AUTONOMIC NERVOUS SYSTEM 2 of 3

SYMPATHOMIMETIC DRUGS

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FIGHT OR FLIGHT RESPONSE

OVERVIEW

Definition

Which drugs?

Where do they act?

Receptor activation

Physiological effects

of α & β activation

Uses & adverse effects

Individual agents

SYMPATHOMIMETICS

Classification

- direct/indirect
- receptors

α BLOCKERS)

β BLOCKERS)

Including ISA

DEFINITION

Sympathomimetic

= sympathetic + mimic

‘drugs that mimic (copy) the actions of the sympathetic nervous system’ i.e. of Adr & NA

α blockers) drugs that prevent the α or β

β blockers) actions of sympathomimetics

WHICH DRUGS? (1/2)

Sympathomimetics:

ADRENALINE, dopamine, dobutamine, NORADRENALINE, phenylephrine;

amphetamine, ephedrine, tyramine;

ISOPRENALINE, SALBUTAMOL;

α blockers:

labetolol, PHENTOLAMINE, phenoxybenzamine, PRAZOSIN;

WHICH DRUGS (2/2)

β blockers:

ATENOLOL, labetolol, metoprolol, practolol, PROPRANOLOL;

Others:

cocaine, guanethidine, hexamethonium, MAO inhibitors, methyldopa, TCA's, reserpine

WHERE THE SNS CAN BE INTERFERED WITH

2. Guanethidine:prevents NA release
3. Reserpine: Depletes NA reserves
4. Methyldopa: false transmitter

1. hexamethonium

5. MAOI: prevent destruction of NA
6. TCA's & cocaine: prevent NA reuptake
7. Amphetamine: indirect release of NA
8. Adrenaline & Propranolol: receptor binding

CLASSIFICATION (1/2): Mode of action

NA neurotransmitter stored and released

⟶ activates receptor

- Direct – adrenoreceptor agonists: Adr, NA, isoprenaline (entirely); dopamine, phenylephrine (mainly)
- Indirect – causes the release of stored NA: amphetamine, tyramine (entirely); ephedrine (mainly)

CLASSIFICATION (2/2): Receptors

Ahlquist (1948)

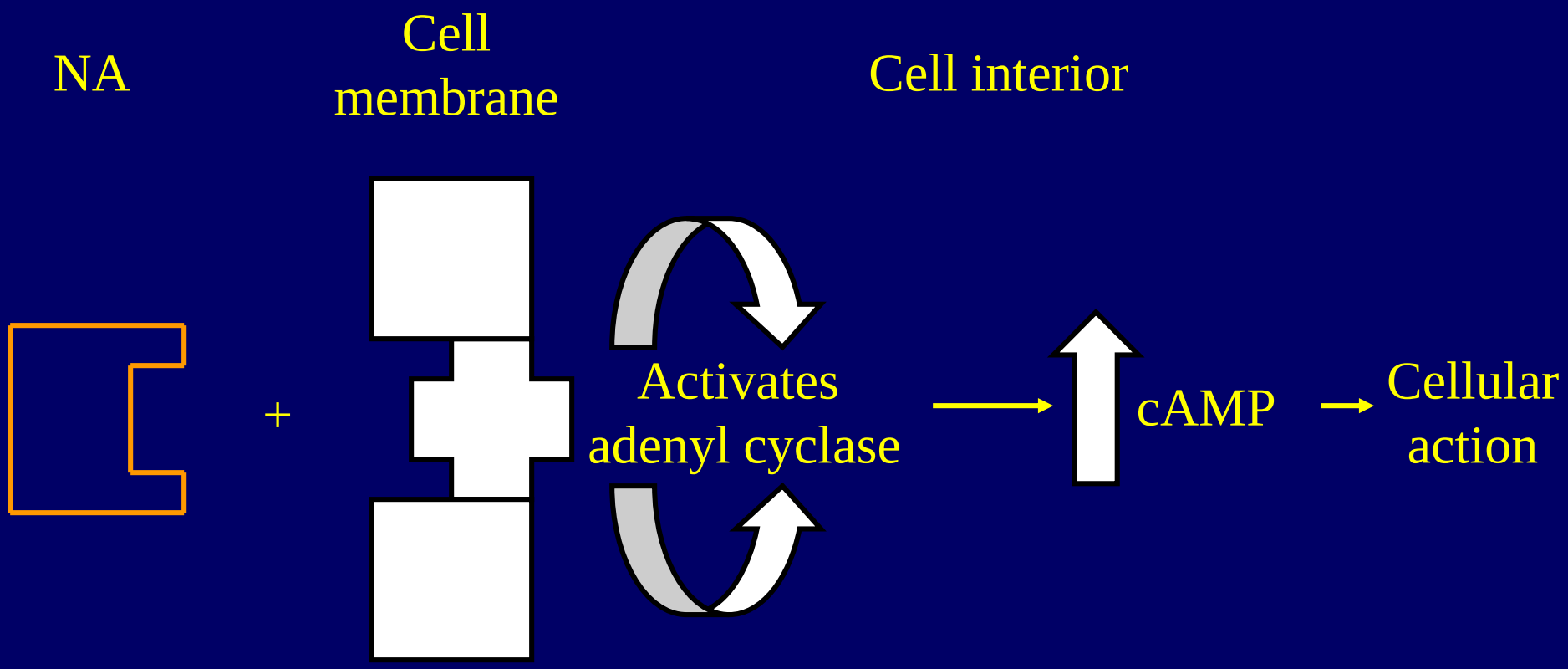
Noted adrenaline had 3 distinct actions: cardiac stimulation, vasoconstriction, vasodilatation

The only available antagonist at the time was phenoxybenzamine – only prevented the the vasoconstriction, not the other actions

Postulated two different sorts of receptors α & β

Confirmed 10 years later by dichlorisoprenaline, the first β blocker

CONSEQUENCES OF RECEPTOR ACTIVATION



PHYSIOLOGICAL ACTION OF RECEPTOR STIMULATION

- α_1 receptors

Mydriasis

Vasoconstriction (peripheral)

Uterine contraction

Sweating

Ejaculation

Bladder sphincter contraction

Intestinal relaxation

- β receptors

Increased automaticity	β_1
Increased contractility	β_1
Vasodilatation (muscles)	β_2
Bronchial, uterine, intestinal relaxation	β_2
Hypokalaemia, hepatic glycogenolysis	β_2

Detrusor relaxation

SELECTIVE vs SPECIFIC RECEPTOR ACTIVATION

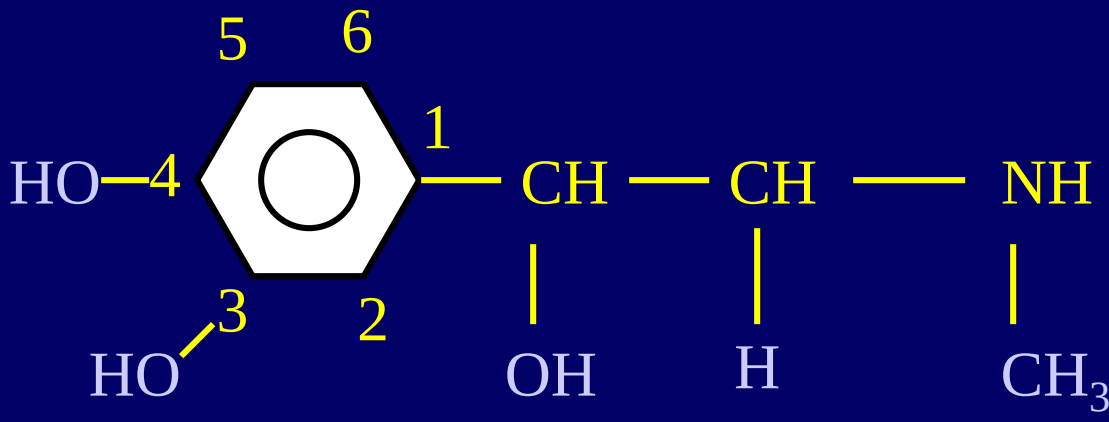
A relative concept: selective <u>not specific</u>

If drug A has 100x more affinity for receptor 1 than 2, then increasing the dose 100x will increase the activity by 100x at both receptor subtypes.

So increasing dose of salbutamol will have increasing β_2 actions as well as β_1 .

STRUCTURE

Basic structure of sympathomimetic drugs:



e.g adrenaline

Substitutions at 3’ and 4’ = catecholamines: Adr, NA, dopamine, dobutamine & isoprenaline

Non catecholamines has different substitutions
e.g. amphetamine & salbutamol

PHARMACOKINETICS

- GI absorption & metabolism depends on 2 enzymes in liver & kidney (both COMT & MAO) and in nerve endings & gut (MAO only)
- Catecholamines are destroyed by COMT & MAO → $T_{1/2}$ = 2 mins, inactive orally. I.v stat or continuous infusion
- Non catecholamines are effective orally, e.g. salbutamol & ephedrine $T_{1/2}$ 4hr

USES (1/4)

- Adrenaline - α and β action

Circulatory failure: dose 1 mg = 1ml of 1:1000 solution

Anaphylactic shock: route i.m.

Cardiac arrest: route i.v.

As a vasoconstrictor to prolong action of local anaesthetics

Topical mydriatic (↓ intraocular pressure)

USE (2/4)

- Noradrenaline - mainly α, slight β_1 action

Cardiogenic shock: continuous i.v. infusion

- Isoprenaline - β_1 & β_2 (non selective)

Temporary treatment in complete heart block

- Dobutamine – β_1 inotropic > chronotropic

Shock and low output heart failure

USES (3/4)

- Dopamine – dose dependent receptor action

2.5-5μg/kg/min: renal vasodilatation D_{1+2}

Increasing dose β_1 activity on heart

High dose causes tachycardia & hypertension

Drug of choice for shock (n.b. fluid status)

- Salbutamol – β_2 agonist

Bronchodilatation in asthma and to prevent uterine contractions in premature labour

USES (4/4)

- Ephedrine – indirect NA release

Nasal decongestants (vasoconstriction)

Orally or intranasally

ADVERSE EFFECTS

Depend of receptor selectivity and are dose dependent.

α – vasoconstriction: hypertension, gangrene

β_1 – tachycardia, arrhythmia, hypertension

β_2 – vasodilatation: hypotension, tremor, hypoglycaemia, hypokalaemia

SUMMARY

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ISA