Non-Protein Drug Targets

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Cancer Chemotherapy

- Traditionally targeted DNA synthesis – why?
- Issues with adverse effects
- More recent advances in PKIs and mAbs (amongst others)

Advances in approach allows better targeting. Can also be aided by targeted delivery systems, e.g. nanoparticles that release drug in hypoxic environments via altered redox potential of the environment; useful for cancer because tumours are hypoxic.

What are Biopharmaceuticals?

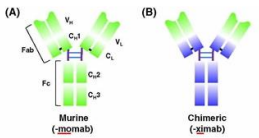
- "A drug of biological origin"
- First generation – copies of endogenous molecules
- Second generation – modified to improve performance

What are Biopharmaceuticals?

- Peptides
- Gene therapy
- Cell therapy
- Monoclonal antibodies

(more info at https://youtu.be/h6sGMaf6Yew)

Monoclonal Antibodies



Lu, R.-M., Hwang, Y.-C., Liu, I.-J., Lee, C.-C., Tsai, H.-Z., Li, H.-J., & Wu, H.-C. (2020). Development of therapeutic antibodies for the treatment of diseases. *Journal of Biomedical Science*, *27*(1), 1–30. https://doi-org.ezproxy.auckland.ac.nz/10.1186/s12929-019-0592-z

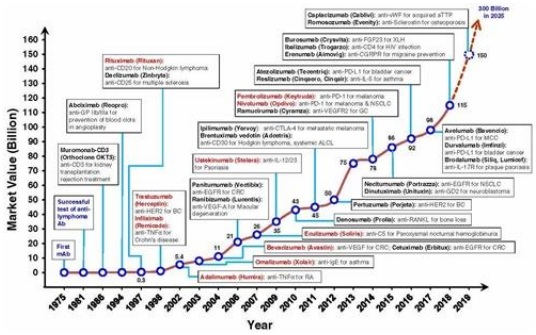
Infliximab is Remicade;

Trastuzumab is Herceptin;

Adalimumab is Humira;

Etanercept (Enbrel) is a fusion protein, part Ab and part TNF-alpha receptor ligand binding site.

Monoclonal Antibodies



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Monoclonals for Cancer

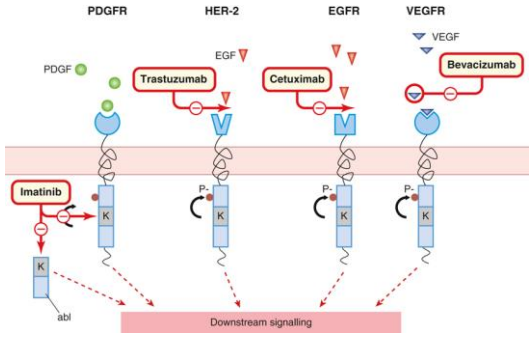
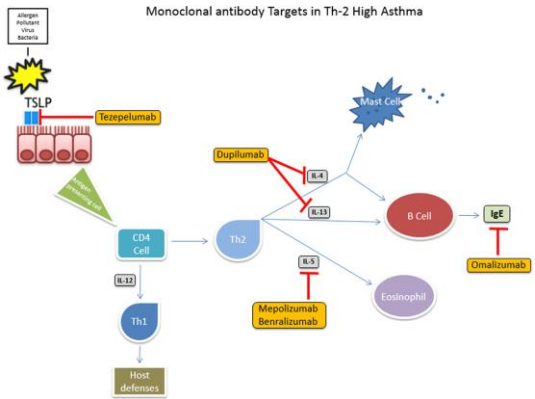


Fig 57.8. Ritter, James M., DPhil FRCP HonFBPhS FMedSci, Rang & Dale's Pharmacology, 57, 716-732
The mechanism of action of anticancer monoclonal antibodies and protein kinase inhibitors. Many tumours overexpress growth factor receptors such as epidermal growth factor receptor (EGFR), the proto-oncogene human epidermal growth factor 2 (HER2) ...

Biologics for Asthma

- Approximately 5% of asthma patients don't respond to traditional therapy
- Target specific chemokines using antibody-based therapy
- Can reduce the need for corticosteroids

Biologics for Asthma



Dorey-Stein ZL, Shenoy KV. Tezepelumab as an Emerging Therapeutic Option for the Treatment of Severe Asthma: Evidence to Date. *Drug Des Devel Ther*. 2021;15:331-338. https://doi.org/10.2147/DDDT.S250825

NOTE: Not expected to learn medicine names on this slide

Renin-Angiotensin-Aldosterone System (RAAS)

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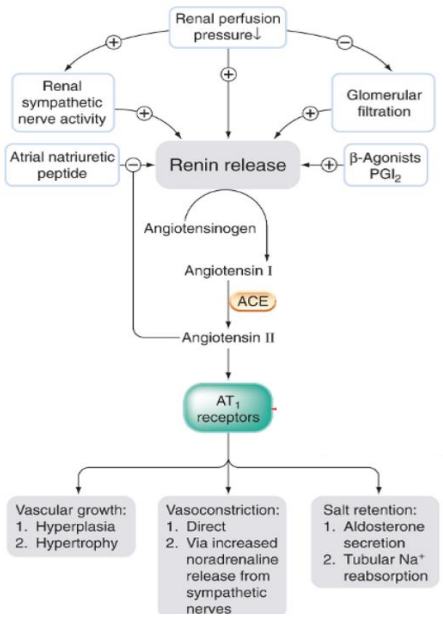
Learning Objectives

1. Explain the physiological role of the RAAS
2. Describe the mechanisms of action for a range of drugs acting on RAAS and relate them to previous Drug Target/Mechanisms of Drug Action lecture.
3. Explain the therapeutic and adverse effects of drugs acting on the RAAS.

Renin – Angiotensin II



For review of the RAAS please refer to:

- Medsci 142, Renal Physiology 3, 25.10-onwards
- Renin Angiotensin Aldosterone system - https://youtu.be/ibjodC7Ft7U

Control of renin release and formation, and action of angiotensin II.
The vascular system. Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS, Rang & Dale's Pharmacology, 22, 265-284

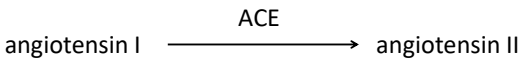
Drugs Targeting the RAAS

- **ACE inhibitors (ACE-I)**
- **Angiotensin receptor antagonists (ARBs)**

- Aldosterone antagonists
- Calcium channel blockers
- Diuretics
- Beta-blockers

Angiotensin Converting Enzyme Inhibitors (ACE-Is)

- Name says it all
- Mimic section of angiotensin I that binds to ACE
- Decreased Ang II levels
- e.g. cilazipril



Dual Effect of ACE-Is

- ACE = kininase II
- Responsible for degrading bradykinin,
  therefore ACE-Is increase bradykinin
- Responsible for two main adverse effects
  1. Dry cough
  2. Angioedema

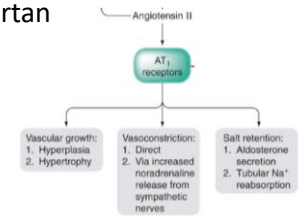
Bradykinin is a peptide that undergoes very similar synthesis and degradation to angiotensin – all a series of cleavages.
Bradykinin causes vasodilation, increase vascular permeability and sensitises pain nerves (in conjunction with prostaglandins)

ACE-I Induced Angioedema

- Most commonly affecting lips, larynx and pharynx
- Frequency = 0.1-0.2%
- ACE-Is result in higher levels of bradykinin ⟶ vasodilation and increased permeability
- Cease medication, supportive care, bradykinin-specific treatment

Angiotensin Receptor Antagonists/Blockers (ARBs)

- Competitive antagonists at AT-1 receptors
- Blocks most activity of the RAAS
- e.g. losartan



Control of renin release and formation, and action of angiotensin II.
The vascular system. Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS, Rang & Dale's Pharmacology, 22, 265-284

ACE-I, ARB or Both?

- Both ACE-Is and ARBs decrease likelihood of some cardiovascular events
- ACE-Is generally more effective, but more likely to display adverse effects
- ARBs possible as substitute
- Combination can be dangerous

Smooth Muscle Contraction

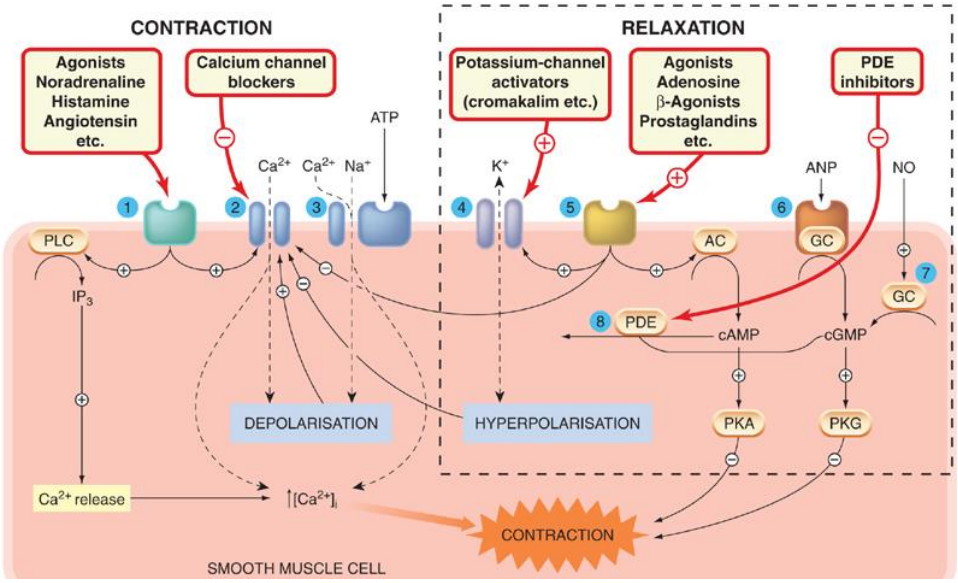


Fig 4.10 - Mechanisms controlling smooth muscle contraction and relaxation. How drugs act : cellular aspects – excitation, contraction and secretion. Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS, Rang & Dale's Pharmacology, 4, 50-66. Copyright © 2016, Elsevier Ltd

Aldosterone Antagonists

- e.g. spironolactone
- Antagonist at mineralocorticoid receptor
- Inhibits Na^+ reabsorption caused by aldosterone

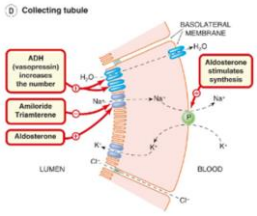


Fig 28-5
The kidney and urinary system
Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS, Rang & Dale's Pharmacology, 29, 355-366
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Calcium Channel Blockers

- Calcium channels are particularly important in muscle excitation and contraction
- Block channels inhibits smooth muscle contraction
  ⟶ decreased vasoconstriction
  ⟶ decreased blood pressure
- e.g. verapamil, nifedipine

Diuretics

- Ang II serves to promote retention of sodium and water ∴diuretics will oppose this action
- Primarily serve to increase excretion of sodium
- Variety of targets within the renal tubules
- Amiloride particularly relevant in counteracting RAAS activity

Diuretics

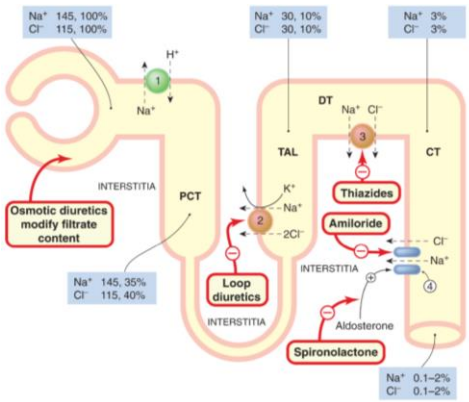

Fig 28.4. The kidney and urinary system. Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS, Rang & Dale's Pharmacology, 29, 355-366Copyright © 2016

Beta Blockers

- Main action on SNS, but this interacts with RAAS
- Competitive antagonists at β-adrenergic receptors, primarily β_1
- Decrease cardiac contractility, decrease renin secretion
- e.g. atenolol

ACE and COVID-19

- Widespread, membrane-bound enzyme
- ACE2 catalyses the breakdown of Ang II
- ACE2 expression regulated by AT-1 receptor
- Attachment site for SARS-CoV-2
- April 2021, **no** evidence that ARBs or ACE-Is increase likelihood or severity of Covid-19

Several analyses of hospital admissions, medical centre patients from different countries looking at ARB/ACE-I use and COVID infection.

2021 Update:

Aleksova A, Gagno G, Sinagra G, Beltrami AP, Janjusevic M, Ippolito G, Zumla A, Fluca AL, Ferro F. Effects of SARS-CoV-2 on Cardiovascular System: The Dual Role of Angiotensin-Converting Enzyme 2 (ACE2) as the Virus Receptor and Homeostasis Regulator-Review. Int J Mol Sci. 2021 Apr 26;22(9):4526. doi: 10.3390/ijms22094526. PMID: 33926110; PMCID: PMC8123609.

Almutlaq M, Alamro AA, Alroqi F, Barhoumi T. Classical and Counter-regulatory Renin-angiotensin System: potential key roles in COVID-19 pathophysiology. CJC Open. 2021 Apr 15. doi: 10.1016/j.cjco.2021.04.004. Epub ahead of print. PMID: 33875979; PMCID: PMC8046706.

Summary

- RAAS involved in regulation of blood pressure
- Pathology of RAAS involved in cardiovascular diseases
- Drugs exist that act on a variety of targets, including enzymes, receptors (GPCRs and steroid) and ion channels

Question: How are medicines that work on the RAAS useful in heart failure?