn et al. 2010
Acquired immune

- Seropositive Parvovirus B19 IgG antibodies
- Seropositive Herpes Simplex IgG antibodies
- Increased immunoreactivity against Campylobacter Jejuni
- Increased autoantibodies against neuronal structures
- Casereports of CRPS in patients with autoimmune disease and Rubella and Hepatitis vaccination

van de Vusse et al. 2001; Gross et al. 2007; Muneshig et al. 2003; Goebel et al. 2005; Blaes et al. 2004; Vrolijk de Mos et al. Subm 2008
ANA: auto-inflammatory or auto-immune

ANA in CRPS is in the range of Rheumatoid Arthritis – auto-inflammatory diseases

Lyons et al 2005; Hooijkaas et al 2006; Dirckx et al 2015
Soluble Interleukin-2 Receptor (sIL2R)

- Level of sIL2r in serum is a value for autoinflammation, reflects T-cell activation
- Increased sIL2Rα levels in
  - lymphoid and non lymphoid malignancies
  - rheumatoid arthritis
  - sarcoidosis
- Useful in determining disease activity in CRPS?

sIL2R in CRPS patients versus healthy controls

sIL2R is first Value for Disease Activity in CRPS which can be measured in serum

Bharwani et al 2017
Pathophysiology CRPS

Higher centers

Central nervous system

Spinal cord

Central Sensitisation
- Disturbance autonomic nervous system
- Allodynia
- Dystonia

Neuropeptides
- cGRP

Nerve damage

Tissue damage
- Genetic
- Immune acquired

Inflammation
- Tumor
- Calor
- Dolor
- Functio laesa

Bloodvessel

Endothelial dysfunction

Mast cells

IL6
TNFa

sIL2R
CRPS subtypes

Inflammation

Dystonia

Treat mechanism based

Vasomotor disturbance

Neuropathic pain

Bruehl 2002c
CRPS

Other diagnoses excluded

Yes

Measure sIL2R

Inflammation

Pain/sensory disorder

Vasomotor disturbances

Motor disorder

Psychologic factors

Therapy adequate

Yes

Yes

Check Differential Diagnosis

Start active Physiotherapy

Anti-inflammatory drugs

Analgetics/co-analgetics

Vasodilators

Muscle relaxants/spasmolytics

Psychologic interventions

Consider invasive treatment

No

No

No
Thank you for your attention

University Centre for Pain Medicine Rotterdam
WWW.Erasmusmc.nl/pijn
Successful treatment of CRPS 1 with anti-TNF

Case report n =2
Infliximab 3 mg/kg i.v.
Follow up 6 weeks
Reduction inflammatory signs and symptoms of CRPS

Huygen et al 2004
A Double Blind, Randomized, Placebo Controlled Trial of Anti-TNFα Chimeric Monoclonal Antibody in CRPS

Preliminary results randomised controlled trial n=13 (6 active, 7 placebo)

Significant decrease in levels TNFa in blisterfluid at 10 weeks after treatment

Dirckx et al 2013
Immuno modulating treatment – partial confirmation in other studies (responders +/- non-responders -)

- Intravenous regional block with low dose tumor necrosis factor-alpha antibody infliximab (+)

- Treatment with subcutaneous Humira (+/-)

- Treatment with thalidomide derivate (+/-)

- Treatment with corticosteroids (+/-)

Bernateck et al. 2007; Eisenberg 2013; Schwartzman et al, 2003; Manning et al 2014; Kalita et al, 2006
NO donation

Endothelial cells

L-arginine → NO

ENOS

NO

Smooth muscle cells

Isosorbidedinitrate

sGC → cGMP

PDE-5

GMP

Vasodilatation
Vasodilative effects of ISDN in CRPS

Pilotstudy N = 5
Isosorbidedinitrate 1%
4 times daily
Follow up 10 weeks

<table>
<thead>
<tr>
<th>Week</th>
<th>CRPS fingertips</th>
<th>Contralateral fingertips</th>
<th>CRPS total hand</th>
<th>Contralateral total hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28 ± 4.5</td>
<td>30 ± 3.8</td>
<td>29 ± 3.7</td>
<td>32 ± 1.9</td>
</tr>
<tr>
<td>2</td>
<td>34 ± 1.3</td>
<td>34 ± 1.1</td>
<td>33 ± 1.5</td>
<td>34 ± 1.1</td>
</tr>
<tr>
<td>10</td>
<td>33 ± 2.1</td>
<td>31 ± 4.0</td>
<td>33 ± 1.6</td>
<td>31 ± 3.0</td>
</tr>
</tbody>
</table>

Thermographic data: mean temperature in ° Celsius ± SD in 5 patients

Groeneweg et al. 2006
Vasodilative effects of ISDN in CRPS

RCT N = 24
Isosorbidedinitrate 1%
4 times daily versus placebo
Follow up 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Isosorbidedinitrate 1%</th>
<th>Placebo</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>start</td>
<td>end</td>
<td>start</td>
<td>end</td>
</tr>
<tr>
<td>Pain intensity VAS (0-100 mm)</td>
<td>45.2 ± 15.7</td>
<td>41.8 ± 22.4</td>
<td>51.7 ± 18.9</td>
<td>43.4 ± 20.7</td>
</tr>
</tbody>
</table>

Groeneweg et al. 2009
Phosphodiesterase 5 inhibition

PDE-5 inhibitor

Endothelial cells

L-arginine → NO (ENOS)

Smooth muscle cells

sGC → cGMP → GMP

Vasodilatation

Inhibition

PDE-5 inhibitor

GMP
Vasodilative effects of Tadalafil in CRPS

RCT N = 24
Tadalafil 20 mg once daily versus placebo
Follow up 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Tadalafil</th>
<th>Placebo</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>start</td>
<td>end</td>
<td>start</td>
<td>end</td>
</tr>
<tr>
<td>Pain intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS (0-100 mm)</td>
<td>61.3 ± 14.1</td>
<td>52.3 ± 19.1</td>
<td>57.0 ± 12.1</td>
<td>56.5 ± 10.8</td>
</tr>
</tbody>
</table>

Groeneweg et al. 2008