Limitations and possibilities of animal models for human allergenic risk evaluation

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State of the art

• An animal model for food allergy should mimic human disease giving rise to relevant symptoms upon challenge

• Is this possible in relation to risk evaluation?
What we don’t know about sensitisation to food allergens in humans

- Route – oral, dermal, respiratory
- Dose response relations
- Frequency of exposure
- Role of digestion
- Role of infection
- Bystander effect of other allergens
- Tolerance induction
- Tolerance to cross-reacting allergens

Design a test system with few animals that predict sensitisation
What are the consequences if predicitive tests need to mimic human disease?

• Elicitation of symptoms require high IgE responses

• High IgE responses require
  – The use of adjuvant
  – And/or a route that is not oral
    • Bypasses the digestive system
    • Can only test extracts or pure proteins
    • Relevance of dose?

• Interpretation of results difficult in relation to risk assessment
Predictive tests for chemical contact sensitisation
The only allergy tests where there are international guidelines

History
Guinea pig maximisation test mimic human disease

Sensitisation - FCA
Elicitation – Finn chambers
Mechanisms of skin sensitisation

Dose-response relation

Concentration/cm²

Potency

Fig. 8 Main steps in the mechanism of skin sensitisation induction. The numbers correspond to the steps described in the text. (1) Skin bioavailability, (2) haptenation, (3) epidermal inflammation, (4) DC activation, (5) DC migration, (6) T-cell proliferation. This figure contains elements of an image in the public domain from the National Cancer Institute

Adler et al. 2011
LOCAL LYMPH NODE ASSAY

Test/vehicle 25 µl

Day 0,1,2

Day 5

3H TdR

5 HOURS

Measures sensitisation, only

Make cell suspension – measure 3H Thymidine
LOCAL LYMPH NODE ASSAYS

**DNCB**

- **Concentration (%w/v)**: 0, 0.05, 0.1, 0.25
- **Stimulation Index**: 0 - 25

**PABA**

- **Concentration (%w/v)**: 0 - 10
- **Stimulation Index**: 0 - 25

**DNCB**

- Shows a linear increase in stimulation index with increasing concentration.

**PABA**

- Shows no significant change in stimulation index with increasing concentration.

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Ian Kimber
Predictive tests for food allergens measuring sensitisation only?

Sensitisation
- Specific serum IgE
  - Functionality of IgE (RBL assay, PCA)

Oral route
- ‘Natural foods’
- No adjuvant
- Animals on a diet free from allergen or cross-reacting allergens

Dose-response relations
Evaluation of **risk** is dependent on knowledge of dose/response relations
Food allergens are major constituents of their ‘parent’ food

• Implication for sensitisation?
  – In chemical contact allergy the dose that sensitises is larger than the dose that may elicit reaction

• Implication for risk assessment?

• Exceptions?
  – LTP’s
  – Wheat alpha-amylase inhibitor
    – Extremely resistant to proteolysis
Conclusion I

• It is currently not possible to include dose/response relations in the interpretation of sensitisation studies

• Consequences
  – Hazard identification – possible sensitiser (oral)
  – Risk characterisation - ?
Animal models measuring sensitisation
Examples of use

- Digestibility and sensitisation
- Matrix effects
- Properties of related allergens
- Tolerance
- Processing
- Epitope mapping
Sensitisation – what is important?
Protein?     Matrix?     Processing?

Peanut
43% fat
29-42 mg/g
Ara h 1

Hazelnut
54% fat
7-16 mg/g
Cor a 11

Soy
18% fat
96-114 mg/g
Gly m 5

Pea
1% fat
3-36 mg/g
Pis s 1

7 S globulins
All 4 7S are labile to digestion
Day 0
Day 0

Day 14
Day 14

Day 28
Day 28

Day 35

100 µg 7S per rat

100 µg 7S per rat

100 µg 7S per rat

Day 0

100 µg 7S per rat

Day 14

100 µg 7S per rat

Day 28

100 µg 7S per rat

Day 35
Sensitisation studies with purified 7S globulins

F0 = Soy free diet contaminated with soy
1-25 µg soy/g diet
Sensitisation studies with purified 7S globulins

F0 = Soy free diet contaminated with soy
F1+F2 = Soy free diet WITHOUT soy contamination
Rat Basophilic Leukaemia cell assay

IgE

Kroghsbo et al. 2011
Conclusion II

• I.p. studies may be used to make comparisons, but care should be taken what to compare (no digestion involved)

• Oral studies without adjuvant can be used to study
  – Whole foods (extracts may be misleading)
  – Processing
  – Matrix effects
  – Limitations because of relatively low IgE response

• Tolerance may heavily influence the quality of the response

• Lack of knowledge on dose-response relations limit results to predict hazard

• This makes it impossible to estimate risk
Thank you (-;

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