Anti-Inflammatory medications: Drugs that poison the gut

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Learning objectives

Global learning objective
You will be able to appreciate the particular importance of efficacy vs. side effects in the treatment of gastrointestinal inflammation and name examples.

Individual learning objectives

Knowledge
You can discriminate acute vs. chronic inflammation
You know the main categories of anti-inflammatory drugs
You can explain the special situation of the gut and why the delicate balance of its microbiota is of particular importance
You are able to name (a) chronic inflammatory bowel disease(s) and can give examples of therapeutic drugs with their effect(s) and side-effect(s), as well as novel, alternative strategies

Relevance
-chronic inflammation is always pathological
-some are widely used
-side effects often in GI
-nutrition, infection, well-being
-chronic inflammation
-increasing importance in developed countries
-personalized therapy
Content

• Inflammation: acute vs. chronic, morphological patterns
• Categories of anti-inflammatory drugs
• Examples of inflammatory disorders in the GI tract and their treatments
• Inflammatory bowel diseases: a challenge for successful therapy with acceptable side-effects.
• The dilemma with GI disorders and drugs that poison the gut: some statements

Inflammation

“rubor calor tumor dolor”

Acute vs. chronic inflammation

Acute inflammation:
- initial response to harmful stimuli
- edema (exudation of blood plasma)
- recruitment of leukocytes in response to inflammatory mediators released by resident macrophages, dendritic cells or mast cells (cytokines, chemokines, histamines, leukotrienes, prostaglandins)
- hyperalgesia (bradykinine, histamines, substance P)
- acute phase proteins (e.g. CRP, complement factors)
- coagulation/fibrinolysis
- complement, antibodies, T cells (DTH)

Aims: fight/eliminate “aggressor”, warn the host, initiate wound healing/tissue repair
**Inflammation**

*Chronic inflammation:*
- Persistence of injurious agent -> inflammation cannot resolve
- "Chronic wound"
- Immune attack against “self” (autoaggression/autoimmunity)
- Dominant presence of macrophages
- Granuloma formation
- Mostly accompanied by tissue destruction
- **Chronic inflammation is always pathological**

Common root of:  
- degenerative diseases  
- perpetuating diseases  
- chronic pain

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**Morphologic patterns of inflammation**

- Granulomatous inflammation (e.g. tuberculosis, tuberculous leprosy, Crohn’s disease)
- Fibrinous inflammation (scars)
- Purulent inflammation (pus, abscesses)
- Serous inflammation (e.g. skin blisters)
- Ulcerative inflammation: epithelial damage leads to exposition of lower layers -> excavation, ulceration (e.g. Ulcerative colitis)
- Destructive inflammation: tissue lesions (e.g. lepromatous leprosy), fistulization (Crohn’s disease)
Categories of anti-inflammatory drugs

- NSAIDs (non-steroidal anti-inflammatory drugs)
  - Relieve pain, reduce swelling and fever, may inhibit coagulation
  - Inhibition of cyclooxygenase 1 and/or 2 -> inhibition of prostaglandins
  - Most prominent representatives are Aspirin or Ibuprofen
- Aminosalicylates (e.g. 5-ASA), related to NSAIDs
- Antihistamines (block histamin receptors -> prevent allergic reactions)
- Steroids
  - Endogenous steroids: cholesterol, corticosteroids, sexual hormones
    (most prominent representative is cortisone)
  - Potent immunosuppressive as well as anti-inflammatory effects
- Immunosuppressants
  - Cytostatics
  - Calcineurin inhibitors
- Biologicals
  - Antibodies that neutralize/inhibit pro-inflammatory signalling
- Antibiotics, pre-/probiotics

Action of NSAIDs (simplified)

- Selective COX-2 inhibitors theoretically desirable but practically often not very effective
Main anti-inflammatory effects of corticosteroids

Corticosteroids (or simply “steroids”)

- Lipocortin-1 synthesis
- Suppression of phospholipase A2
- Inhibition of pro-inflammatory cytokine production
  - (Induction of T cell apoptosis)
- Inhibition of leukocyte inflammatory events
  - (inhibition of NO-synthetase)
- Inhibition of prostaglandin + leukotrienes

* - inhibition of NF-κB and AP-1
  - induction of IκBα
  - ... many promoter regions with glucocorticoid responsive elements (GRE), negative GRE (nGRE)

Downside:
- Weakening of the immune system -> enhanced risk for (secondary) infection or reactivation of latent infections
- Other side effects due to interference with endogenous cortisol homeostasis
  -> more research needed to better understand and refine steroidal therapy (reduce side effects)

Examples of inflammatory disorders of the GI tract

1. Esophagitis
2. Gastritis
3. Duodenitis
4. IBD (Crohn’s disease, ulcerative colitis)
5. IBS
6. Celiac disease
7. Diverticulitis
The special situation in the GI tract

- The GI tract represents a huge surface which is constantly exposed to a complex microbiota.
- Each individual has its “personal” composition of the microbiota.
- Towards the distal part of the intestine, we find the densest microbial populations on the planet.
- This dense microbiota is separated from sterile tissues by a single layer of epithelial cells covered with mucus.
- A great challenge is the absorption of nutrients while keeping microbes at bay.
- Symbiotic mutualism has evolved between the host and its microbiota.
- This commensalism is in delicate balance between tolerance and prevention of infection while maintaining physiologic function.
- In this delicate balance, it is easy to imagine that drugs intended to treat a problem are likely to create another one.

1. Esophagitis

- Gastroesophageal reflux disease (GERD)
  - incompetence of the lower esophageal sphincter
  - may lead to Barrett’s esophagus
  - therapies mostly aimed at prevention/reduction of reflux
    - antihistamines (improvement in about 50%)
- Candida esophagitis
  - yeast C. albicans spreads from mouth down to esophagus
  - sign of a weakened immune system
  - may result from inhalation of corticosteroids
  - antifungal therapy
  - pain relieve (NSAIDs)
2. Gastritis/peptic ulcer disease

- Gastritis
  - inflammatory changes in the gastric mucosa
- Peptic ulcer disease (PUD)
  - discrete mucosal defect in gastrointestinal tract exposed to acid and pepsin (stomach + proximal duodenum)
- Same causes: H. pylori, smoking, alcohol, stress, NSAIDs
- Main therapies:
  - Proton pump blockers, acid reduction
  - H. pylori eradication: antibiotics + proton pump blockers

3. Duodenitis

- Similar risk factors as for gastritis/PUD
- Often infections with salmonella, shigella, viruses or amoeba (Giardia)
- Main therapies:
  - avoidance of NSAIDs
  - antibiotics
4. IBD

a.) Crohn’s disease

- Idiopathic disease, can affect all parts of the GI
- Multifactorial etiology:
  - genetic predisposition
  - microflora/dysbiosis
  - dysregulated immune response
  - infection (?)
  - environment
- Transmural, discontinuous (skip areas)
- Many disease phenotypes:
  - depending on location
  - pure inflammatory (mild)
  - complicated (stricturing, penetrating)
- Frequent extraintestinal manifestations
  - skin rashes
  - arthritis
  - inflammation of the eyes
- Not curable so far

Crohn’s disease: general aspects regarding therapy

- Requires individual therapy with frequent adjustments, often combinations
- Main goals of therapy:
  - control symptoms
  - maintain remission
  - prevent relapse
- Three main groups of medications:
  - Anti-inflammatory drugs
  - Immunosuppressants
  - Biologicals
- Main problems:
  - Adverse effects (e.g. with cytostatics)
  - Therapy resistance
  - Excessive use of pain killers may harm the GI tract and lead to addiction
**Crohn’s disease: Anti-inflammatory drugs**

1. **Aminosalicylates:**
   - 5-aminosalicylates (5-ASA) or Salazosulfapyridin
   - Interference with:
     - Leukotrienes
     - Pro-inflammatory interleukins
     - Their receptors
     - Free oxygen radicals
   - 5-ASA is normally well tolerated but shows little effect in Crohn’s disease.
   - Salazosulfapyridin used with left sided colon affection but not with ileitis.
   - Frequent side effects such as nausea, abdominal pain and skin rashes.

2. **Cannabis-derived drugs:**
   - Anti-inflammatory
   - Tissue healing

**Crohn’s disease: Immunosuppressants**

1. **Cytostatics:**
   - Azathioprine, 6-Mercaptopurine (6-MP), Methotrexate (MTX)
   - Interference with:
     - T and B cell proliferation
     - DNA-synthesis (-> proliferation in general)
     - Cell proliferation by antagonizing folic acid
   - Frequent drug intolerance e.g. severe leuko- erythro- and thrombopenia.
   - Generally affect cells with high proliferation rates. Hepatotoxicity.

2. **Steroids:**
   - Synthetic corticosteroids (Budenoside, Prednisone)
   - Hydrocortisone (indicated with severe attacks)
   - Side effects and problems as discussed before
**Crohn’s disease: Biologicals**

1. **Anti-TNF antibodies:**
   - Infliximab (chimeric)
   - Adalimumab (fully humanized)
   - Certolizumab (pegylated Fab’ fragment)
2. **Soluble TNF receptor-IgG fusion protein**
   - Etanercept
3. **Anti-alpha4 integrin antibody**
   - Used in therapy-resistant patients
   - Maintenance of remission
   - It is currently discussed, whether anti-TNF therapy may prevent disease exacerbations when used early after first diagnosis

**Side effects and concerns:**
- May reactivate latent infections
- Generation of anti-antibodies may lead to loss of efficacy
- Allergic reactions including anaphylaxis may occur with Infliximab

**Mechanism of anti-TNF therapy not completely understood:** neutralization of TNF vs. induction of activation-induced cell death vs. antibody-mediated cytotoxicity vs. inhibition of inflammatory cell migration ... how does it lead to the rapid healing of fistulae?

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**Crohn’s disease: Other treatments**

1. **Opioid receptor antagonist:**
   - Naltrexone (clinical trial -> 67% remission!)
2. **Antibiotics**
   - Hygiene hypothesis vs. infectious origin?
3. **Probiotics, fecal transplantation (see 6.)**
   - Shift of “unhealthy” microbiota -> hygiene hypothesis
4. **Helminths**
   - Unbalanced helper T cell (Th) balance, i.e. lack of Th2 experiences -> hygiene hypothesis
5. **Thalidomide:** Potent anti-inflammatory and immunosuppressant. Successful in clinical trials with therapy-refractory patients. May be used as bridge therapy. May lead to peripheral neuropathies upon long term usage.
6. **Fecal transplantation:** Stunning results in some donor/recipient combinations!

-> Much more research efforts are needed to better understand how the current therapies work, to better cope with side effects, to determine individual needs to improve medical schemes or come up with novel therapeutic strategies.
4. IBD  

b.) Ulcerative colitis

- Idiopathic disease, affects colon
- Multifactorial etiology:
  - genetic predisposition
  - microflora/dysbiosis
  - dysregulated immune response
  - infection
  - environment
- Affects mucosa
- Continuous
- Rare extraintestinal manifestations
- Colectomy "cures" the disease

Ulcerative colitis

- Major differences compared to treatment of Crohn’s disease:

  **Anti-inflammatory drugs**
  - 5-aminosalicylates (5-ASA) more effective for treatment and maintenance of remission in ulcerative colitis than in Crohn’s disease
  - Calcineurin inhibitor (Tacrolimus) is in clinical trials and shows promising results in patients refractory to conventional therapy including steroids or even anti-TNF. However, side effects including hypertension and gastrointestinal disturbances are frequent.

  **Immunosuppressants**
  - Adrenocorticotropic (ACTH) hormone to stimulate adrenal gland to produce glucocorticoids

  **Biologics**
  - Mainly use of Infliximab
Complex diseases such as IBD need a lot more research to improve therapy


Anti-inflammatory actions of phosphatidylinositol.
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Abstract
Chronic inflammatory T-cell-mediated diseases such as inflammatory bowel disease (IBD) are often treated with immunosuppressants including corticosteroids. In addition to the intended T-cell suppression, these farmacons give rise to many side effects. Recently, immunosuppressive phospholipids have been proposed as less-toxic alternatives. We aimed to investigate the immunoregulatory capacities of the naturally occurring phospholipid phosphatidylinositol (PI).

Systemic PI treatment dramatically reduced disease severity and intestinal inflammation in murine 2,4,6-trinitrobenzene sulfonic acid (TNBS) colitis. Moreover, PI treatment inhibited the inflammatory T-cell response in these mice, as T cells derived from colon-draining LN of PI-treated mice secreted less IL-17 and IFN-γ upon polyclonal restimulation when compared to those of saline-treated mice. Further characterization of the suppressive capacity of PI revealed that the phospholipid suppressed Th cell differentiation in vitro irrespective of their cytokine profile by inhibiting proliferation and IL-2 release. In particular, PI diminished IL-2 mRNA expression and inhibited ERK1, ERK-2, p38- and JNK-phosphorylation. Crucially, PI did not ablate Treg differentiation or the antigen-presenting capacity of DCs in vitro. These data validate PI as a pluripotent physiological immune suppressant.

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5. IBS (irritable bowel syndrome)

- Functional bowel disorder of unclear bowel origin (sometimes post-infectious)
- Chronic abdominal pain, discomfort, and alteration of bowel habits without detectable organic cause.
- Hypersensitivity to certain stimuli
- Disorder of the interaction between brain and GI (?!)
- Increased anti-flagellin antibody prevalence (Schoepfer et al. 2008)

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<thead>
<tr>
<th>Anti-inflammatory drugs</th>
<th>Probiotics</th>
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<tbody>
<tr>
<td>No effect in post-infectious IBS so far</td>
<td>Have anti-inflammatory capacity and show some beneficial effects</td>
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6. Celiac disease (Sprue)

- Autoimmune disorder of the small intestine
  - chronic diarrhea
  - growth retardation
- Villous atrophy ("flattening" of mucosa)
- Caused by immune reaction against gliadin (prolin-rich sequence of gluten) in wheat
- Tissue transglutaminase modifies gluten -> T cells cross-react with small-bowel tissue -> inflammatory reaction
- Avoidance of gluten "cures" the disease

In rare cases, no improvement on gluten-free diet:
-> Steroids and other immunosuppressants

7. Diverticulitis

- Diverticulitis develops from diverticulosis
- Pouches (diverticula) form on the outside of the (sigmoid) colon due to pressure
- Diverticulitis results if diverticula become inflamed

Initial episode -> broad spectrum antibiotics
Recurrent acute attacks or complications -> surgery
**“Drugs that poison the gut”: Leaky Gut Syndrome**
(http://www.leakygut.co.uk)

**NSAIDS** (Non-Steroidal Anti Inflammatory Drugs) are pain relief medications that are said to increase intestinal permeability by damaging the villi in the intestine and blocking prostaglandins that would stimulate tissue repair.

**Steroids** suppress the immune system, kill ‘friendly’ bacteria, cause the proliferation of fungal infections in the gut, all of which contribute to the development of a leaky gut.

**Cytotoxic** drugs kill bad cells as well as good cells.

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**Summary**

- Inflammatory reactions in the GI tract show many phenotypes and there are numerous ways how to interfere with inflammation.
- Of the most challenging diseases are the inflammatory bowel diseases, particularly Crohn’s disease:
  - individual (complicated) patterns of disease manifestations ask for personalized therapy
  - frequent revision of therapy
  - anti-inflammatory
  - immunosuppression
  - biologicals
  - antibiotics, pre-/probiotics
  - leukapheresis
  - ... and combinations
- Intestinal homeostasis = delicate balance -> high risk for adverse reactions
  (NSAIDs can cause same symptoms as those intended to cure!)
- Cooperative efforts of basic and clinical research are needed to improve safety and efficacy of current therapies, as well as to reveal novel patho-mechanisms which can be addressed with future therapies.