Pharmacology 659

Adrenergic Agonists and Antagonists

Charles B. Smith, M.D., Ph.D.
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317A MSRB III
7343-763-9825
cbsmith@umich.edu
Adrenalin
Epinephrine
Classification of Adrenergic Agonists
Monoaminergic Synapse
Classification of Adrenergic Agonists

- Directly-acting adrenergic agonists act at adrenergic receptors located on effector cells.
- Indirectly-acting adrenergic agonists act by displacing norepinephrine from noradrenergic neurons.
- Mixed-acting agonists have both actions.
Monoaminergic Synapse

Cartoon of monoaminergic synapse
DIRECTLY-ACTING AGONIST

(log molar concentration)

RESPONSE (percent maximum response)

CONTROL
RESERPINE
DENERVATION COCAINE
Monoaminergic Synapse
Classification of indirectly acting agonists

INDIRECTLY-ACTING AGONIST
(log molar concentration)

RESPONSE (percent maximum response)

CONTROL
COCAINE
RESERPINE
DENERVATION
Classification of mixed acting agonists
Blood Pressure

A

B

Henry Hallett Dale
(1875-1968)
Nobel Prize - 1936
Definition of $\alpha$-Adrenergic Receptors

- Relative potencies of agonists
  
  Epinephrine $>$
  Norepinephrine $>>>$ Isoproterenol

- Selective antagonists
  
  Phenoxybenzamine
  Phentolamine
**α-Adrenergic Receptors**

**α₁-Receptors**
- Agonist
  - Phenylephrine
- Selective antagonist
  - Prazosin

**α₂-Receptors**
- Agonists
  - Clonidine
  - α-Methyldopa
- Selective antagonists
  - Idazoxan
  - Yohimbine
Definition of $\beta$-Adrenergic Receptors

- Relative potencies of agonists
  - Isoproterenol > Epinephrine >> Norepinephrine

- Selective antagonist
  - Propranolol
\(\beta\)-Adrenergic Receptors

\(\beta_1\)-Receptors

- Agonist
  
  Iso > Epi = NE
  Dobutamine

- Selective antagonists
  
  Metoprolol
  Atenolol

\(\beta_2\)-Receptors

- Agonist
  
  Iso > Epi >> NE
  Terbutaline

- Selective antagonists
  
  ICI 118551
\[\beta\]-Adrenergic Receptors

\[\beta_3\]-Receptors

- Agonist

  Iso = NE > Epi  
  BRL 37344

- Selective antagonists

  ICI 118551  
  CGP 20712A
Structure-Activity Relationships
Structure-Activity Relationships

Epinephrine
Structure-Activity Relationships

Direct activity at $\alpha$- and $\beta$- receptors requires -OH groups at the 3 and 4 positions of the ring.
Structure-Activity Relationships

- Substitution of a -OH on the β- carbon increases activity directly at α- and β- receptors
Structure-Activity Relationships

A two carbon side chain between the terminal -N and the benzene ring confers greatest activity overall.
Structure-Activity Relationships

Substitution on the terminal -N increases β-receptor activity.
Structure-Activity Relationships

Substitution on the $\alpha$-carbon confers resistance to oxidative deamination.
Structure-Activity Relationships

- A two carbon side chain between the terminal -N and the benzene ring confers greatest activity.
- Substitution on the terminal -N increases β-receptor activity.
- Direct activity at α- and β- receptors requires -OH groups at the 3 and 4 positions of the ring.
- Substitution on the α- carbon confers resistance to oxidative deamination.
- Substitution of α -OH on the β- carbon increases activity directly at α- and β- receptors.