Drug Desensitizations to Chemotherapeutics and Biologicals: The Brigham and Women's Hospital Experience

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DISCLOSURES

- No financial relationships to disclose

LEARNING OBJECTIVES

Upon completion of this learning activity, you should be able to…

- Determine which patients can and which patients cannot be desensitized.
- Summarize severity grading and how it informs the choice of rapid drug desensitization protocol (and venue) to use for appropriate patients.
- Apply your understanding of the pathobiology of HSRs to chemotherapeutic agents and biologics to select appropriate premedications, treatment medications, and post medications for drug allergic patients undergoing rapid drug desensitization.
- Consider a mathematical model of how drug desensitization might work

If a patient is hypersensitive to a drug: Strategies for Dealing with Drug HSRs

- Stop treatment if possible
- Treat through
  - provide symptomatic control of adverse effects
- Premedications (depending on the reaction)
  - Examples: Antihistamines H1 and H2, IV fluids for IV medications, Steroids, NSAIDs
- Alternative therapy
  - Will it be as effective? Ex: antibiotics, chemotherapy
- But many of these have failed and sometimes even led to the death of patients!

Motivation for Drug Desensitization

- Why would you *ever* even think about drug desensitization?!
  - Violation of the 0th law of allergy

WARNING

TAXOL® (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See **DOSAGE AND ADMINISTRATION**.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

TAXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf

Algorithm for Considering Drug Desensitization

0) ask if desensitization is an option logistically

1) ask about the type of reaction: Will it be amenable to desensitization?

2) ask about the reaction severity: What desensitization protocol and premedications should you use?

3) ask about risk-benefit ratio*

Logistics of Rapid Drug Desensitization (RDD)

- Nurses and pharmacists >> MD
- Resources to treat a reaction: people, Epi, O2, IV fluids, other components of a standard code cart, rapid transport to nearby ED

Contraindications for Desensitization

- Some drug hypersensitivity reactions are *not* amenable to desensitization
  - Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
  - Abacavir hypersensitivity in HIV patients with HLA-B*5701
  - Erythema mutliforme (EM), Steven's Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN)*
  - Warfarin induced skin necrosis

Grading of Reaction Severity

Grade	Defined by
1=Mild (skin and SC only)	Generalized erythema, urticaria periorbital edema, angioedema
2=Moderate (Respiratory, CV, GI)	Dyspnea, Stridor, Wheezing Nausea, Vomiting, Dizziness, Diaphoresis, Chest/Throat tightness Abdominal pain ("colic")
3=Severe ($\downarrow O_2$, $\downarrow$BP, Neurologic)	Cyanosis, O_2 Sat <92%, SBP <90mmHg in adults Confusion, syncope, incontinence

Brown JACI 2004;114:371-376

Oral Desensitizations

- Aspirin or other NSAIDs
- Oral antibiotics such as trimethoprim+ sulfamethoxazole
- Oral anti-rheumatic agents such as allopurinol

Aspirin Desensitization

- Determine the nature of the reaction
  - Type 1 = Aspirin exacerbated respiratory disease (AERD)
  - Type 2 = urticaria or angioedema to multiple NSAIDs in pt with chronic urticaria or angioedema
  - Type 3 = urticaria or angioedema to multiple NSAIDs in pt without chronic urticaria or angioedema
  - Type 4 = "blended" reactions with respiratory and mucocutaneous symptoms and signs

  - Type 5 = pruritus, urticaria, or angioedema to a single NSAID
  - Type 6 = Anaphylaxis to a single NSAID

Aspirin Desensitization

- Type 1 or 4
  - Start ASA at 40.5 mg PO
  - Interval = 180 minutes
  - Increments = double
  - Premedications = leukotriene modifier (montelukast or zileuton)
- Type 2 or 3
  - Start ASA at 81 mg PO
  - Interval = 180 minutes
  - Increments = double
  - Premedications = none (withhold antihistamines but have available to treat)
- Type 5 or 6 {Rarely indicated}
  - Start ASA at 162 mg PO
  - Interval = 180 minutes
  - Increments = double
  - Premedications = none

Trimethoprim + Sulfamethoxazole Desensitization

TABLE I. TMP-SMX graded administration protocols: TMP-SMX 6 step (1 day)*†

Step	Dose of TMP/SMX, mg/mg
1	0.02/0.004
2	0.2/0.04
3	2/0.4
4	20/4
5	200/40
6	Final dose: single, 400/80 PO, or double, 800/160 mg PO

PO, orally.
*Dosing intervals are flexible and could be scheduled at 15, 30, or 60 min apart.
†Modified from the desensitization protocol by Gluckstein and Ruskin.[12]

TABLE III. TMP-SMX graded administration protocols: TMP-SMX 10 step (>1 day)*†

Step	Dose of TMP/SMX, mg/mg
1	2/0.4
2	4/0.8
3	8/1.6
4	16/3.2
5	40/8
6	80/16
7	160/32
8	320/64
9	400/80
10	800/160

*Dosing interval is daily.
†Reprinted from reference 9.

Successful Outpatient Graded Administration of Trimethoprim-Sulfamethoxazole in Patients Without HIV and With a History of Sulfonamide Adverse Drug Reaction

Regan C. Pyle, DO[a], Joseph H. Butterfield, MD[a], Gerald W. Volcheck, MD[a], Jenna C. Podjasek, MD[a], Matthew A. Rank, MD[b], James T.C. Li, MD, PhD[a], Amitha Harish, MD[c], Kimberly L. Poe, RN[a], and Miguel A. Park, MD[a]
Rochester, Minn; Scottsdale, Ariz; and Portsmouth, NH

TABLE II. TMP-SMX graded administration protocols: TMP-SMX 14 step (1 day)*†

Step	Dose of TMP/SMX, mg/mg
1	0.08/0.016
2	0.16/0.032
3	0.32/0.064
4	0.64/0.128
5	1.28/0.256
6	2.5/0.512
7	5/1
8	10/2
9	20/4
10	40/8
11	80/16
12	160/32
13	320/64
14	440/88

*Dosing interval is 15 minutes apart.
†A shorter version of our 20-step TMP-SMX desensitization inpatient protocol. Modified from the desensitization protocol outlined by Kalanadhabhatta et al.[13]

JACI In Practice 2014 Jan-Feb, pg. 52

Allopurinol Desensitization

The solution is 1mg per 5mL (one milligram per five milliliters)

Days	Volume to take by mouth (milliliters)	Dose (mg)
1-3	0.25	0.05
4-6	0.5	0.10
7-9	1	0.20
10-12	2.5	0.50
13-15	5	1
16-18	25	5
19-21	50	10
22-24	take one quarter of a 100mg tablet	25
25-27	take half of a 100mg tablet	50
28-30	take a 100mg tablet	100

Intravenous RDD

- Antibiotics
  - Beta lactam antibiotics
- Chemotherapeutics
  - Taxanes (paclitaxel, docetaxel),
  - Platins (carboplatin, cisplatin, oxaliplatin)
  - Doxorubicin
- Biologics (for malignancies, rheumatologic, GI, and other autoimmune indications)
  - Infliximab
  - Rituximab
  - Brentuximab

Example RDD Protocol

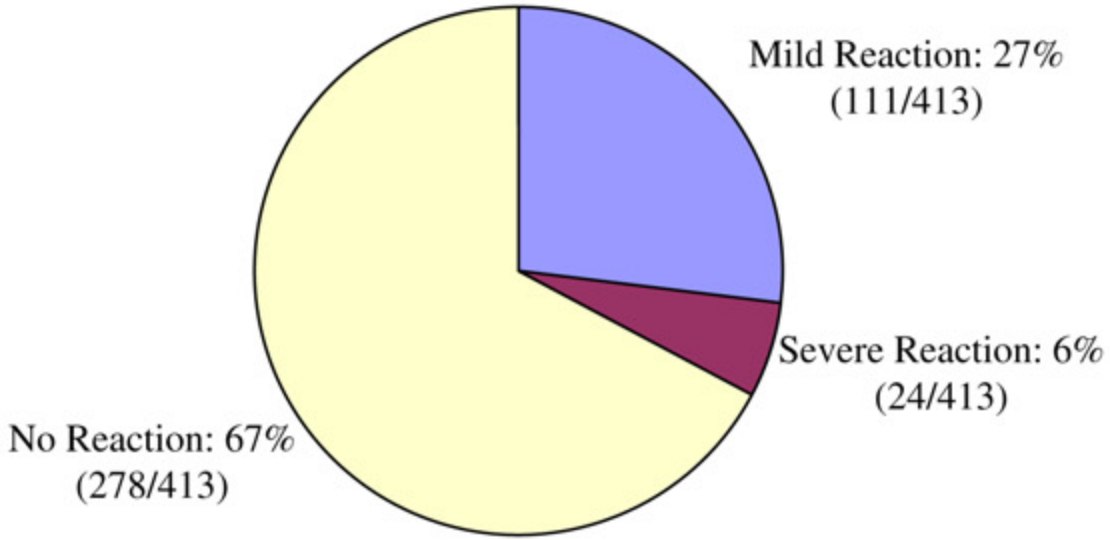
TABLE II. Desensitization protocol for rituximab IV (851 mg): protocol for administration

Step no.	Solution no.	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0170	0.0170
2	1	5.0	15	1.25	0.0426	0.0596
3	1	10.0	15	2.50	0.0851	0.1447
4	1	20.0	15	5.00	0.1702	0.3149
5	2	5.0	15	1.25	0.4255	0.7404
6	2	10.0	15	2.50	0.8510	1.5914
7	2	20.0	15	5.00	1.7020	3.2934
8	2	40.0	15	10.00	3.4040	6.6974
9	3	10.0	15	2.50	8.4430	15.1404
10	3	20.0	15	5.00	16.8861	32.0264
11	3	40.0	15	10.00	33.7721	65.7986
12	3	75.0	186	232.50	785.2014	851.0000

Total time = 351 minutes (5.85 hours).

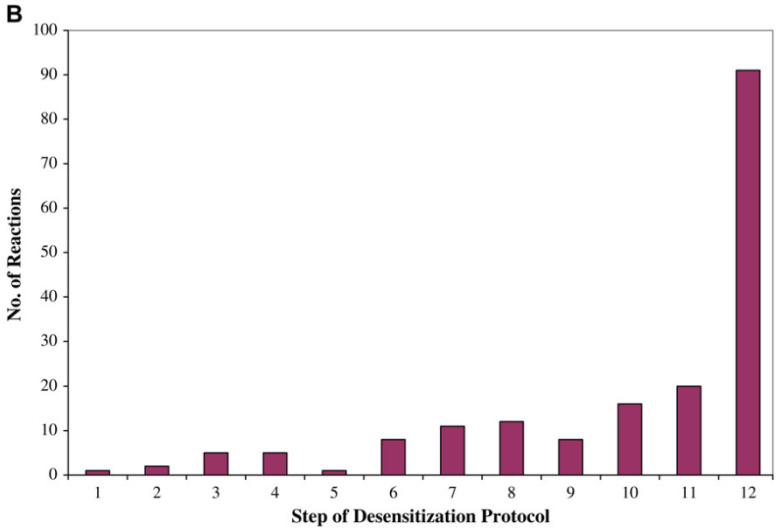
Castells MC *et al.* JACI 2008;122(3):574–80.

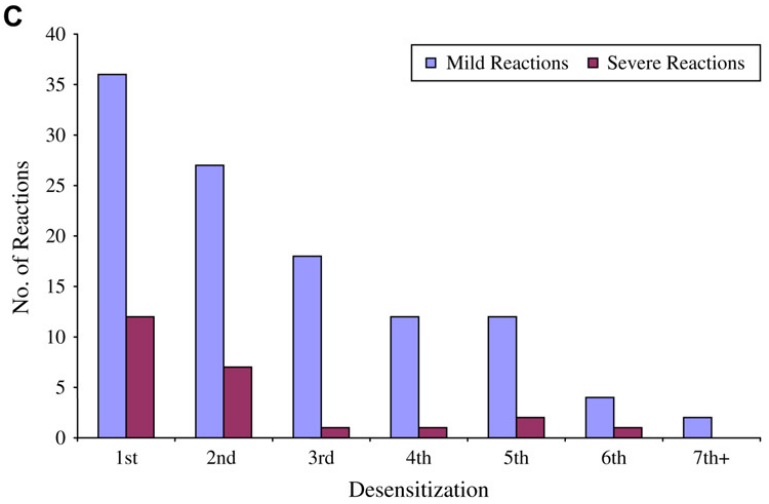
Reactions during RDD to chemotherapeutics (n=413)



Castells MC *et al.* JACI 2008;122(3):574–80.

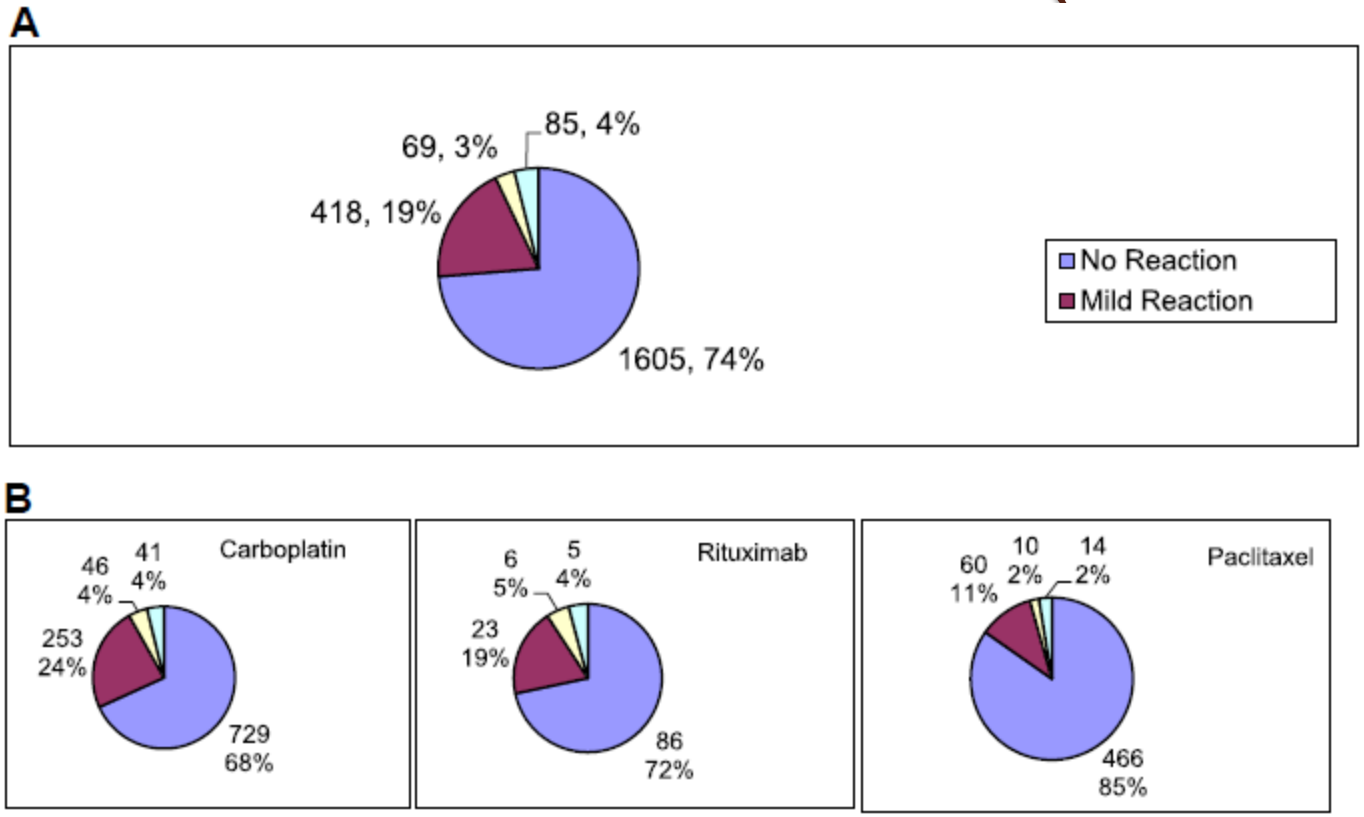
Reactions during RDD to chemotherapeutics





Castells MC *et al.* JACI 2008;122(3):574–80.

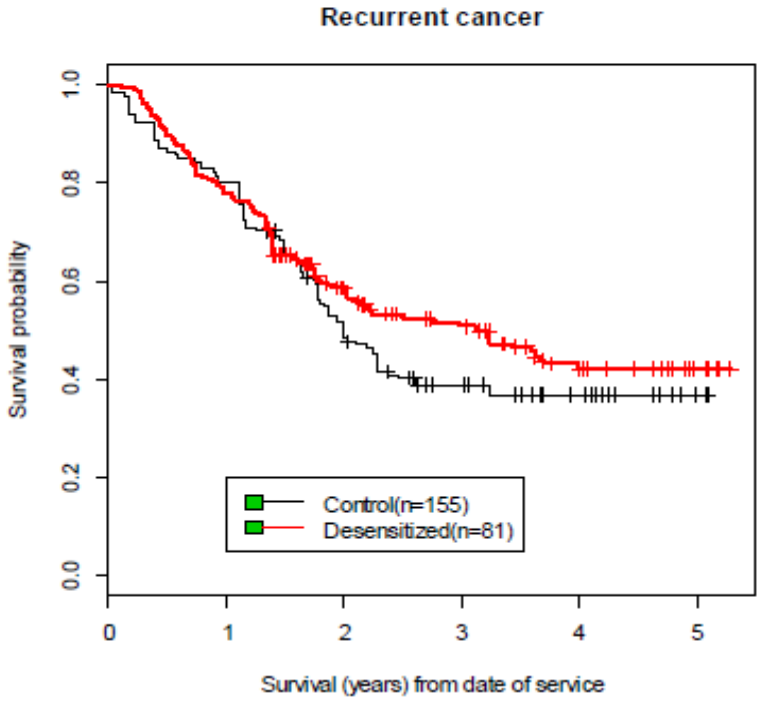
Desensitization Reactions (n=2177)



Sloane DE et al. JACI In Practice 2016, pg. 497

Survival with Desensitization

B Plot of Kaplan-Meier survival curves from propensity-weighted data on carboplatin-treated recurrent cancer patients

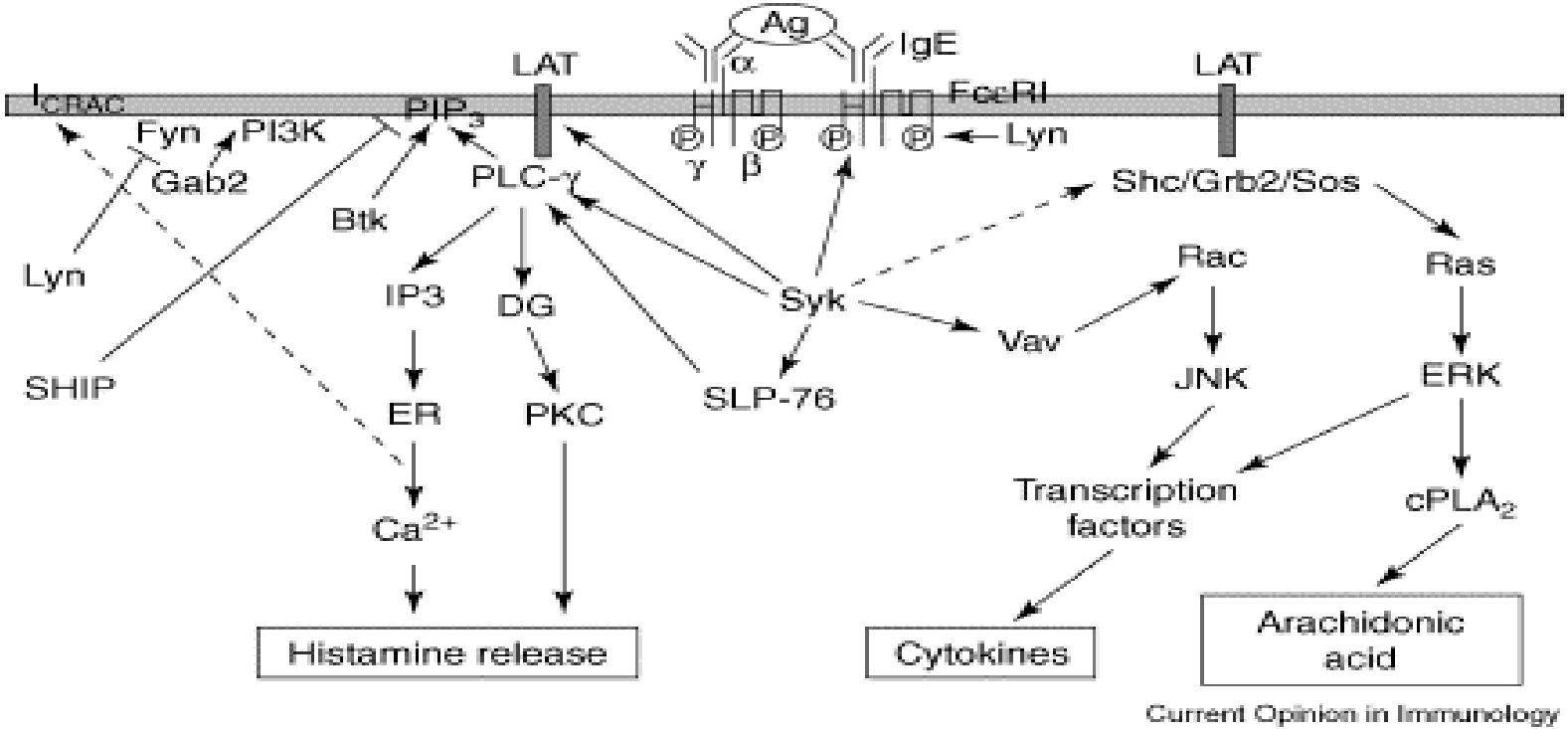


Sloane DE *et al.* JACI In Practice 2016, pg. 497

Hypotheses about Desensitization Mechanisms

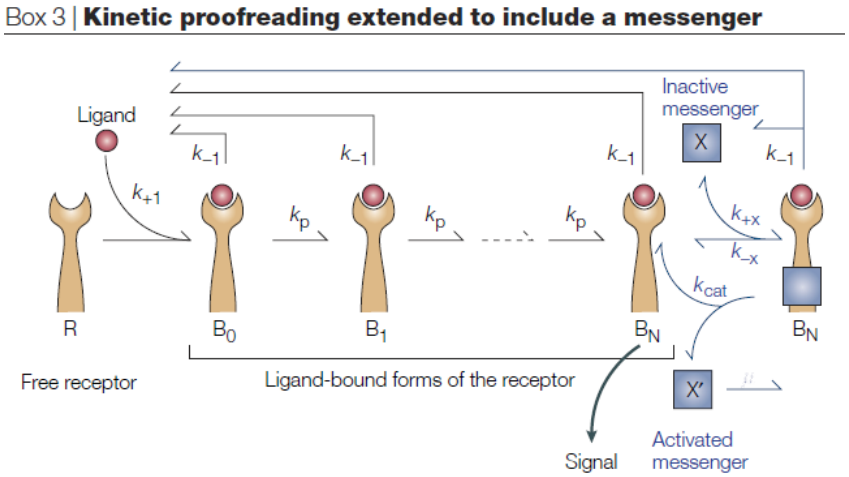
- Mast cell mediator depletion.
  - (*Nope*)
- Removal *via* endocytosis of mast cell surface drug specific IgE.
  - (*Nope*)
- Decay or other inactivation of activating signal transduction components.
  - (*Maybe*)

Hypothetical Mechanisms of Mast Cell Desensitization



Siraganian R. Mast cell signal transduction from the high-affinity IgE receptor. Current Opinion in Immunology 2003;15:639-646.

Kinetic Proofreading

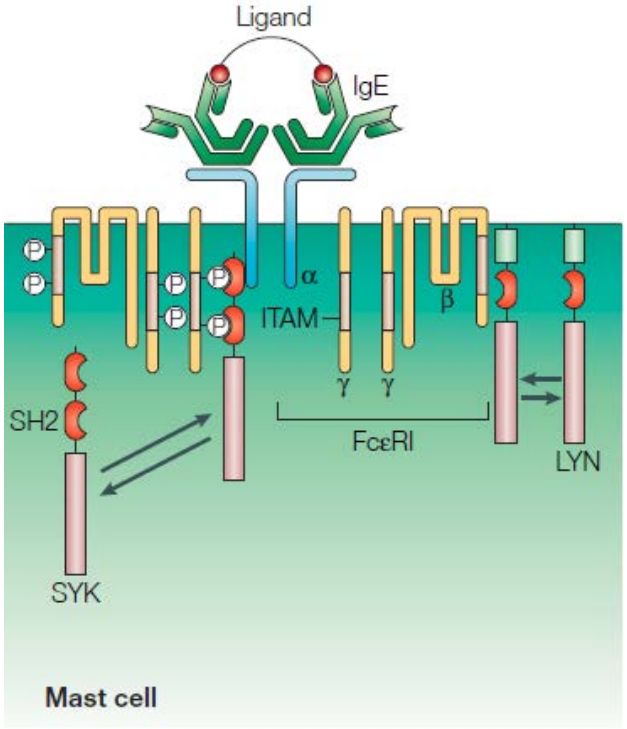


- Receptors only send a signal if they complete a series of steps dependent on continued ligand binding for at least a critical dwell time (t_{dwell})

Goldstein B, *et al*. Nat Rev Immunol. 2004;4:445-456.

Kinetic proofreading in mast cells

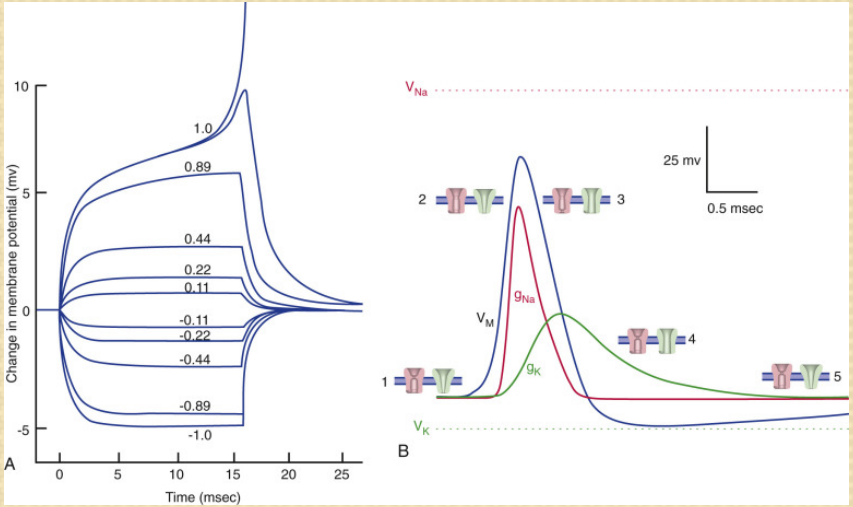
FcεRI-mediated signalling. The effects of kinetic proofreading have been experimentally detected not only during signalling through TCRs but also for signalling through FcεRI[15,50,51], and extended forms of McKeithan's model that incorporate features of FcεRI signalling have been used to study this system[52,53]. Torigoe *et al.*[15] found that doses of rapidly and slowly dissociating ligands that induced similar levels of receptor phosphorylation generated distinct levels of downstream activation, in terms of SYK phosphorylation. In agreement with the extended models[52,53], the slowly dissociating ligand generated stronger downstream responses than the rapidly dissociating ligand, and the differences increased with the distance downstream[15].



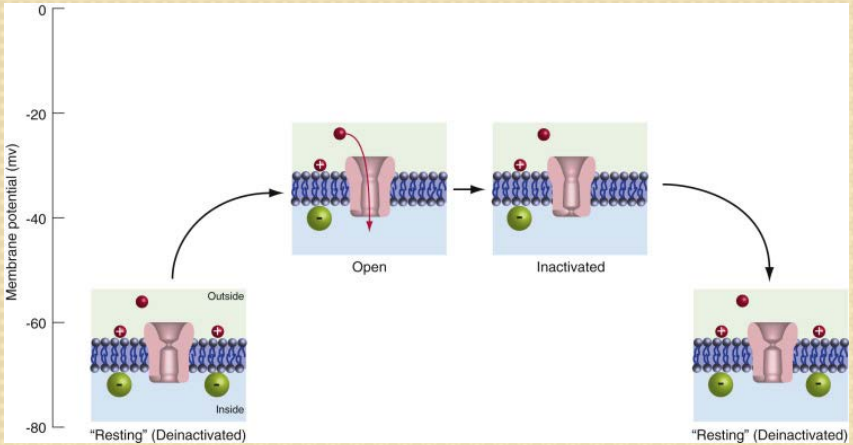
Goldstein B, *et al*. Nat Rev Immunol. 2004;4:445-456.

Neuron Threshold and Action Potential

Voltage Gated Na+ membrane channels



Electrical Signaling by Neurons Figure 7-11
from Vanderah, TW., *et al.* Nolte's The Human Brain. 2016.
Pg. 154-181.



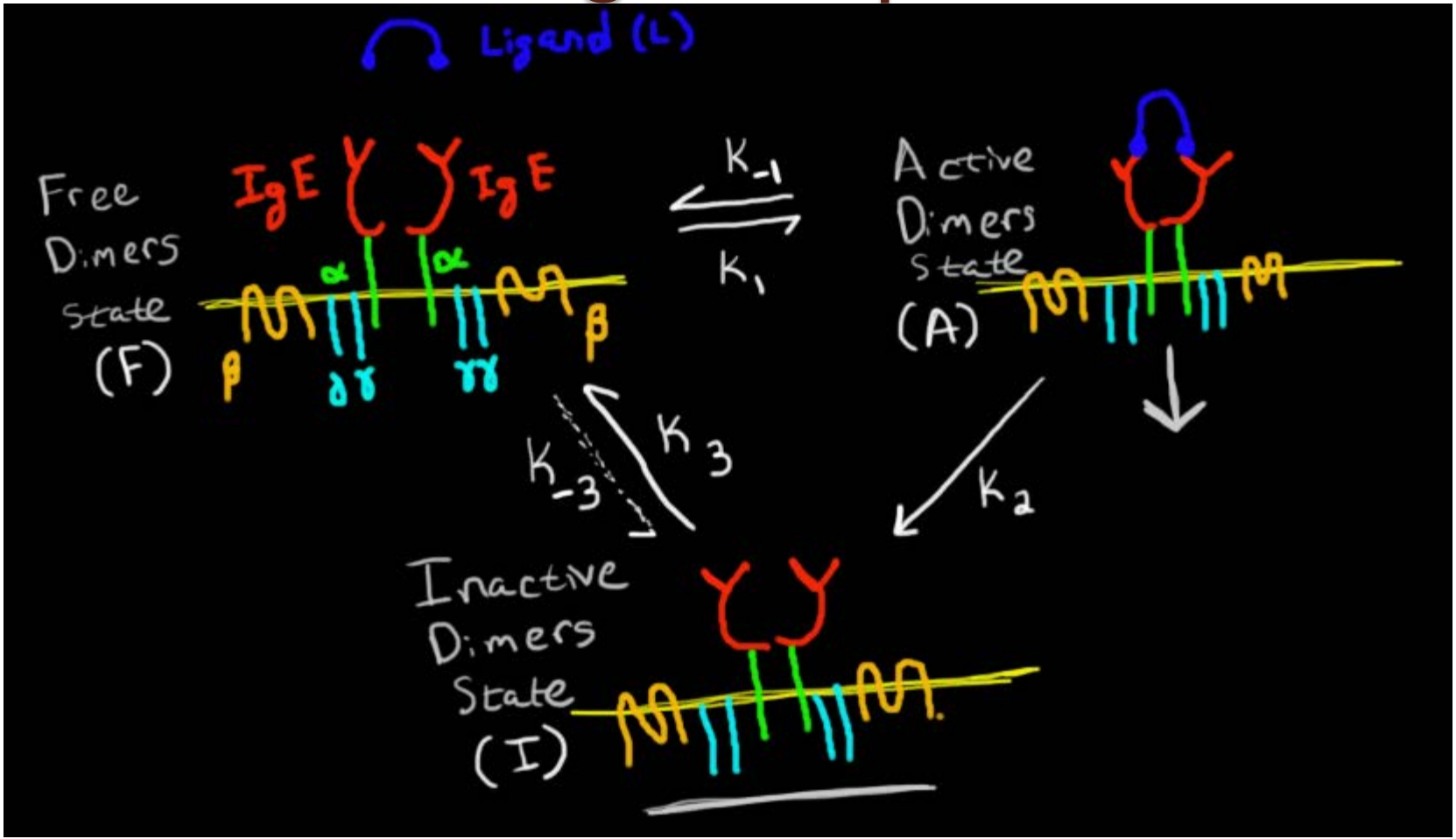
Electrical Signaling by Neurons Figure 7-10
from Vanderah, TW., *et al.* Nolte's The Human Brain. 2016.
Pg. 154-181.

Analogy: Neuronal Cell Activation

Hypothesis

- By analogy with neuronal voltage gated Na^+ channels, if the allergen/ligand dissociates too early ($t < t_{dwell}$), the receptor enters a refractory state until it either recovers or is replaced.
- If the allergen/ligand binds long enough to activate the receptor, a signal is sent, but the cell only activates if a critical number of receptors activate.
- Thus, if enough immune receptors are induced to enter the refractory state by **sub-threshold** doses of ligand, the mast cell will be temporarily unresponsive, until enough receptors exit the refractory state or are replaced by fully functioning receptors.
- When a sufficient number of a patient's mast cells are rendered transiently unresponsive, we call this the clinically "desensitized" state.

A Model of IgE Receptor Kinetics



Presumptions of the model

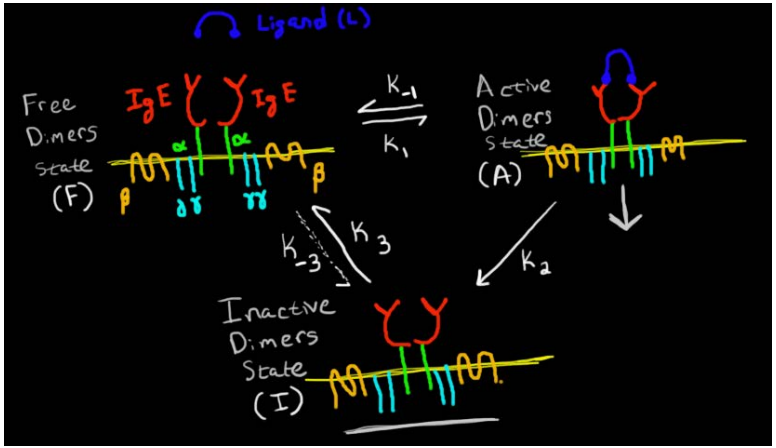
- The total number of IgE receptors on a given mast cell (T) stays the same, and is the total of the free, active, and inactive dimers: T = F + A + I
- The activation threshold of a mast cell is when the fraction of all the receptors T that is active (A) is stable, such as 10%: $\frac{A}{T} = \frac{A}{(F+A+I)} = 0.1$
- So as long as $\frac{A}{T} < 0.1$, no activation occurs.

Let's do the math

$$\frac{dA}{dt} = k_1 FL - k_{-1} A - k_2 A$$

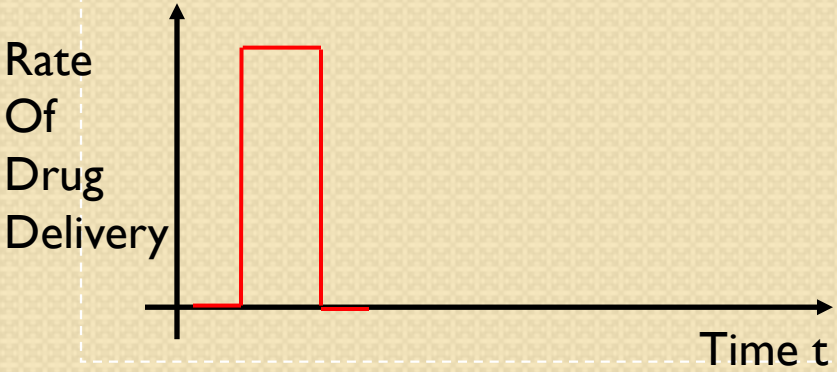
$$\frac{dI}{dt} = k_2 A + k_{-3} F - k_3 I$$

$$\frac{dF}{dt} = k_{-1} A + k_3 I - k_1 FL$$



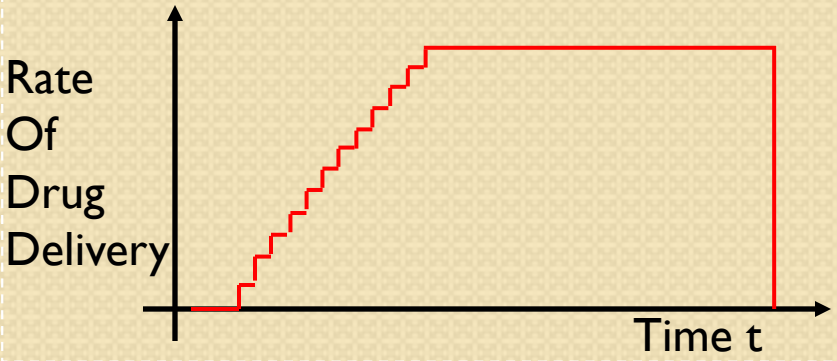
Regular/Standard Administration

- L(t) = a square wave



RDD Administration

- L(t) = geometric progression in 2-2.5 fold steps



The critical difference?

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