Pharmacology of the Sympathetic Nervous System I

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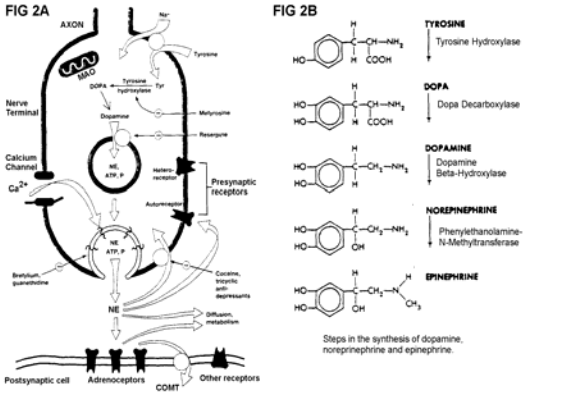
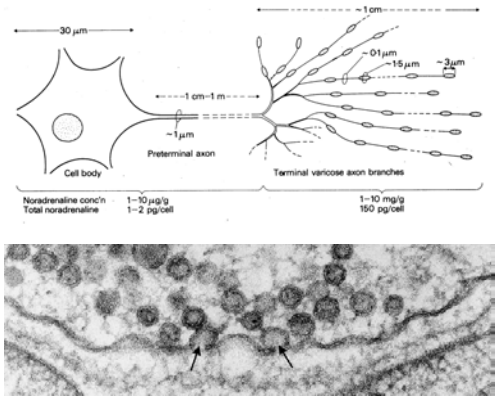
Sympathetic Nervous System

Norepinephrine (NE)	=	Noradrenaline (NA)
Epinephrine (EPI)	=	Adrenaline (AD, ADR)
Noradrenergic	=	Adrenergic
Isoproterenol	=	Isoprenaline (ISO)

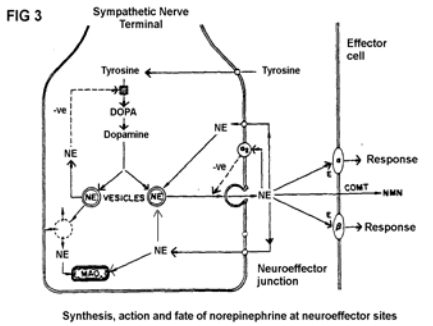
Adrenergic Nerve Terminal



Noradrenergic Neuron



Neuronal (Uptake1) vs Extraneuronal (Uptake2)



Neuronal Uptake
Uptake 1
70-80%

Cocaine
TCA

MAO

Extraneuronal
Uptake 2
10-20%

COMT

MAO vs COMT

	Mitochondrial outer membrane	cytosol
	symp. nerve, placenta (MAO_A) platelets (MAO_B) liver, kidney, brain (MAO_A + MAO_B)	most tissues, not in symp. nerve
	increases NE level in symp. neuron, potentiates release by tyramine-like drugs	no effect

MAO vs COMT

COMT

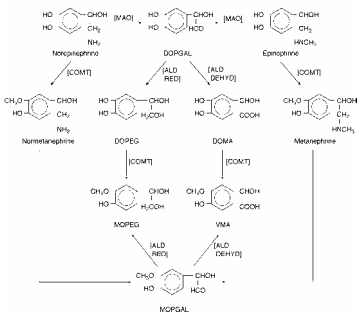
MAO

Inhibitors: Pyrogallol, Tropolone

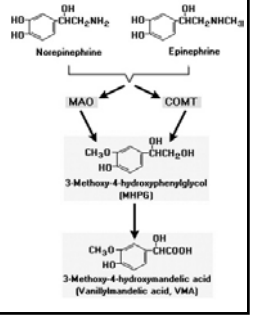
Inhibitors:	**Non-selective**	
Depression	**Tranylcypromine, Pargyline**	
Inhibitors:	**Selective**	
Depression	**MAO-A**	**Clorgiline**
Parkinson' D	**MAO-B**	**Selegiline**

Metabolism of Catecholamines

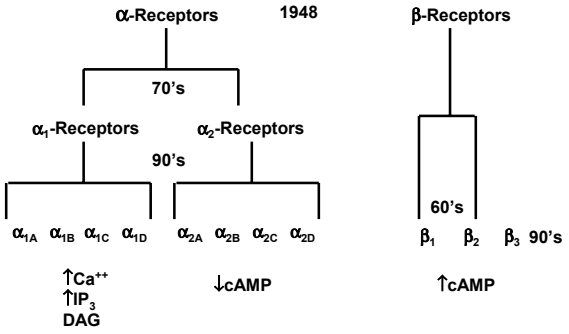
Metabolism by either MAO or COMT, inactivates drug



Major Metabolites
VMA
MOPEG



Receptor Subtypes



Adrenergic Agents – Relative Selectivity

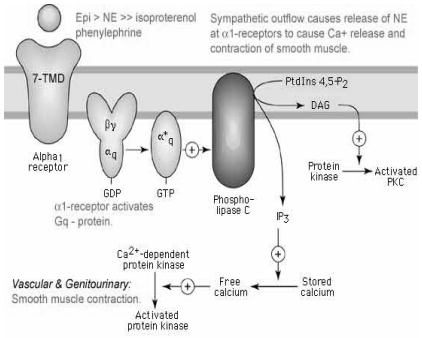
RECEPTOR	TISSUE	ACTIONS
$Alpha_1$ EPI > or = NE >> ISO	most vascular smooth muscle pupillary dilator muscle pilomotor smooth muscle vas deferens liver intestinal smooth muscle intestinal sphincters	contraction contraction (dilation) erects hair contraction glycogenolysis relaxation contraction
$Alpha_2$ NE > EPI >> ISO	some vascular smooth muscle nerve terminals (NE & Ach) platelets fat cells	contraction inhibit transmitter release aggregation inhibition of lipolysis
$Beta_1$ ISO > EPI = NE	heart coronary blood vessels kidney	↑ force, rate, conduction velocity dilatation renin release
$Beta_2$ ISO > or = EPI >> NE	bronchial smooth muscle uterine smooth muscle intestinal smooth muscle vascular smooth muscle liver NA nerve terminals	relaxation relaxation relaxation relaxation glycogenolysis facilitation of release
$Beta_3$ ISO = NE > EPI	fat cells	lipolysis

Second Messengers

Receptor	Location	G Protein	Second Messenger

X

Phospholipase C

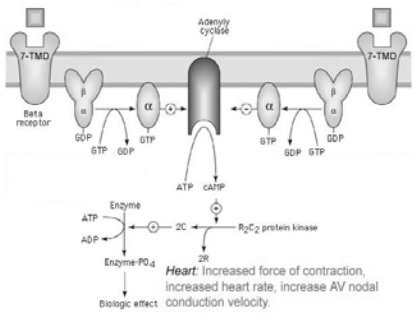


G-Protein coupled receptors

Adrenergic
Alpha1-receptors

Cholinergic
M1
M3
M5

Adenylate Cyclase



G-Protein coupled receptors

Stimulate
All Beta-receptors
D1, D5-receptors

Inhibit
Alpha2-receptors
D2, D3, D4-receptors
M2, M4-receptors

Hepatocyte

norepinephrine / epinephrine

α1-AR
↓
IP_3 / DAG
↓
Ca++ / PKC
↓
Ca++-dependent phosphorylase K.
↓
phosphorylase a
↓
glycogenolysis

β2-AR
↓
↑cAMP
↓
protein kinase A
↓
phosphorylase kinase
↓
phosphorylase a
↓
glycogenolysis

↑ glucose-1-P

Vasculature

norepinephrine / epinephrine

α1-AR
↓
IP_3 / DAG
↓
Ca++ / PKC
↓
Vasoconstriction
↓
Increase resistance
↓
Increase BP

β2-AR
↓
↑cAMP
↓
protein kinase A
↓
Vasodilation
↓
Decrease resistance
↓
Decrease BP

??????

Catecholamines

A. Norepinephrine (limited use, pressor agent, shock)
- Activates: both alpha, $beta_1$, $beta_3$, $beta_2$ (weakest)
- Substrate for MAO & COMT, does not cross BBB

B. Epinephrine (DOC - Allergic reaction)
- Activates both alpha, $beta_1$, $beta_2$, $beta_3$ (weakest)
- Substrate for MAO & COMT, does not cross BBB

C. Dopamine (DOC – shock)
- Precursor of NE and EPI
- Activates $alpha_1$, dopamine receptors
- Substrate for MAO & COMT, does not cross BBB

D. Isoproterenol (asthma, cardiac stimulant)
- Activates all beta receptors
- Substrate for COMT, does not cross BBB

None effective orally

Do not cross BBB

Actions brief

DOC

Drug of Choice

Non-Catecholamines – Beta agonists

- **Selective beta2-agonists:**
  albuterol, ritodrine, metaproterenol, terbutaline

  Uses: asthma, premature labor

  Oral: Onset 1-2 hrs, duration 4-6 hrs
  Inhal: Onset 5-10 min, duration 3-4 hrs (fewer side effects)

- **Adverse effects:** cardiovascular (↑HR, ↓BP)

- **Selective beta1-agonists:**
  dobutamine, prenalternol

  Uses: Congestive heart failure
  Increase force, no change in HR or oxygen demand

Non-Catecholamines – Alpha agonists

- **Selective alpha1-agonists:**
  methoxamine, phenylephrine,
  metaraminol (direct & indirect actions, orally active)

  Uses: hypotension or shock, nasal decongestant

- **Selective alpha2-agonists:**
  clonidine, α-methyldopa (prodrug), guanfacine

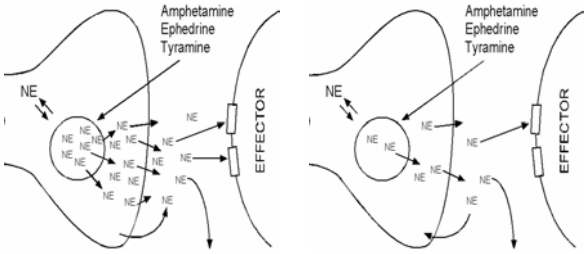
  Uses: hypertension (CNS action)
  opioid withdrawal (decrease severity)

  Side effects: impotence, dry mouth, rebound HT

Indirectly-acting Sympathomimetics (displace transmitter)

- **Amphetamine, methamphetamine, methylpenidate**
  CNS stimulant, performance enhancer, physical & mental abuse
  ↑alertness, mood, self-confidence, concentration, psychological dependence, tolerance, tachyphylaxis
- Uses: ADHD, appetite suppression (?), narcolepsy
- Toxicity: cardiovascular, restlessness, tremor, insomnia
- **Ephedrine (mixed)**
  - direct action (alpha- and beta-receptors)
  - indirect action to release norepinephrine
- Uses: nasal decongestant
- **Tyramine** (not a drug, interaction with MAO inhibitors)

Tachyphylaxis



Indirectly-acting Sympathomimetics (cont.)

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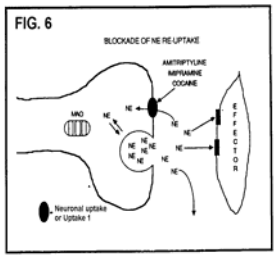
Neuronal Uptake Inhibition



Inhibit neuronal uptake (Uptake1)
Can prevent the action of indirectly acting agents (e.g. amphetamine) and can potentiate the effects of NE (ie. not removed from synaptic junction).

Neuronal Uptake 1: 70-80%

Cocaine

Tricyclic antidepressants (Imipramine, amitriptylline)
High dose: block alpha- & M-rec.

Atomoxetine (used for ADHD)

Guanethedine (competes for uptake)

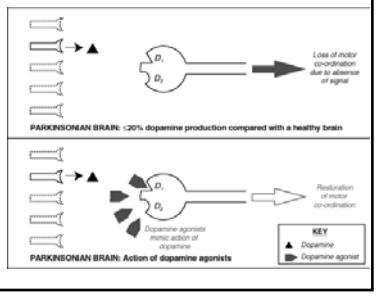
MAO vs COMT

	Mitochondrial outer membrane	cytosol
	symp. nerve, placenta (MAO_A) platelets (MAO_B) liver, kidney, brain (MAO_A + MAO_B)	most tissues, not in symp. nerve
	Increases NE level in symp. neuron, potentiates release by tyramine-like drugs	no effect
	Pargyline, tranylcypromine (non-selective) Clorgyline (MAO_A-selective) Selegiline (MAO_B-selective)	pyrogallol
	Mental depression (non-selective or MAO_A-selective) Parkinson's disease (MAO_B-selective)	none
	MAO inhibitors potentiate effects of tyramine (due mainly to blocking metabolism of tyramine by MAO in liver)	none

Parkinson's Disease

- General population 1:1000, over 60 1:75
- Tremor, stiffness, or clumsiness, usually involving one side, difficulty walking, fatigue, depression
- Progressive destruction of the dopaminergic nigrostriatal pathway
- Elevated cholinergic activity

- **Treatment:**
- MAO inhibitors:
- Dopamine agonists: bromocriptine
- L-Dopa
- Anticholinergics: benztropine
- Decarboxylase inhibitor: carbidopa
- Amantadine: Inhibit D-uptake, M-rec, NMDA-block, release dopamine



Tyramine Interaction with MAO Inhibitors

Can cause hypertensive crisis (↑BP, ↑HR)

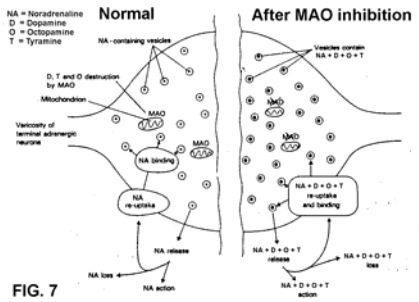
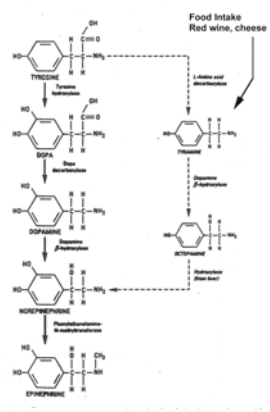


FIG. 7

Aged cheese & red wine are rich in tyramine

MAOI and Tyramine Crisis



↑Blood pressure, ↑Heart rate
Treatment: α-blocker or labetalol (α-, β-blocker)

Normally dietary tyramine is metabolized by MAO

With MAO inhibition, octopamine is produced and stored in vesicles with NE

Aged cheese, red wine are rich in tyramine

Tyramine Interaction with MAO Inhibitors

Can cause hypertensive crisis (↑BP, ↑HR)

Aged cheese & red wine are rich in tyramine

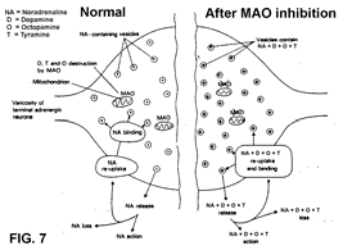
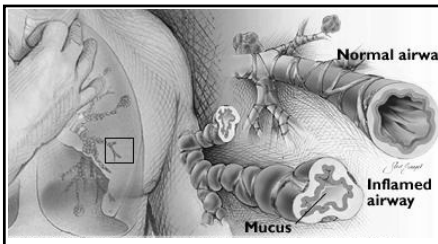


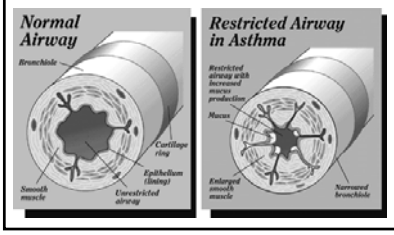
FIG. 7

Therapeutic uses: Sympathomimetics 1

- **Asthma (major use)**
  - bronchodilation with ↓airway resistance
  - beta2-selective agents eg. albuterol
- **Allergic Reactions**
  - acute hypersensitivity reactions (food, bee sting, drug allergy)
  - epinephrine (DOC)
- **Nasal Decongestant (common use)**
  - vasoconstriction (ephedrine, phenylephrine)
- **Hypotension (acute)**
  - intoxication with antihypertensive agents, spinal anesthesia, hemorrhage
  - phenylephrine, methoxamine, metaraminol



Asthma



Albuterol
Terbutaline,
Metaproterenol

β_2-selective agonists

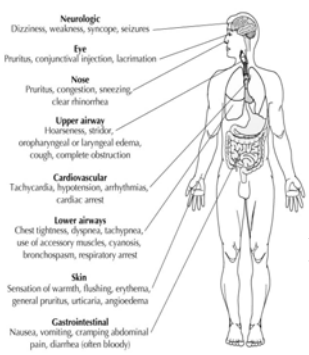
- bronchodilation

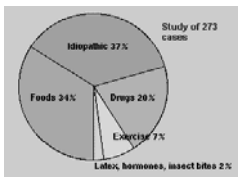
Inhalation vs oral
- less side effects

Ritodrine
- premature labor

Epinephrine

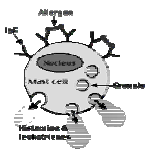
Anaphylaxis





bronchoconstriction
↑secretions
↓blood pressure

Epinephrine
- bronchodilation
- vasoconstriction



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- **Hypotension (acute)**
  - intoxication with antihypertensive agents, spinal anesthesia, hemorrhage
  - phenylephrine, methoxamine, metaraminol

Therapeutic uses: Sympathomimetics 2

- **Hypertension (chronic)**
  - centrally acting α2-receptor agonists (clonidine, α-methyl-dopa)
- **Shock (need to treat cause)**
  - dopamine (DOC), epinephrine, NE
  - blood loss, cardiac failure, septic shock, cardiac obstruction
  - inadequate perfusion of tissues, need to maintain BP and cerebral blood flow
- **Congestive Heart Failure**
  - dobutamine (acute)
- **Cardiac Heart Block & Cardiac Arrest**
  - epinephrine or isoproterenol

Therapeutic uses: Sympathomimetics 3

- **Ophthalmic**
  - dilate the pupil (phenylephrine)
  - glaucoma (epinephrine) also beta-blocking agents used (common)
- **Uterine Contractions**
  - suppress premature labor
  - ritodrine, terbutaline (not FDA approved)
- **Hyperactivity Disorder (ADHD)**
  - amphetamines, methylphenidate (ritalin)
  - NE uptake inhibition: atomoxetine
- **Others: [obesity], nacrolepsy**
  - amphetamines-like agents

Toxic effects of Sympathomimetics

- **Extensions of their receptor-mediated effects**
- **Cardiovascular (main)**
  - cardiac stimulation (β-AR, arrhythmias)
  - hypertension (α-AR, hemorrhage)
- **CNS**
  Especially those that cross BBB (ie. amphetamine)
  - restlessness
  - dizziness
  - insomnia
- **Alpha2-receptor agonists**
  - dry mouth, sedation, impotence