Drugs 101

Allergy

Adverse reaction to harmless material

- body creates a situation

Allergy requires prior exposure

- Immune system responds to something
  - Epitopes of molecules from pathogens
- Immune system “remembers” that material
  - Memory cells
- Subsequent exposure produces reaction
  - Protection from pathogens
  - Allergy to harmless material
    - makes you become ill rather than protecting you

Allergic rhinitis – Hay fever

Hay fever is a reaction to pollen

- response to particular particle on pollen

Cold-like symptoms

- treat allergies like a cold
- similar medications
    - cross-treat with meds

Some people get a geographic tongue

- swelling of the tongue

Atopic dermatitis from surface exposure

- inflammation of the skin
    - rash
- common on face, back

Contact dermatitis from irritants

- Hand washing makes it worse
- Common with industrial powders

- not response to chemical itself, but reaction to the abrasion

Exposure to large amounts of powder

- ie. sand has dermititis listed on fact sheet
    - also listed as carcinogen
        -breathing in

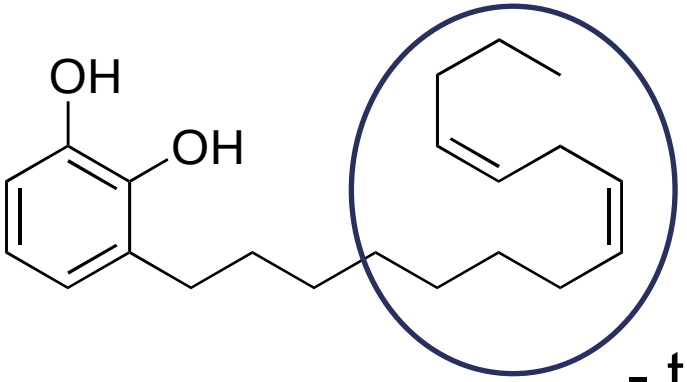
Contact dermatitis from immune reaction

- typically response to a chemical
    - poison oak, poison ivy
        - not everyone reacts to them

Immune reactions at the site of contact

- blisters
    - caused by immune system, not the chemical material

Urushiol produces the reaction



- poison oak, ivy, many others

- this chain varies

Latex from rubber tree sap

- increasing allergy to latex
- natural latex produces immune response
    - not man made rubber

Latex gloves and condoms

Nickel is a common allergen

- 17% of women
- 3% of men

are allergic

Nickel alloys are common

- very common in many alloys (used to make metals stronger)

Many piercings made of stainless steel

- stainless steel often contains some nickel

Allergies to henna tattos on skin

Dust allergies are common

- dust primarily made of skin flakes
    - humans constantly shed skin
- allergy is not to skin, but the feces of the dust mites that live on the dust

Dust mites love mattresses

- over time mattresses will gain weight as they accumulate dust mite feces

Mattresses can contain large amounts of droppings

Allergies to pets

Most reactions are to pet saliva

- from cleaning selves
- proteins from saliva dry out and flake off

Mold and fungi produce many allergies

- most potent carcinogens found in mold and fungi

Mold can be a serious problem

- creates strong immune reactions

Food can give allergy or intolerance

- Allergy (more dangerous)
  - Immune system reacts to the food
- Intolerance (more of an annoyance)
  - Substances in food produce adverse reaction
    - ie something in food body doesnt like

Food intolerance affects about 30 % of adults

- fairly common

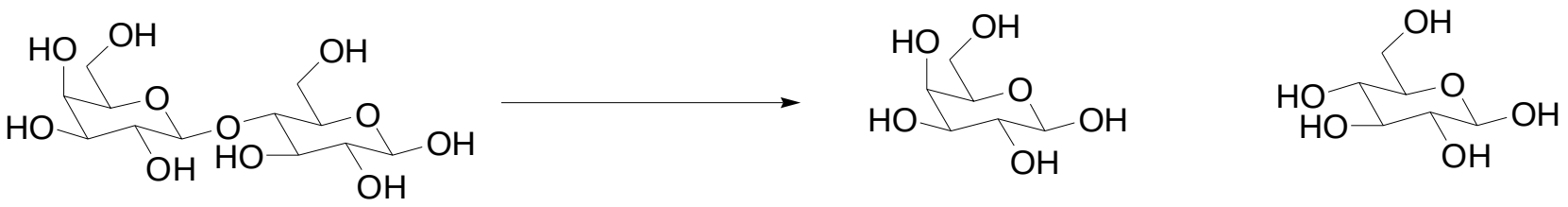
Lactose intolerance is inability to digest lactose

- lactose - sugar present in cows milk
    - if ancestors were from part of world that did not consume dairy, more likely to have this condition

Bacteria digest food instead

- you dont digest, but bacteria do digest lactose
    - bacteria grow, creates gas, indigestion

Lactase is available as a supplement



Lactose

Headaches from food

Spices can irritate stomach

Food allergies affect about 4 % of adults

- can have severe health consequence
- allergies will often give a systemic reaction
    - rash, swelling etc....unconnected to digestive system

Common food allergens

- milk, nuts, fish, eggs
    - fish and shellfish allergies are not connected
    - usually have either/or

Signs of food allergy – bags under eyes

- constantly inflaming tissues of face
- creates dark under eyes, constant look

Signs of food allergy – dark under eyes

Peanut allergy common in North America

- unique to North America

Peanut allergy rare outside North America

Peanut free schools common only in North America

Young children eat peanuts outside North America

Possible explanations

Outside north america

- people eat more
- children eat them when younger
- consume raw (inside N. America we roast them)

Allergy to bee stings

- swelling, soreness--> immune sytem response

Spider and insect bites can give strong reactions

- injected directly to blood
- strong reactions

Rare allergies - allergy to sunlight

- sun causes rash no matter how intense the light
- usually exposure to other chemical that causes it
    - ie marigolds chemical - body links with light and causes reaction with sunlight

Aquagenic allergy – allergy to water

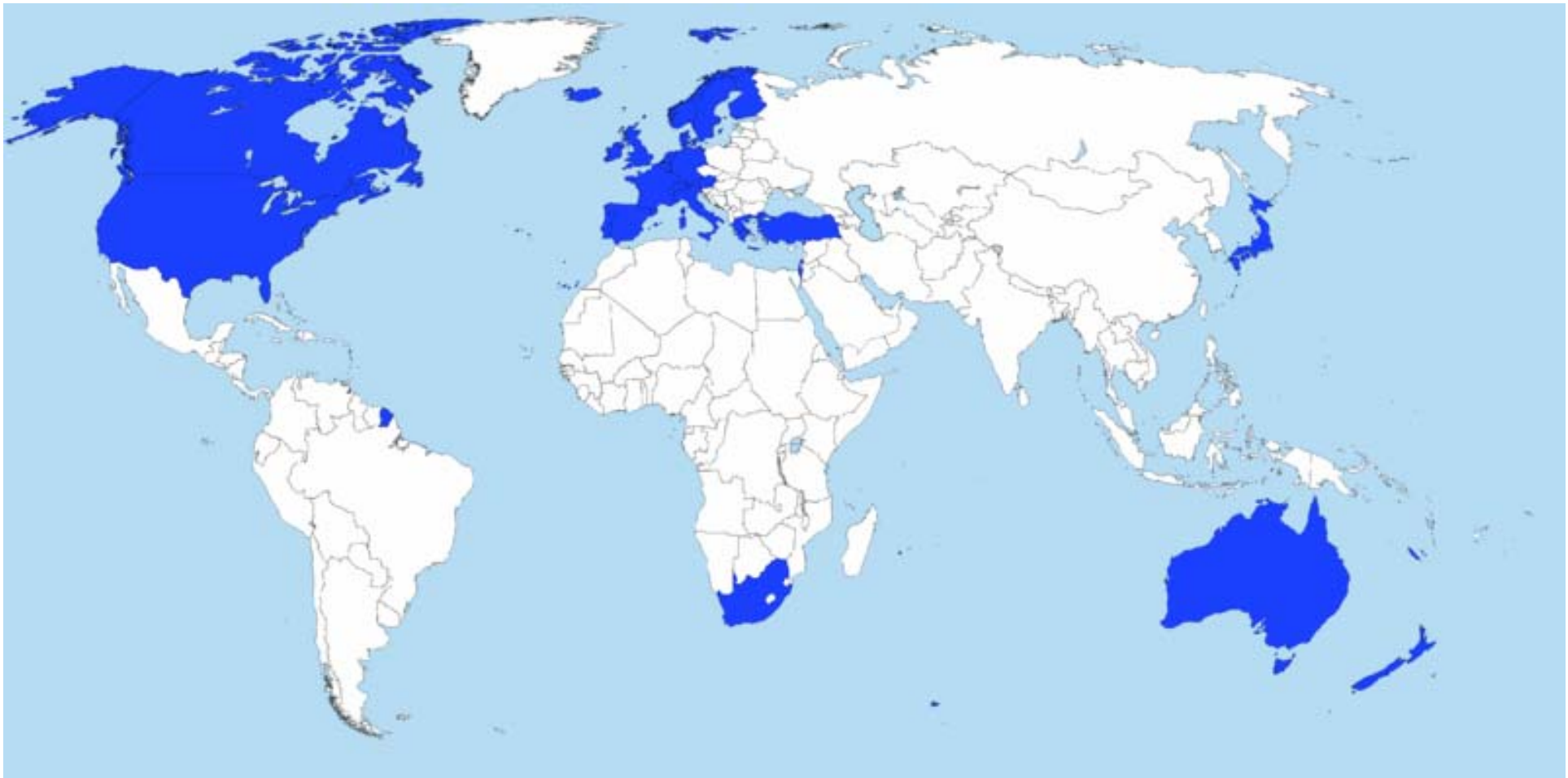
- dermatitis response to water

20th Century disease – "allergy" to man-made substances

- usually live life within a single room
- "allergic" to all man made materials
- usually obsessive about health and/or have a traumatic experience
    - psychiatric problem
- all in there head and body causes reaction

Allergy is a disease of the developed world

- Rates have doubled since 1980



Hay fever was a rare condition in 1900

- ie Ragweed

Are we exposed to more substances?

- because of industrialization
    - plastics, synthetics, etc
- exposure to chemicals the problem?
    - no, developing countries are exposed to alot more than N. America

Industrial pollution more common in developing world

Wider variety in diet in developed countries

Hygene hypothesis for allergy

Hay fever, hygiene, and household size

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David P Strachan , MRCP, *lecturer in epidemiology*

Br Med J 1989;**299**:1259-60

Hay fever has been described as a "post industrial revolution epidemic,"[1] and successive morbidity surveys from British general practice suggest that its prevalence has continued to increase over the past 30 years.[2] Other evidence suggests a recent increase in the prevalence of asthma[2] and childhood eczema.[3] This paper suggests a possible explanation for these trends over time.

Subjects, methods, and results

I studied the epidemiology of hay fever in a national sample of 17 414 British children born during one week in March 1958 and followed up to the age of 23 years (the National Child Development Study). Three outcomes were investigated: (*a*) self reported "hay fever during the past 12 months" at age 23; (*b*) parental report of "hay fever or allergic rhinitis in the past 12 months" at age 11; (*c*) parental recall of "eczema in the first year of life" elicited when the child was 7. Cross tabulations were performed with the SAS statistical package, and multiple logistic regression models were fitted with the LR program in the BMDP statistical package.

Of the 16 perinatal, social, and environmental factors studied the most striking associations with hay fever were those for family size and position in the household in childhood. The table shows that at both 11 and 23 years of age hay fever was inversely related to the number of children in the household at age 11 (when it is assumed most families were complete). When prevalence figures were adjusted by multiple logistic regression for other significant determinants of hay fever in this cohort (see table) the associations with numbers of older and younger children in the household persisted. These trends in adjusted prevalence were independent of one another and each was significant ($p<0{\cdot}01$, see table), but the trends by number of older children were significantly steeper ($\chi^2=11{\cdot}6$, df=1, $p<0{\cdot}01$ at age 11; $\chi^2=19{\cdot}5$, df=1, $p<0{\cdot}01$ at age 23). A further analysis of hay fever occurring at 23 by birth

Prevalence of hay fever and of eczema in infancy by position in the household. Numbers in parentheses

	Prevalence of hay fever in previous year							Prevalence of eczema in first year of life			
	At age 23				At age 11						
	Crude*	Crude†	Adjusted‡	χ^2§	Crude*	Crude†	Adjusted‡	χ^2§	Crude*	Crude†	Adjusted‡	χ^2§
No of older children (under 21) in household at age 11‖:												
0	20·4 (910/4 470)	20·5 (810/3 942)	20·4		9·6 (542/5 622)	10·0 (389/3 895)	10·0		6·0 (308/5 096)	6·2 (245/3 952)	6·1	
1	15·7 (583/3 703)	15·5 (515/3 323)	15·0		8·4 (398/4 721)	8·3 (273/3 286)	7·9		5·2 (225/4 331)	5·3 (177/3 320)	5·2	

Children in daycare less likely to be allergic

- daycare chilkdren have less allergies
    - children who get sick more as a child are less likely to have allergies when older

Children in large families have less allergies

- younger children also have less allergies than older

Some kids tend to have fewer allergies

- more disease and getting dirty as a child, less chance of allergies when older

Some kids have more allergies

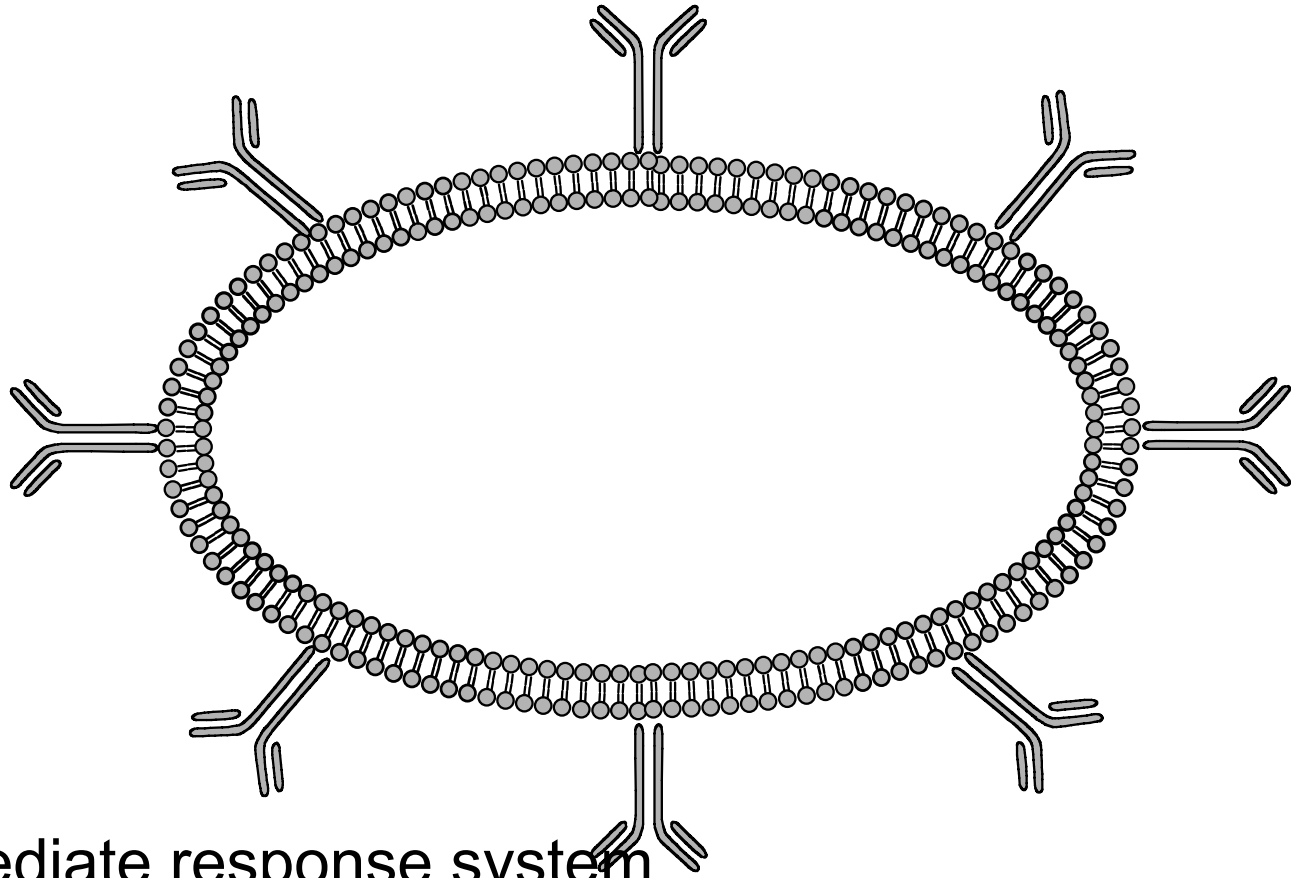
- being to clean causes allergies

Allergy requires prior exposure

- Involves immune system memory
- Hypersensitivity on 1st exposure
  - Unknown previous exposure

- allergies require previous exposure

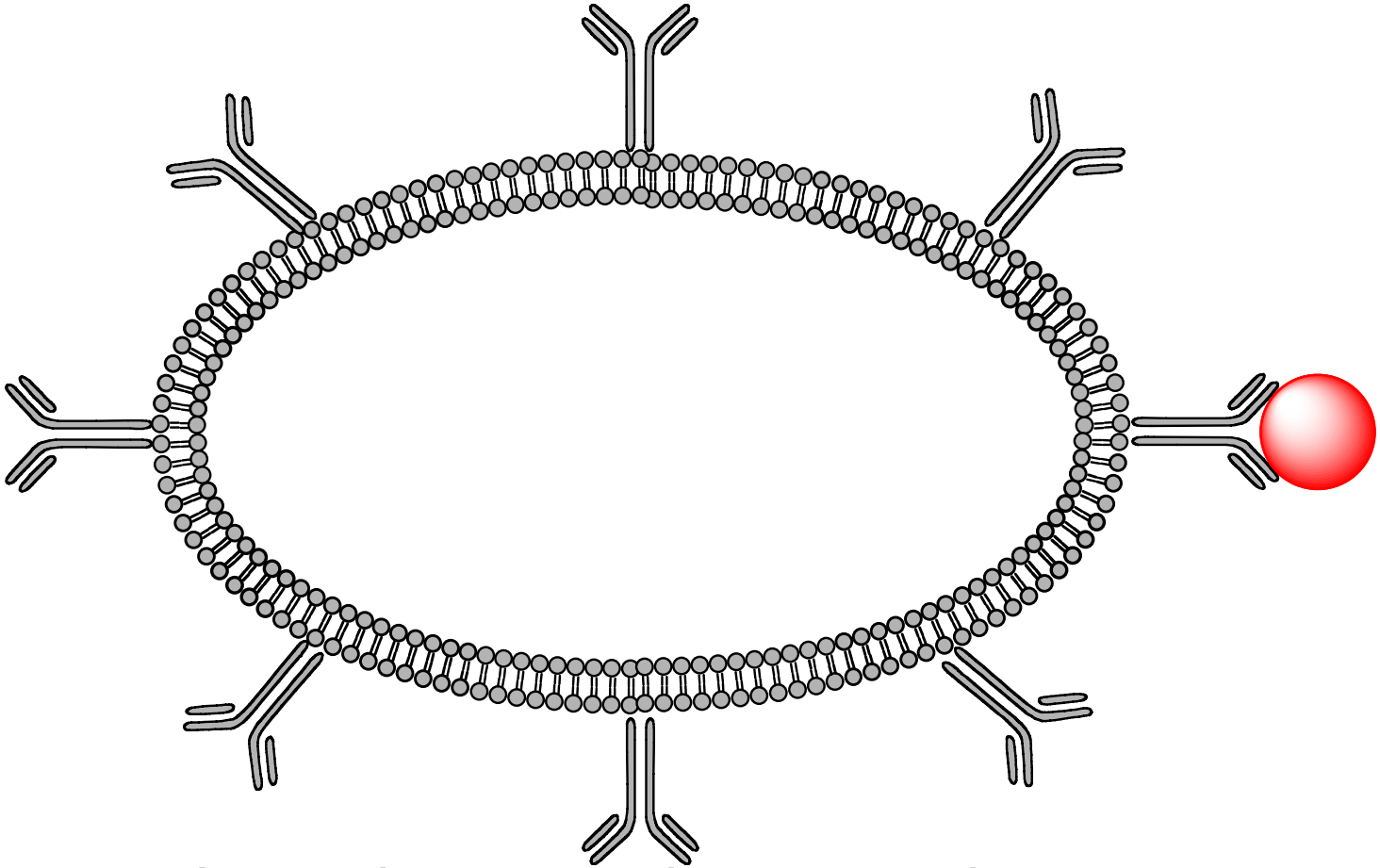
Mast cells display IgE antibodies



- immediate response system
    - innate system

ige*

Allergin contacts the IgE molecules



- creates cell shape change, and cell explodes

Mast cell degranulation releases histamine

controlled explosion
- releases histamine
    - causes reaction

Histamine produces allergy symptoms

- what we go after to control allegies

Managing allergy

- Avoidance
- Antihistamines
- Decongestants
- Immune modulators
- Immunotherapy

Allergy tests look for reactions

- poke with a bunch of needles on back and look where reactions take place

Avoidance best for food allergy

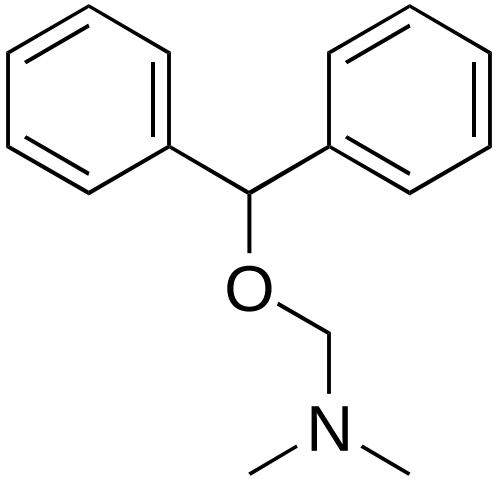
- Difficulty may be finding out what to avoid
- Processed foods contain variable ingredients

- often foods dont list certain substances that are in the food
    - amount not required by law

Tracking down food allergy - logbook

- when there is a reaction, write down what was eaten and the reaction

Antihistamines are often taken

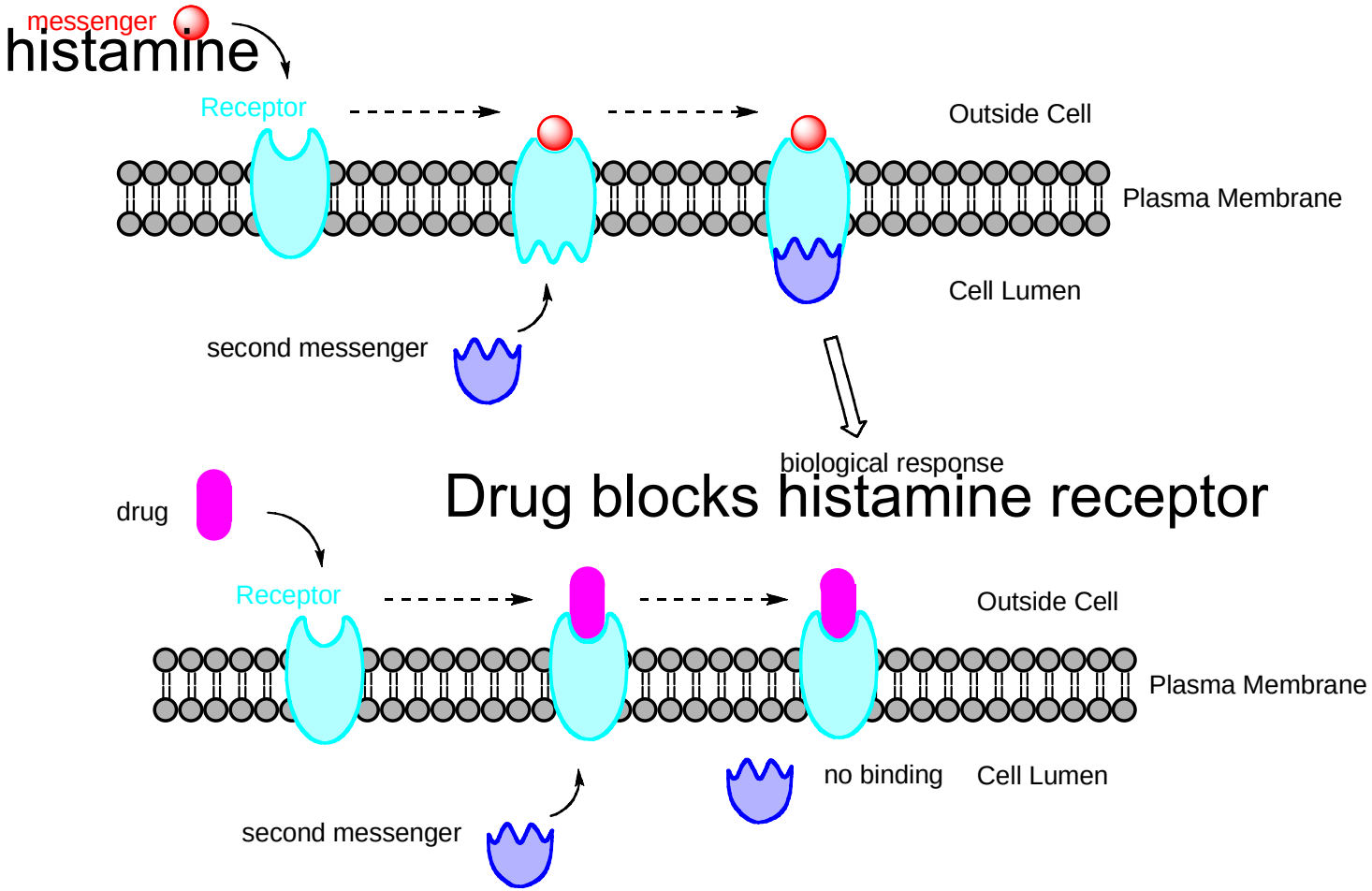


Diphenhydramine

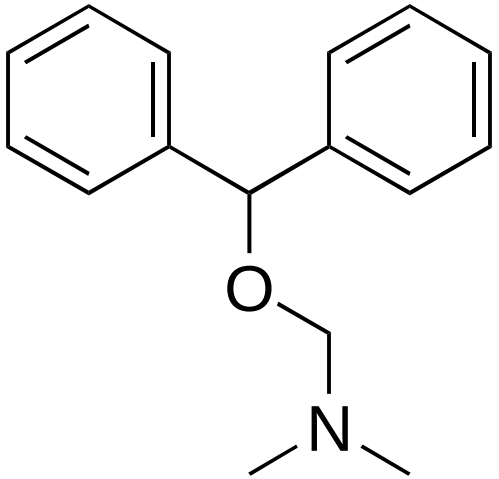
- ie. Benadryl
  - 1st generation antihistamine
  - fast acting

(blocking)

Antihistamines are histamine antagonists



Diphenhydramine is in Benadryl



Diphenhydramine

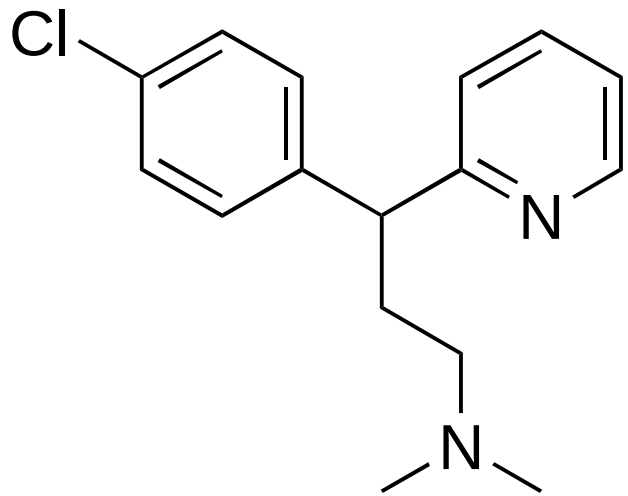
Generic versions are available

Diphenhydramine makes you sleepy

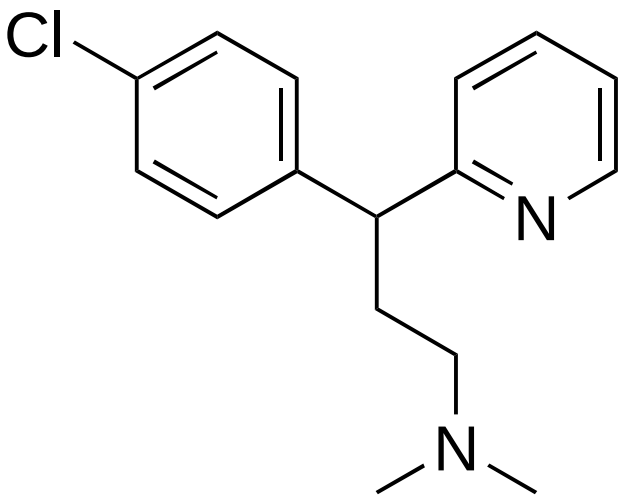
- 1st generation antihistamines make you sleepy
    - used in sleeping pills

Chlorpheniramine is in Chlor-Tripolon

- Side effect is drowsiness

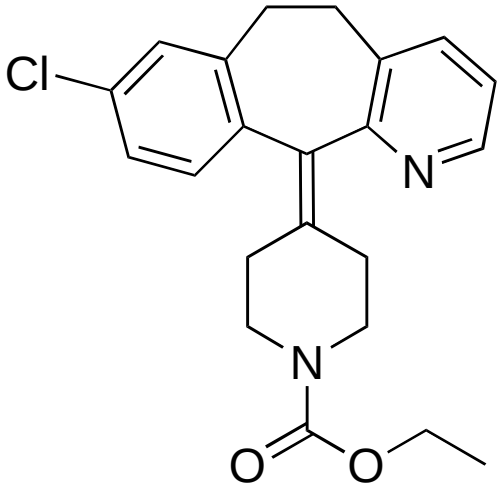


First generation antihistamines can enter the brain



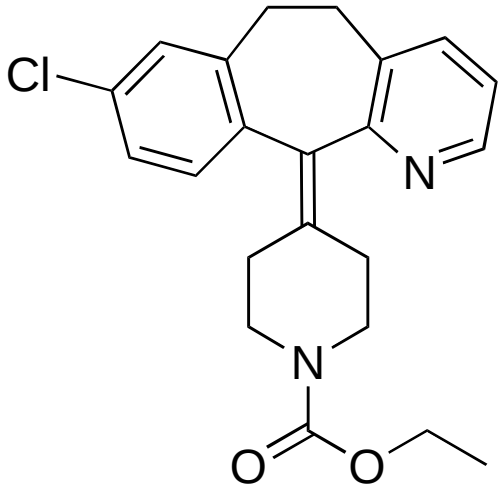
Chlorpheniramine is in cold medications

Loratadine is a second generation antihistamine



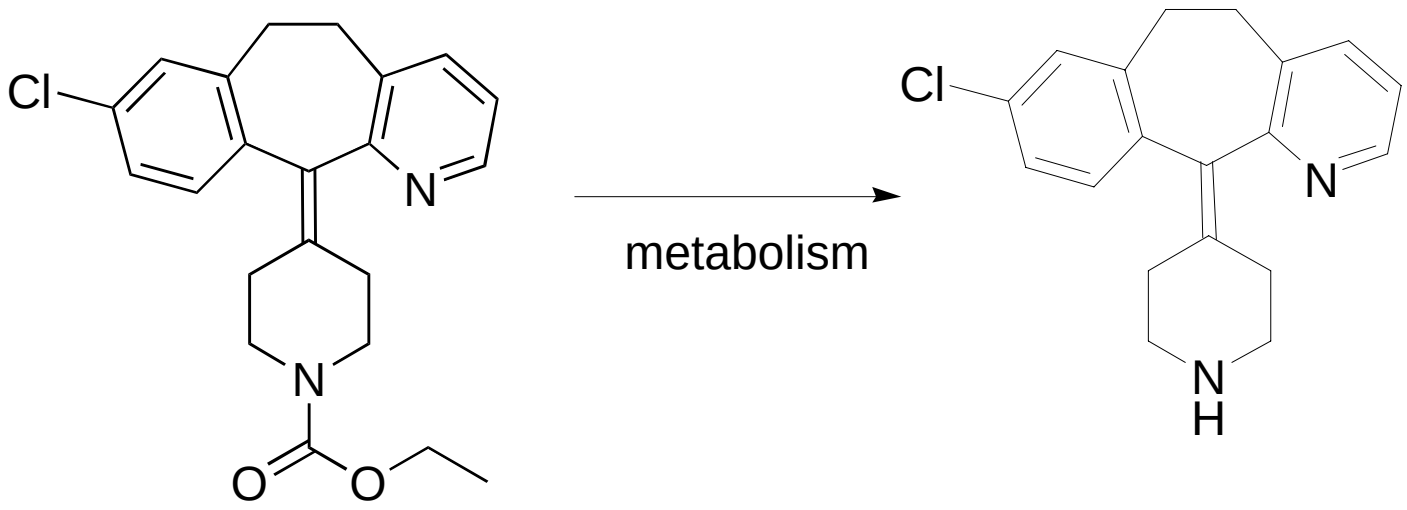
- does not enter the brain
  - no sleepy side-effect

Loratadine does not enter the brain



Loratadine

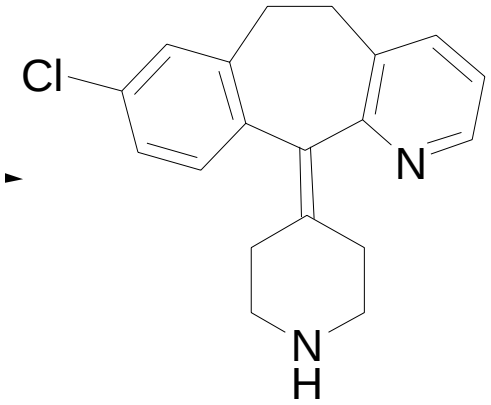
Body converts Loratadine to Desloratadine



Loratidine
(Claritin)

Desloratidine

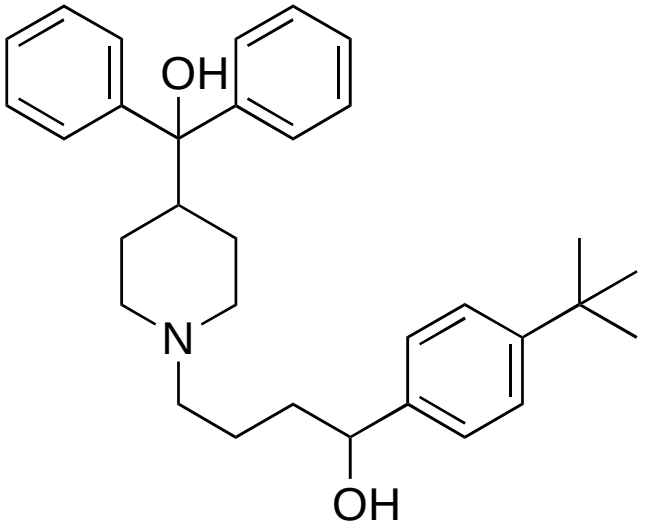
Desloratidine is in Aerius



- works same as loratidine
  - made to make more money
    - patent

Seldane contained terfenadine

- first of the 3rd generation antihistamines



(anti-fungal med)

Drug-drug interactions with Ketoconazole

Terfenadine-Ketoconazole Interaction

Pharmacokinetic and Electrocardiographic Consequences

Peter K. Honig, MD, MPH; Dale C. Wortham, MD; Kaveh Zamani, PhD; Dale P. Conner, PharmD; James C. Mullin, MD; Louis R. Cantilena, MD, PhD

Objective.—To examine prospectively the effects of ketoconazole on the pharmacokinetics and electrocardiographic repolarization pharmacodynamics (corrected QT intervals) of terfenadine in men and women.

Design.—Prospective cohort study with each subject serving as his or her own control.

Setting.—Outpatient cardiology clinic and inpatient telemetry unit for monitoring period.

Participants.—Six healthy volunteers (four men and two women, aged 24 to 35 years) not taking any prescription or over-the-counter medications.

Intervention.—After achieving a steady state while taking terfenadine (60 mg every 12 hours for 7 days), daily concomitant oral ketoconazole (200 mg every 12 hours) was added to the subjects' regimen. Pharmacokinetic profiles were obtained while subjects were taking terfenadine alone and after the addition of ketoconazole. Electrocardiograms were obtained at baseline, after 1 week of taking terfenadine alone, and at the time of the second pharmacokinetic profile after the addition of ketoconazole to the regimen.

Main Outcome Measures.—Terfenadine and its acid metabolite serum concentrations and corrected QT intervals.

Results.—All subjects had detectable levels of unmetabolized terfenadine after the addition of ketoconazole, which was associated with QT prolongation. Only two of the six subjects could complete the entire course of ketoconazole coadministration. Four subjects received a shortened duration of ketoconazole therapy because of significant electrocardiographic repolarization abnormalities. There was a significant change in the area under the curve of the acid metabolite of terfenadine after the addition of ketoconazole administration.

Conclusions.—Ketoconazole alters the metabolism of terfenadine in normal men and women and results in the accumulation of unmetabolized parent drug, which is associated with significant prolongation of the corrected QT interval. This drug combination should be avoided.

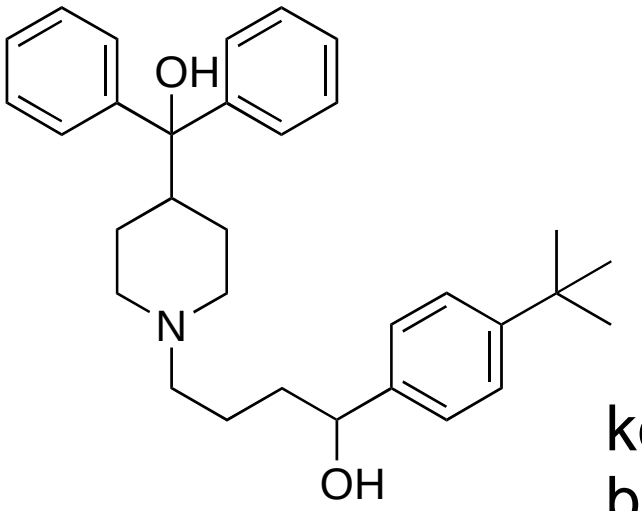
(*JAMA*. 1993;269:1513-1518)

taminic properties (Fig 1). As a result, it is unusual to find detectable parent terfenadine in the plasma of patients who are taking the drug.[3] Recently, unmetabolized terfenadine has been shown to be a potent blocker of at least one potassium current in cat ventricular myocytes.[4] Several reports to the Spontaneous Reporting System of the FDA involving a possible association between terfenadine and altered cardiac repolarization allowed the FDA to identify certain risk factors for this event, including overdose and hepatic compromise.[5] Both of these clinical situations are accompanied by altered terfenadine metabolism and the accumulation of the parent compound that is thought to be responsible for QT prolongation and the induction of potentially lethal ventricular arrhythmias. This was affirmed in a prospective controlled study in which erythromycin altered the pharmacokinetics of terfenadine, leading to accumulation of parent terfenadine that was associated with altered cardiac repolarization in a subset of individuals.[6]

See also pp 1532 and 1550.

Ketoconazole, an oral antifungal agent, is known to be a potent inhibitor of the metabolism of a variety of drugs includ-

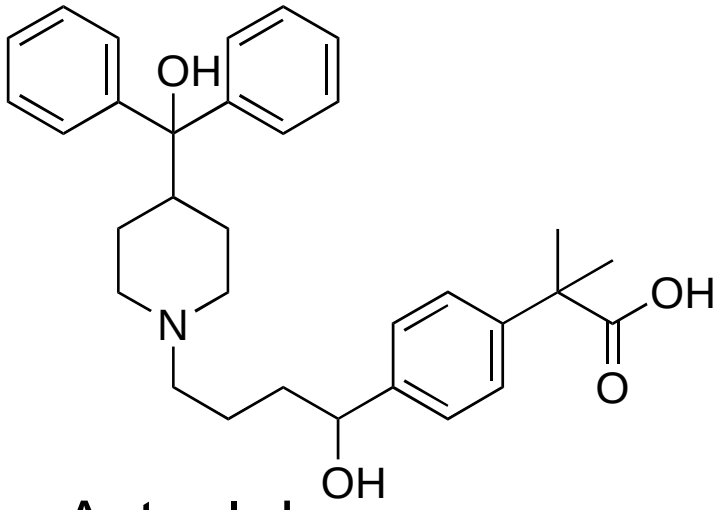
Terfenadine is activated in the body



Prodrug

Liver

ketoconazole blocks liver activity

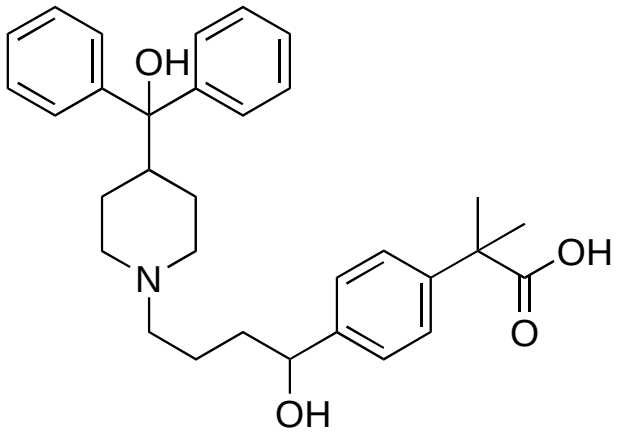


Actual drug

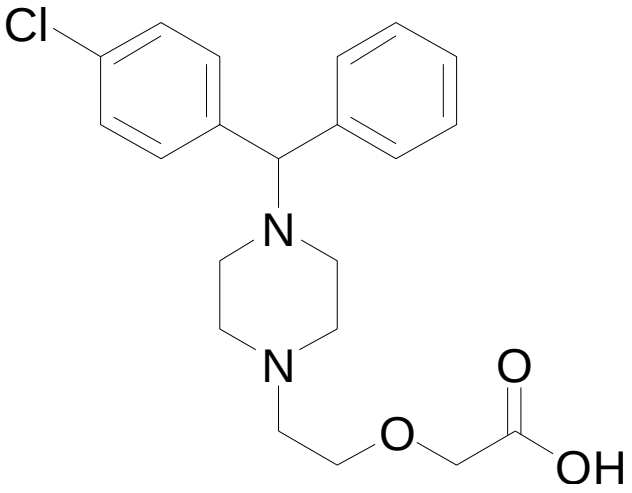
Fexofenadine

Cardiac problems

Allegra contains fexofenadine



Reactine contains cetirizine



- 3rd generation

6 most common antihistamines:

Various generations of antihistamines

- First generation (drowsiness)
  - Diphenhydramine (1940's, Benadryl, generic available)
  - Chlorpheniramine (1940's, Chlor-Tripolon, generic available)
- Second generation (non-drowsy)
  - Loratadine (1989, Claritin, generic available)
  - Desloratadine (2002, Aerius, generic available)
- Third generation (non-drowsy)
  - Fexofenadine (1996, Allegra, generic available)
  - Cetirizine (1996, Reactine, generic available)

Buyer beware! Price for 100 tablets

Benadryl (Dipheniramine)	$32.45
Life-Brand Dipheniramine	$44.95
Chlor-Tripolon (chlorpheniramine) (pheniram)	$43.71
Claritin (Loratadine)	$63.32
Life-Brand Loratadine	$81.23
Aerius (Desloratidine)	$83.30
Life-Brand Desloratadine	$71.98
Allegra (Fexofenadine)	$68.95
Life-Brand Fexofenadine	$61.96
Reactine (Cetirizine)	$62.05
Life-Brand Cetirizine	$56.23

essentially the same, diff. $

- often allergy meds generic are more expensive
  - look at price per tablet (pharmacies do this)

Buying in bulk is best value

- conflict of interest on expiry dates
    - left up to drug companies
    - want you to continue to buy

Pseudoephedrine for decongestion

Steroid decongestants

- not anabolic
    - just refers to chemical structure
    - wont build muscle
- just anti inflammatory

Rhinocort spray

Pulmicort is an anti-inflammatory steroid

Anaphylaxis is very serious

- severe swelling
- life threatening

Epi-Pen for strong allergic reactions

- short term solution to give you time to get to hospital

Know how to use it

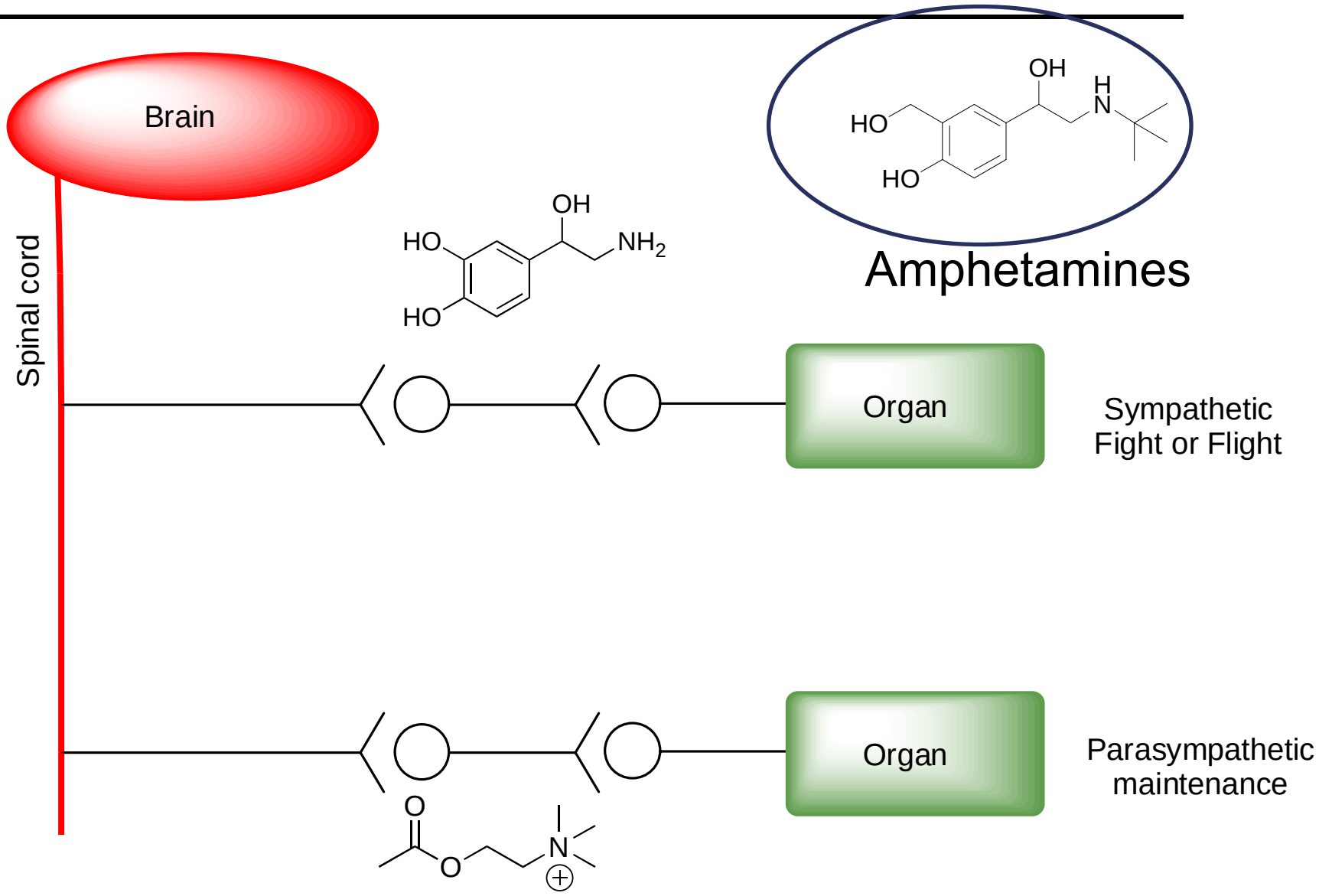
- spring loaded needle

Up to 50 % of allergies progress to asthma

- airways pinched off
- usually underlying allergy

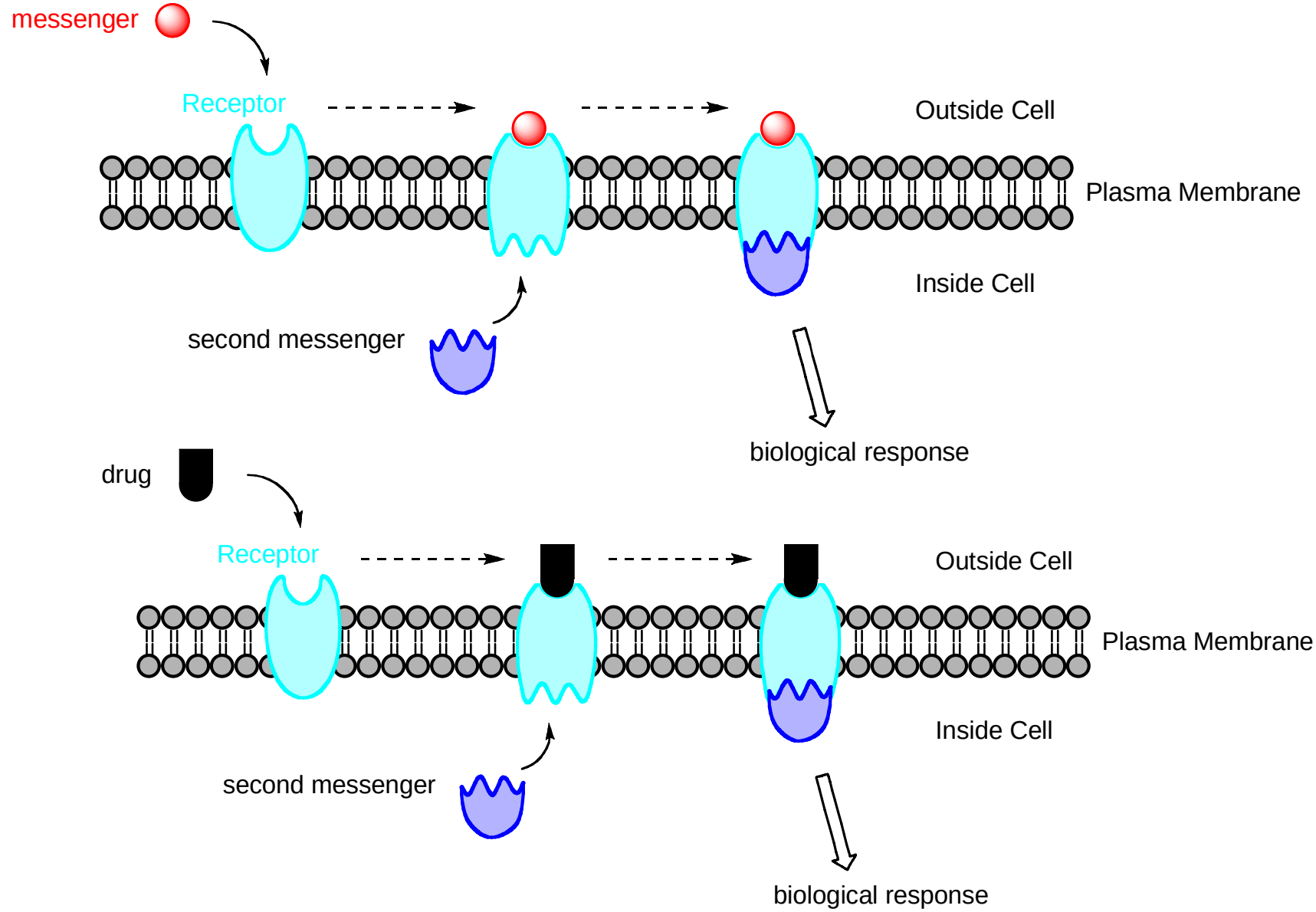
Original drugs targeted nerve signals

Salbutamol targets nerves to bronchii



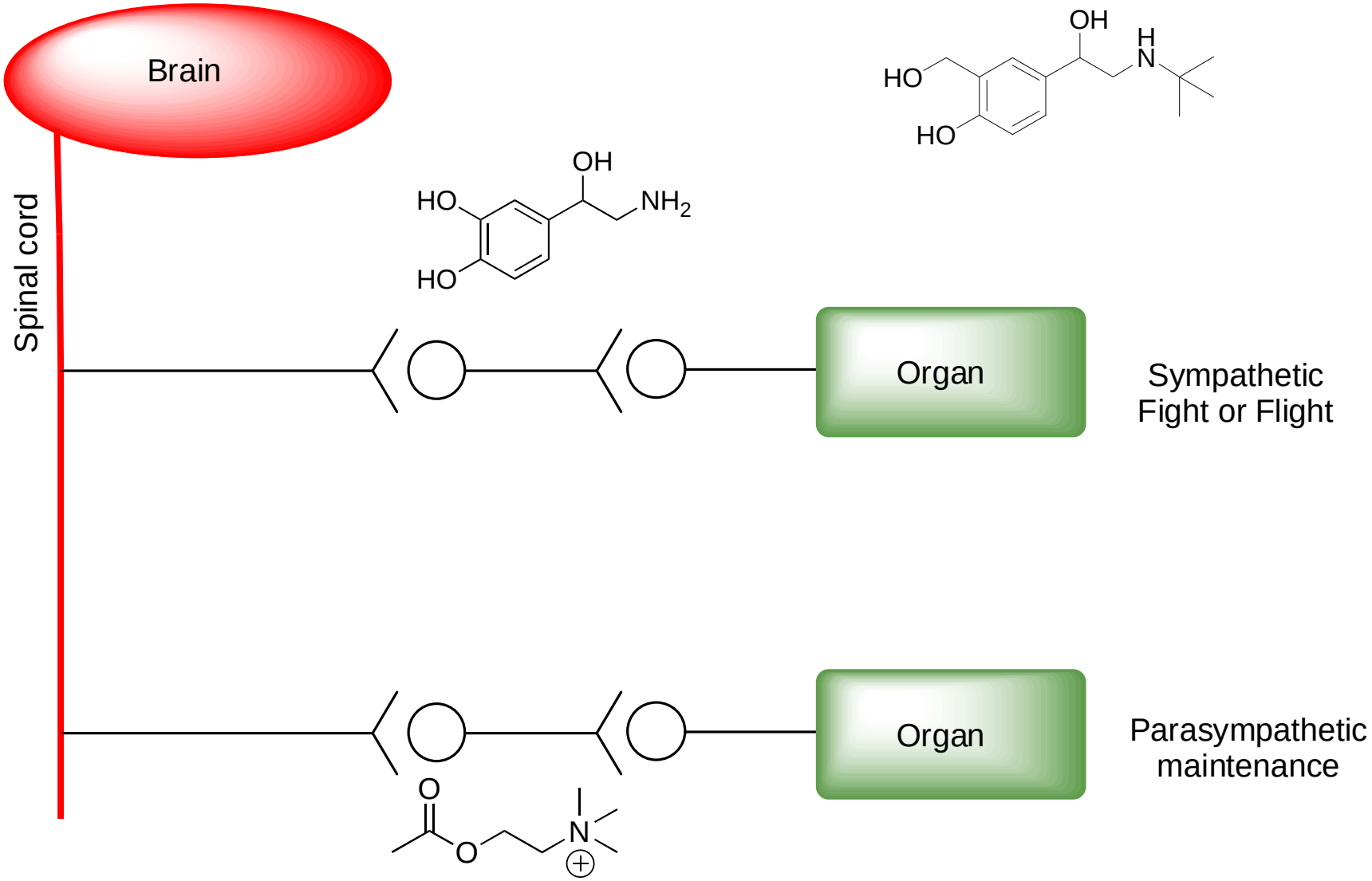
simulate localized flight or flight response in airways

Salbutamol is a selective adrenaline agonist



Adrenaline agonists open airways in the lungs

High doses will stimulate the heart

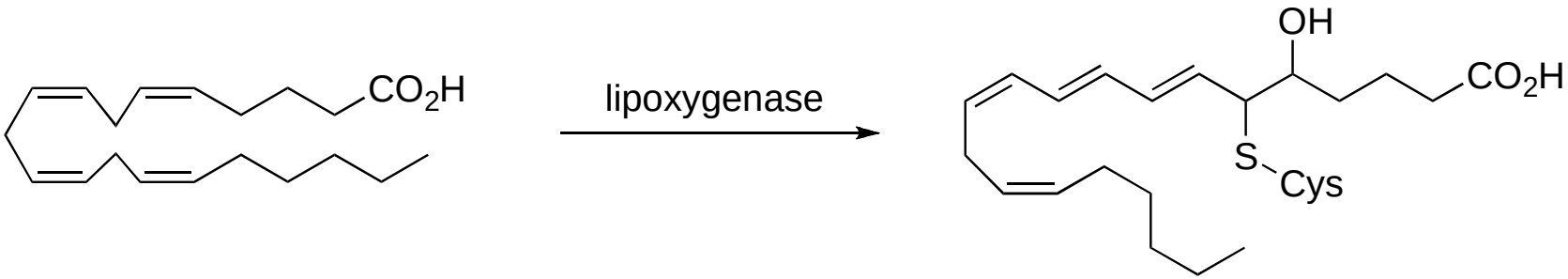


Over use caused heart attacks

- over stimulates the heart
- patients fault

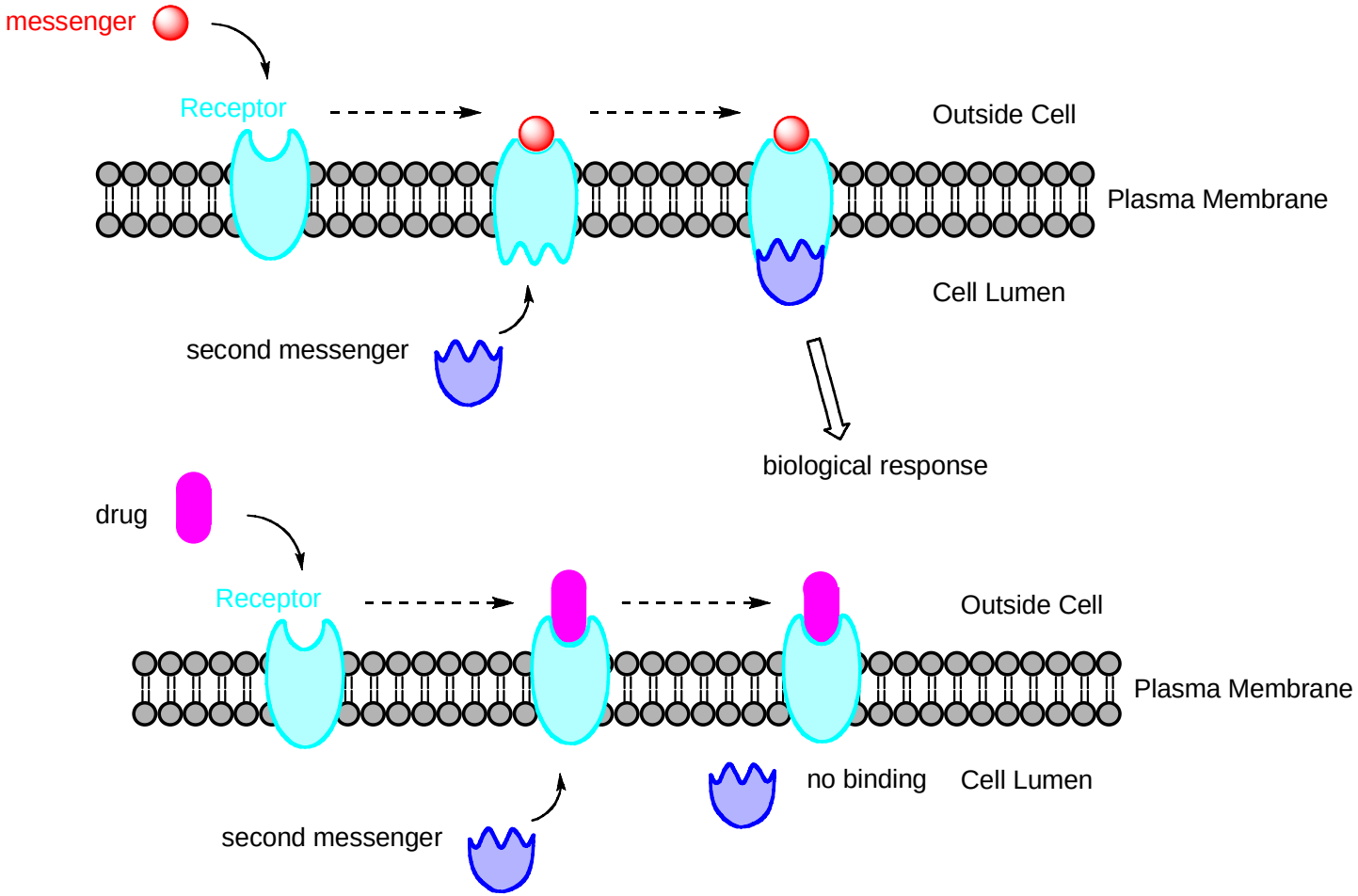
Flovent inhaler delivers measured doses

Leukotrienes associated with asthma



(leukotryine antagonist)

Singulair is a leukotriene antagonist



Singulair is very effective

- developed in montreal

Persistence pays off

- Identify the allergen
  - Avoid it when you can
- Try antihistamines
  - First, second or third generation
  - Experiment and see which works best for you
- Prescription steroids

Various generations of antihistamines

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