Mechanism of delayed drug hypersensitivity – allergy versus tolerance

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1. Mechanism of drug hypersensitivity

2. Mechanism of «tolerance» to drugs
Drug hypersensitivity: MECHANISM

It`s all about drug binding to proteins: how & where

How
Covalent or non-covalent

Where
Immune receptor or not
Immune reactions to drugs *how and where*

**Covalent**
- sharing of electron pairs between atoms
- Stable complex, not easily reversible, drug-protein "adduct"
- modified protein = antigen

**Non covalent**
- Electrostatic, OH, van der Waal ...
- π–effects
- Hydrophobic effects
- labile, reversible drug-protein complex
- Immune receptor (HLA, TCR, Ab) or not (e.g. albumin)
**Traditional view** on immune reactions to drugs:

- DHR to drugs are due to antigen formation
- Only **covalent**-bonds can generate new antigen and → allergy
- **non-covalent** is irrelevant, as such drug-protein complexes are ignored

→ **Contact dermatitis**
Contact dermatitis ≠ systemic drug hypersensitivity

Contact dermatitis

- restricted, localized (contact) aerea,
- local inflammation

Covalent (hapten)

generalized, systemic
Non-covalent!
Classification of DHR based on drug binding to proteins

**Allergy**

*amoxicillin*

**Pharmacological-Immune (p-i)** (TCR, HLA & Ab)

**Pseudo-allergic** (e.g. MasRPGPRX2)

**P-i**

*carbamazepin*

**Pseudo-allergic**

*ciproxoflaxacin*
**Classification of DHR based on**

**a)** how do drugs bind to proteins &

**b)** to which proteins (IMMUNE RECEPTOR OR NOT)

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**Type A**

- Allergic/immune

**Type B = DHR**

- Pseudo-allergic

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**Covalent:**
- Formation of a new antigen;

**Pharmacological** *(non-covalent)* interaction with immune receptors (HLA, TCR) or preformed IgE or IgG antibody/CDR.

**IgE:** Anaphylaxis, urticaria
**T cells:** MPE
**IgG:** Haemolytic anaemia, immun-complex d.

**Complete T cell responses:**
- MPE, DRESS, SJS/TEN, AGEP, hepatitis

**Preformed IgE or IgG:**
- Anaphylaxis, blood cell dyscrasias

**MRPGPRX2/Mast cells**
- anaphylaxis/urticaria
**Cyclooxygenase ↓ / Leukotriens ↑**
- bronchospasm, asthma, urticaria
**Bradykinin ↑:** angioedema
NOT THE DRUG, BUT ITS INTERACTION WITH PROTEIN (A-P-P) DETERMINES THE CLINIC

amoxicillin

[Chemical structure of amoxicillin]

Hapten / Covalent Antigen / Allergy

T cell to cipro

DRESS

IgE to cipro

(Urticaria/Anaphyl)

p-i

(TCR, HLA & Ab)

Pseudo-allergy

(e.g. MasRPGPRX2)

mast cell degranulation

MasRPGPRX2

(Urt/Anaphylaxis)

Activated mast cell
Traditional view on immune reactions to drugs:

- DHR to drugs is due to antigen formation
- Covalent is «bad», as stable bonds can generate new antigen
- Non-covalent is irrelevant, as such complexes are ignored

New view on immune reactions to drugs:
How & where the drug binds to protein determines the clinic (allergy – p-i - pseudoallergy)

- Covalent: Antigen formation with allergy or silent immunity
- Non covalent (pharmacological) interactions can cause DHR, if the drug binds to immune receptors (p-i: peptide binding region of HLA or TCR, or of preformed antibodies)
- Pseudo-allergy: various interactions with effector mechanism wø immunity
Mechanism of delayed drug hypersensitivity – allergy versus tolerance

1. Mechanism of drug hypersensitivity
2. Mechanism of «tolerance» to drugs
   - Ignorance
   - Anergy
   - asymptomatic Immunity
   - Tolerance s.s.
   - Non-responsiveness
“Tolerance” (various tolerance mechanism)

Ignorance
Anergy (asymptomatic)
Immunity
Tolerance (s.s.)
- central
- peripheral
Non-responsiveness

no reaction at all
missing second signal
(no reaction, T-cells)

asymptomatic reaction

Deletion of reactive cells: thymus
active suppression of reactivity:
peripheral T cells (T reg)

effector mechanism: no reaction at
tolerized concentration (MC, basophils)
Ignorance

common / >98% of drug therapies:
no interference drug - immune system

Most small molecules (drugs) are not haptens*
They do not bind by covalent means to proteins
The drugs may bind by non-covalent bindings (electrostatic, van der Waal, hydrogen...) to proteins like albumin, transferrin, ...): transient, labile
→ NO ANTIGEN
The drug is not interacting with immune receptors (HLA, TCR or CDR of preformed antibodies): IGNORANCE

*) if they develop hapten-features during metabolism, the haptens are immediately detoxified (liver)
Anergy

• The drug/metabolite is able to form **covalent** bonds (hapten) (stable, not reversible, NEW ANTIGEN)

• A {hapten/drug – protein} complex forming an antigen is not sufficient for immune-stimulation

• Immune reaction depends on costimulation / danger signals
  
  • If no costimulation: no immune reaction
  • If costimulation: silent immunity
  • If danger signals high: symptomatic immunity (contact dermatitis)
Anergy: beta-lactams (hapten, covalent)

After 7-10d therapy with beta-lactam like amoxicillin: albumin, transferrin, immunoglobulins etc. show hapten-modification (in everybody)

50%
No antibodies*

50%
IgG antibodies

BOTH NO SYMPTOMS

Albumin with beta-lactam binding sites (covalent bonds)

No antibodies: Too low costimulation?

Antibodies: Hapten-antigen formation is not automatically damaging; → «tolerance»

Anergy $\gg$ asymptomatic Immunity (hapten, covalent)

a) **Anergy**
   - No immune reaction
   - Insufficient costimulation?
   - No symptoms

b) **Immunity**
   - IgG
   - Dose dependent effect?
   - No symptoms

Many open questions...
“Tolerance”

- Ignorance
- Anergy
- asymptomatic
- Immunity
- Tolerance (s.s.)
  - central
  - peripheral
- Non-responsiveness

- no reaction at all
- missing second signal (no reaction, T-cells)
- asymptomatic reaction
- Deletion of reactive cells: thymus
- active suppression of reactivity: peripheral T cells (T reg)
- No effector mechanism: no reaction at tolerized concentration (MC, basophils)
Abacavir model*

- **All** B*57:01+ individuals are stimulated in vitro by abacavir (CD8+ T cell response)
- But only **55%** of abacavir exposed, B*57:01+ individuals develop severe drug hypersensitivity reactions (DHR)
- 45% of abacavir exposed are tolerant!
  - Therapy of B*57:01+ mice with abacavir
    - Induces a transient CD8+ T cell reactivity (histology, in vitro)
    - fails to induce abacavir DHR – they are tolerant
  - CD4+ T cells eliminated / DC function impaired: B*57:01+ mice develop «DHR like disease». CD4 / DC mediating tolerance (?)

Abacavir model*:

• **All** B*57:01+ individuals are stimulated in vitro by abacavir (CD8+ T cell response)
• But only **55%** of abacavir exposed develop severe drug hypersensitivity reactions (DHR) –
• **45%** of abacavir exposed are tolerant!

- In carbamazepin-B*15:02 exposed individuals **97%** of exposed do **not** react / are tolerant (SJS/TEN);
- In flucloxacillin-B*57:01 **99,8%** do **not** react / are tolerant (hepatitis)

Abacavir model*: CD4/DC mediated control of CD8 cells

- **All** B*57:01+ individuals are stimulated in vitro by abacavir (CD8+ T cell response)
- But only **55%** of abacavir exposed develop severe drug hypersensitivity reactions (DHR) –
- 45% of abacavir exposed are tolerant!

- **B*57:01/tg mice**: Therapy with abacavir
  - Induces a transient CD8+ T cell reactivity (+ histology, CD8 in vitro)
  - fails to induce abacavir DHR – they are tolerant
- CD4+ T cells eliminated / DC function impaired: B*57:01+ mice develop «DHR like disease». CD4 / DC mediating tolerance (?)

“Tolerance”

- **Ignorance**
  - no reaction at all
- **Anergy**
  - missing second signal (no reaction, T-cells)
- **Immunity**
  - asymptomatic reaction
  - Deletion of reactive cells: thymus
- **Tolerance (s.s.)**
  - active suppression of reactivity: peripheral T cells (T reg)
  - - central
  - - peripheral
- **Non-responsiveness**
  - No effector mechanism: no reaction at tolerized concentration (MC, basophils)
Natural and acquired «unresponsiveness» of effector mechanism (MC) in DHR

• Many individuals have IgE to drug-protein adducts but do not show clinical symptoms upon drug exposure
• The same with protein allergens (pollen): «sensitized» (IgE+/clinic-) => «allergic» (IgE+/clinic+)
• Allergic patients have a failure in this MC-unresponsiveness (→ they react)
• This unresponsiveness is a antigen-specific process in FceRI+ cells (mast cells, basophils): block calcium flux, reduces antigen/IgE/FceRI complex-internalization and prevents the acute and the late-phase reactions as well as mast cell mediator release
• This unresponsiveness is a natural process in sensitization and can be re-introduced by desensitization (transiently)
IgE mediated Hypersensitivity

Mast cells carry drug specific IgE, but do not react to the drug in vivo

Day 7-10

Pichler WJ. Allergy. 2020 Aug 11.
Why no reaction?

1/2020: A 35yr old patient receives a 10d therapy with amoxicillin/clavulanic acid (3x625mg) without problems.

1/2021: he receives again amoxicillin/clavulanic acid;

After first dose he develops anaphylaxis within 20 min: malaise, bronchospasm, urticaria

Allergic work up: i.d. ++ / BAT + (amoxicillin)
Sensitization

1) In initial sensitization by a gradual increase of IgE.

Desensitization (therapeutic)

2) In therapeutic desensitization by a gradual increase of antigen.

Mast Cell (MC) unresponsiveness by antigen-IgE-complexes and Fc-IgE-RI-cross-linking is induced.
“Tolerance” (various tolerance mechanism)

**Ignorance**
- no reaction at all
- missing second signal
- (antigen present, no reaction)

**Anergy**
- asymptomatic reaction (IgG)

**Immunity**
- Deletion of reactive cells: thymus?

**Tolerance (s.s.)**
- central
- peripheral

**Non-responsiveness**
- active suppression of reactivity:
  - peripheral T cells: CD4/DC?
- Unresponsiveness of effector mechanism
  - MC, basophils) at tolerized concentration
Conclusion I: DHR-mechanism

It`s all about drug binding to proteins:

How: covalent

or

& not covalent

Where: immune receptor (HLA, TCR, antibody (CDR)) (→DHR)

or

not immune receptor (→ignorance)

Based on drug-protein binding on can distinguish DHR:

allergic (rare)

p-i (dominant) &

pseudoallergic (frequent)
Conclusion II: Mechanism of «Tolerance»

• «Tolerance» is the «normal», physiological response to most drugs, including haptens

• There are various possibilities to induce «tolerance» of drugs (ignorance - anergy - asymptomatic immunity – tolerance - non-responsiveness); these mechanisms are only partly understood

• Induction of non-responsiveness is the only tolerance mechanism, which is used therapeutically (desensitization of IgE mediated DHR or food allergy)
Thank you for your attention

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Non-covalent links: electrostatic, hydrogen, π, van der Waals...

Covalent links: lysin with open beta-lactam ring

USUAL DRUG PROTEIN (RECEPTOR, ENZYME..) BINDING: «PHARMACOLOGY»
IgE-mediated Hypersensitivity

Rapid Degranulation to non-covalent drug-protein complexes (fake antigen)*

Sensitization
days
no symptoms

Re-exposure
minutes
Urticaria, anaphylaxis, etc.

*Pichler WJ. Allergy. 2020 Aug 11.