Fats and lipid bioactives to quench the fire (inflammation)

Effects of Nutrition and Exercise on Pro-Resolving Lipid Mediators

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Key players in inflammation and its successful resolution

**Respiratory burst/degranulation/NETs**
- Digest damaged tissue
- Trap/kill invading microbes
- ↑ Cytokine release
- ↑ Eicosanoid synthesis

**Phagocytosis/antigen presentation**
- Clear tissue debris
- Clear apoptotic PMNs
- Secrete pro-inflammatory cytokines

**Non-phagocytic/pro-regenerative**
- Release anti-inflammatory cytokines
- Secrete growth factors
- Support tissue repair

**PMNs**
- Differentiation
- Polymorphonuclear Leukocytes (PMN)

**Tissue Monocyte**
- Chemotaxis

**M1 “Killer” Macrophage**
- Respiratory burst/degranulation/NETs
- Digest damaged tissue
- Trap/kill invading microbes
- ↑ Cytokine release
- ↑ Eicosanoid synthesis

**M2 “Repair” Macrophage**
- Non-phagocytic/pro-regenerative
- Release anti-inflammatory cytokines
- Secrete growth factors
- Support tissue repair
Classical roles of PUFA metabolites in the inflammatory response

Cell Membrane Phospholipids

PLA$_2$ → GLUCOCORTICOIDs

Omega-6 PUFA

Arachidonic Acid

NSAIDs

COX-1 & 2

5-LOX

Prostaglandins → ↑ PMN migration, ↑ PMN activation, ↑ Vascular permeability, ↑ Vasodilation, ↑ Pain

Leukotrienes → OMEGA-3 PUFA
Endogenous specialized pro-resolving mediator (SPM) families

<table>
<thead>
<tr>
<th>Precursors</th>
<th>Omega-6</th>
<th>Omega-3</th>
</tr>
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<tbody>
<tr>
<td>Arachidonic acid (AA)</td>
<td>Eicosapentaenoic acid (EPA)</td>
<td>Docosahexaenoic acid (DHA)</td>
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<thead>
<tr>
<th>Families</th>
<th>Lipoxins</th>
<th>Resolvins E-series</th>
<th>Resolvins D-series</th>
<th>Protectins (Neuroprotectin D1)</th>
<th>Maresins</th>
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<tbody>
<tr>
<td>Lipoxins</td>
<td>LXA₄</td>
<td>RvE1</td>
<td>RvD₁</td>
<td>PDr₁</td>
<td>MaR₁</td>
</tr>
</tbody>
</table>

### Omega-6

- **Anti-inflammatory**
  - Stop PMN transmigration and chemotaxis, brake eosinophils
  - Block prostaglandins and leukotrienes
  - Reduce cytokine release and TNF-α release actions

### Omega-3

- **Pro-resolving**
  - Non-phlogistic monocyte recruitment
  - Uptake and removal of apoptotic PMN and microbial particles by macrophages
  - Enhance anti-microbial defense mechanisms and clearance at mucosal surfaces
Effect of dietary PUFA intake on pro-resolving lipid mediators

- Human trials show that supplementation with fish oil containing a mixture of n-3 PUFA can increase blood SPM concentrations.
  - Healthy middle aged adults (Barden et al. 2014)
    - 2.4 g/day for 1 week
  - Subjects with metabolic syndrome (Barden et al. 2015)
    - 2.4 g/day for 4 weeks
  - Chronic kidney disease patients (Mas et al. 2016)
    - 4 g/day for 8 weeks

- Effects on SPM pathway monohydroxy intermediates generally far more consistent and robust than mature SPMs

EPA → 18-HEPE → RvE
DHA → 14-HDoHE → MaR
DHA → 17-HDoHE → RvD
Effect of dietary PUFA intake on pro-resolving lipid mediators

- Oral supplementation with pure n-3 PUFA in young healthy women
  - Pure n-3 EPA – 1g/day
  - Pure n-3 DPA – 1g/day
  - Olive oil (placebo) – 1g/day
Effect of dietary PUFA intake on pro-resolving lipid mediators


- Plasma concentration of the resolvin E intermediate 18-HEPE markedly increased by EPA supplementation

- RvE1 detected in fasting human plasma at ≈ 50 pg/mL
  - But no apparent increase in fasting blood with following EPA supplementation

* p<0.05 vs. pre-supplementation
# p<0.05 vs. day 7 of placebo (OO) trial
Effect of dietary PUFA intake on pro-resolving lipid mediators


- A novel resolvin metabolites of n-3 DPA (22:5 n-3) itself was detected in human plasma
  - A n-3 DPA derived analog of the known DHA derived SPM RvD5

- Supplementation with n-3 DPA (but not EPA) greatly increased plasma levels of 7,17-dihydroxy-DPA

* p<0.05 vs. pre-supplementation
# p<0.05 vs. day 7 of placebo (OO) trial
Exercise as a human model to study acute self-resolving inflammation?

Anti-inflammatory approach to the treatment of soft tissue injury

- Acute traumatic injury
  - Strains, sprains, contusions, fractures, wounds, burns, post-surgery

- Exercise induced muscle injury
  - Delayed onset muscle soreness (DOMs)
    - Muscle pain associated with unaccustomed activity (i.e. resistance exercise)

- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Oral or topical delivery

- RICE
  - Rest, Ice, Compression, Elevation
The effect of NSAIDs on the resolution of exercise-induced inflammation in humans

Pro-inflammatory Lipid Mediators

**Serum prostanoids**

- TXB$_2$
- PGE$_2$
- PGD$_2$

**Pro-inflammatory Lipid Mediators**

- TXB$_2$
- PGE$_2$
- PGF$_{2\alpha}$
- PGI$_2$

**Synthases**

- COX-1 & 2

**Arachadonic Acid**

**Markworth et al. 2013. Am J Physiol Regul Integr Comp Physiol.**
Specialized Pro-Resolving Mediators

**Serum resolvins**

- **n-3 EPA**
  - CYP450
  - 15-LOX
- **n-3 DHA**
  - 17-HDoHE
  - 18-HEPE
  - 5-LOX
- **Resolvin E1**
- **Resolvin D1**

- ↓PMN function and recruitment
- ↓Inflammatory cytokines
- ↑ΜΦ phagocytosis of PMNs
- ↑Monocyte chemotaxis
- ↑M2 macrophage polarization

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Impairs muscle recovery

Current and Ongoing Studies

- **Cold Water Immersion**
  - Delays recovery
  - Impairs muscle gains

- **Hot Water Immersion**
  - Analysis in progress

- **Arachidonic Acid Supplementation**
  - Alterations in SRMs
  - Post-exercise actions
    - SRMs
    - Inflammation and recovery
Implications and future directions

- Anti-inflammatory vs pro-resolving therapeutics for the treatment of soft tissue injury
  - Dietary or supplemental n-3 PUFA?
  - Native SPMs/SPM drug analogs?
  - Cold vs heat application following soft tissue injury?

- Do peripheral tissue cells (myocytes, adipocytes, fibroblasts etc.) participate in SPM biosynthetic circuits?
  - Transcellular biosynthetic routes with invading immune cells?

- Do SPMs play direct roles in soft tissue remodelling independent of their immunomodulatory effects?
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