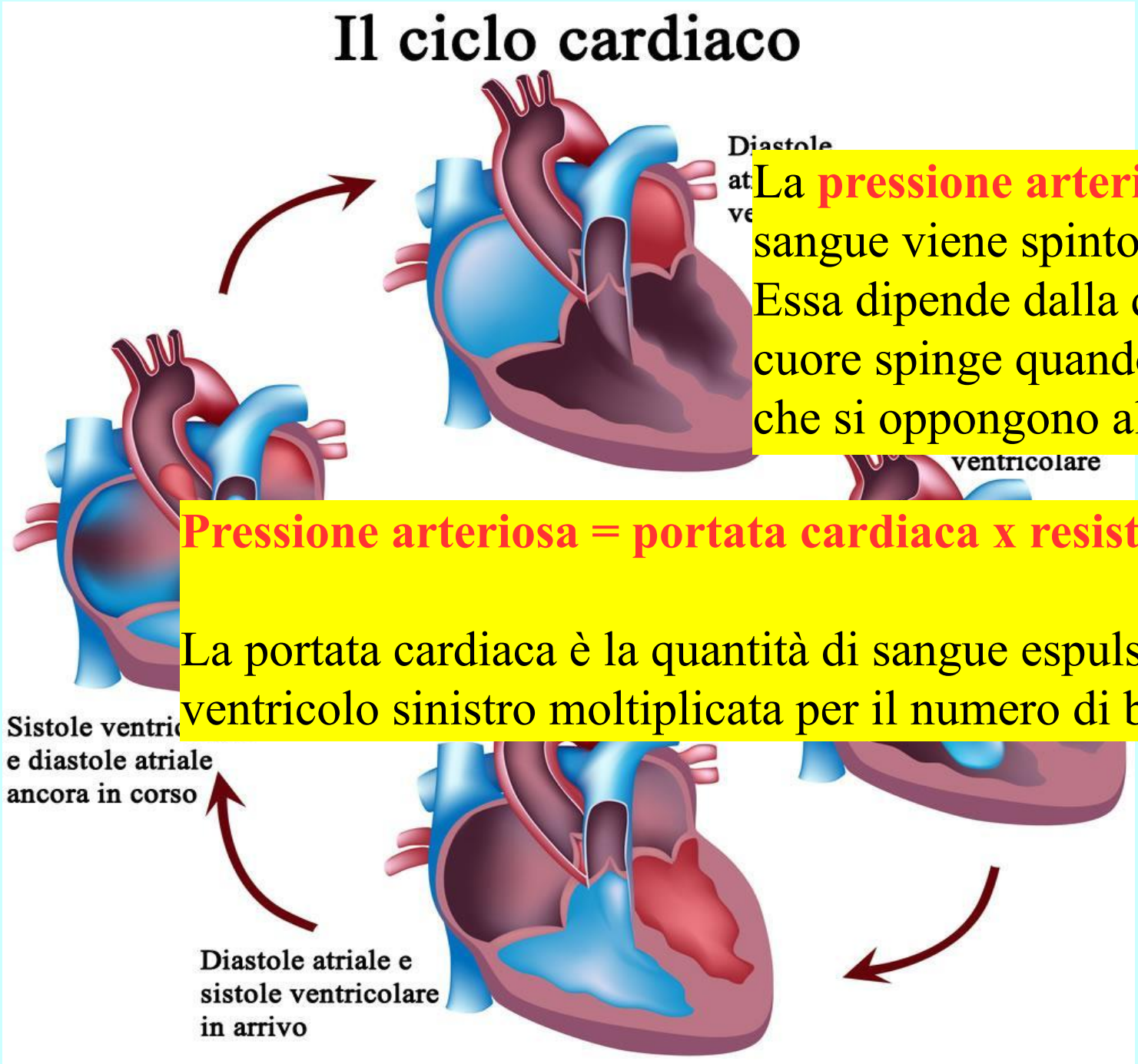
# PRESSIONE




DIASTOLE (espansione)
SISTOLE (contrazione)

La **pressione arteriosa** è quella forza con cui il sangue viene spinto attraverso i vasi.
Essa dipende dalla quantità di sangue che il cuore spinge quando pompa e dalle resistenze che si oppongono al suo libero scorrere.

**Pressione arteriosa = portata cardiaca x resistenze periferiche**

La portata cardiaca è la quantità di sangue espulsa ad ogni sistole dal ventricolo sinistro moltiplicata per il numero di battiti al minuto.

# PRESSIONE

- La pressione arteriosa è quindi determinata da tre fattori principali:
- la quantità di sangue che viene immessa in circolo durante la sistole e sua viscosità (ematocrito)
- la forza di contrazione del cuore
- le resistenze offerte dai vasi (arterie e vene) al passaggio del flusso sanguigno

# IPERTENSIONE

| | BLOOD PRESSURE (MM HG) | |
|---|---|---|
| **CLASSIFICATION** | ***Systolic*** | ***Diastolic*** |
| Normal | <120 | and <80 |
| Pre-hypertension | 120–139 | or 80–89 |
| Hypertension, stage 1 | 140–159 | or 90–99 |
| Hypertension, stage 2 | ≥160 | or ≥100 |

L'IPERTENSIONE viene definita per convenzione un rilevante aumento della pressione del sangue superiore a 140/90 mm Hg, ed è un criterio che caratterizza un gruppo di pazienti il cui rischio di patologie cardiovascolari correlate è sufficientemente alto da meritare attenzione medica.

# IPERTENSIONE

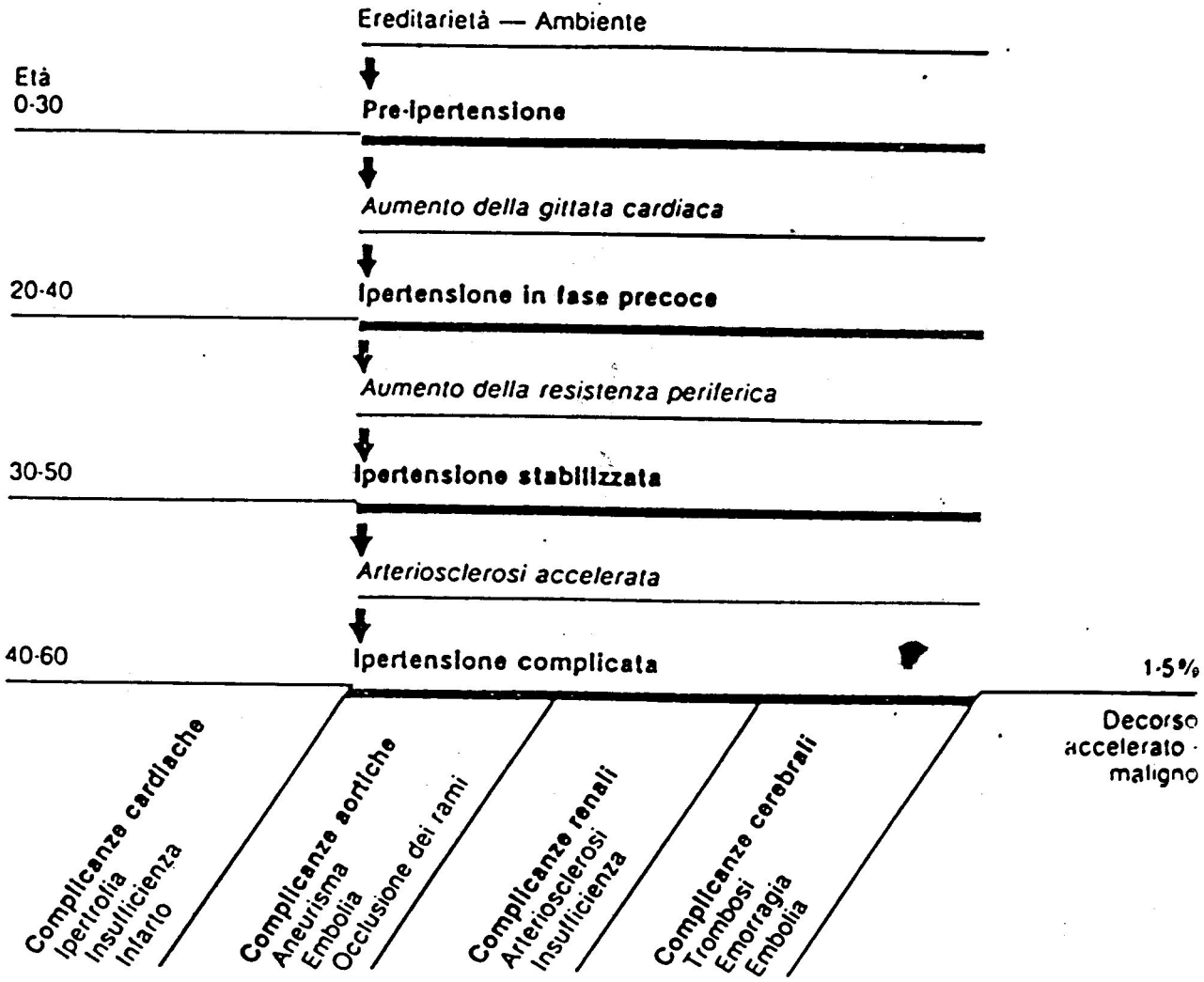
## IPERTENSIONE ESSENZIALE

Nel 90-95% dei casi, circa il 50% della popolazione tra i 60 e 69 anni, la prevalenza aumenta ulteriormente dopo i 70.

## IPERTENSIONE SECONDARIA

- Stenosi di arterie renali (condizione patologica consistente nel restringimento di un vaso sanguigno)
- Feocromocitoma (raro tumore che secerne catecolamine)
- Disfunsioni endocrine

Figura 6
Decorso naturale dell'ipertensione essenziale non trattata.




Adattata da Kaplan, N.M.: *Clinical Hypertension*. Baltimora, Williams & Wilkins. 1978. p. 87.

# REGOLAZIONE DELLA PRESSIONE DEL SANGUE

- **Tempi di risposta rapidi (secondi)**
  - Barorecettori
  - Chemorecettori
  - Recettori ischemici centrali

- **Tempi di risposta intermedi (minuti e ore)**
  - Sistema renina-angiotensina (RAS)
  - Rilassamento dei vasi per effetto della pressione
  - Permeabilità dei capillari

- **Controllo a lungo termine (ore e giorni)**
  - Funzione renale in relazione al RAS, sistema nervoso simpatico, Fattore natriuretico atriale (ANF), vasopressina, endotelina e ossido di azoto (NO).

- **Controllo genetico**

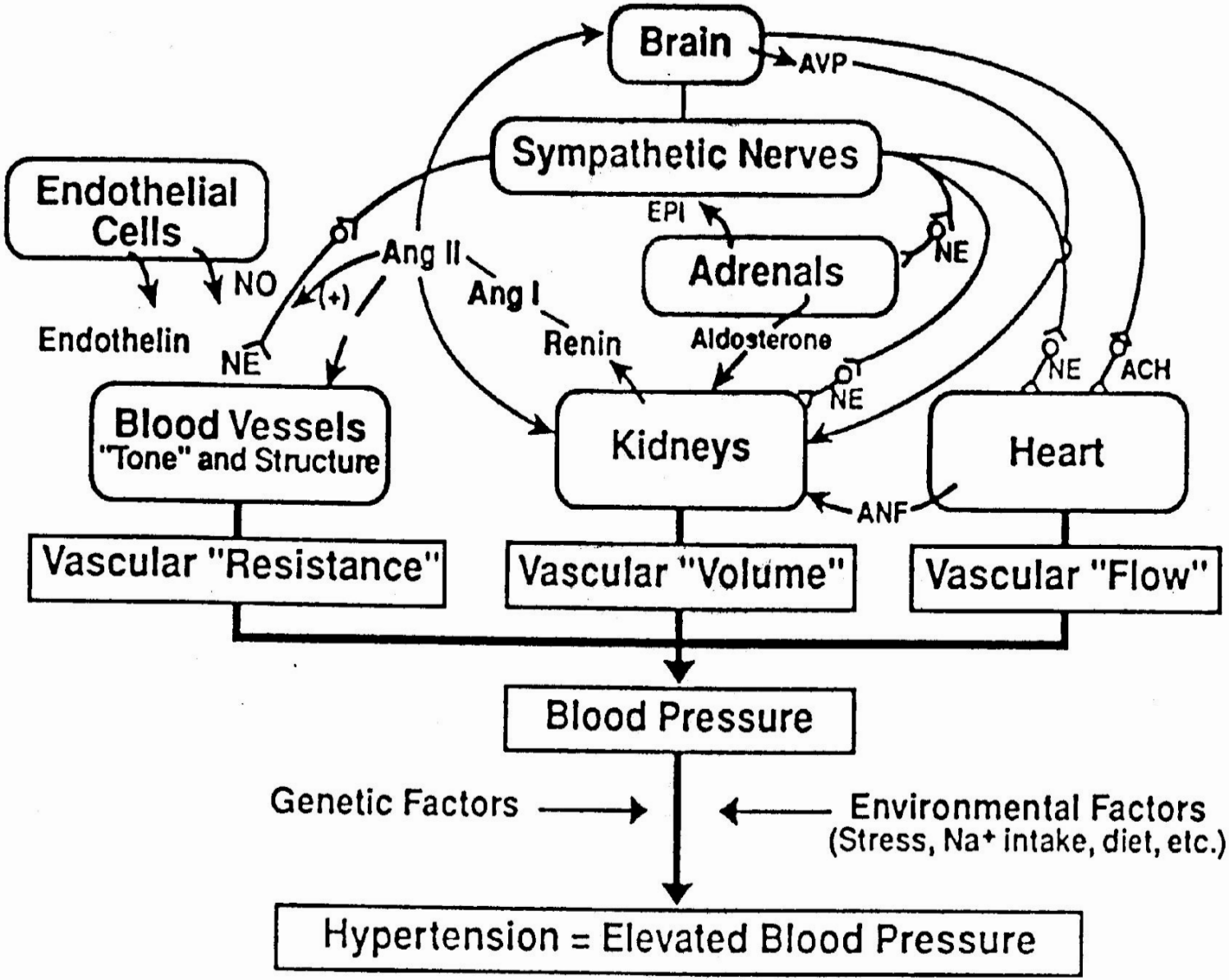
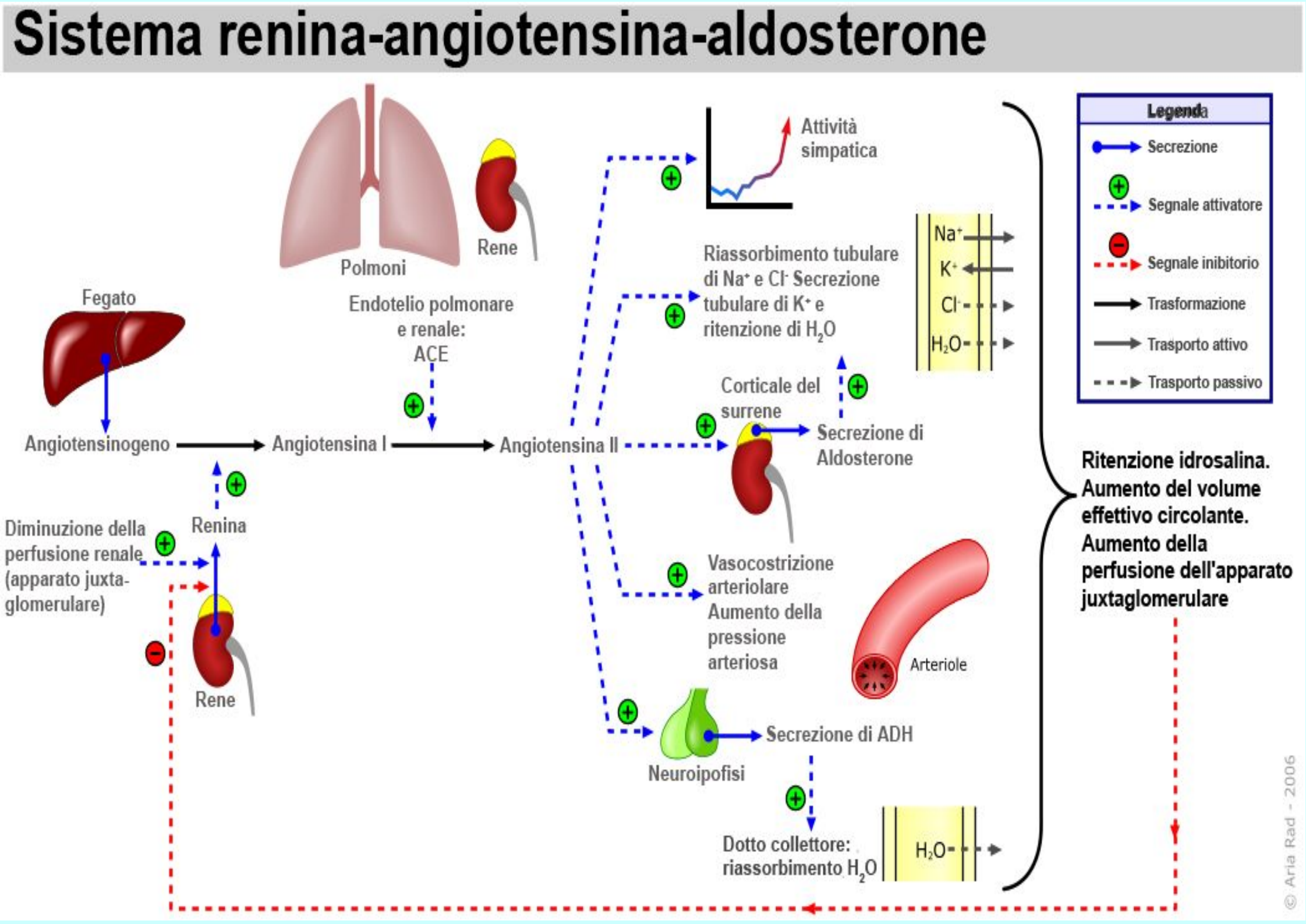



**Fig. 29.1** The interplay between cardiovascular organ systems to regulate "normal" blood pressure and the genetic and environmental factors that lead to hypertension.

# Sistema renina-angiotensina-aldosterone



# EZIOLOGIA DELL'IPERTENSIONE

- **Fattori neurali**
  - Stress: stimolo centrale → aumentata gittata cardiaca → aumentata resistenza vascolare (ipertono simpatico)

- **Fattori ormonali**
  - Sistema Renina-Angiotensina-Aldosterone
  - Angiotensina II
    - Azione vasocostrittrice
    - Rilascio di aldosterone
    - Rilascio di catecolammine

- **Fattori elettrolitici**

- **Fattori vascolari**
  - Ispessimento della parete vascolare

- **Fattori ereditari**

## Table 32–2 Classification of Antihypertensive Drugs by Their Primary Site or Mechanism of Action

*Diuretics* (Chapter 28)

1. Thiazides and related agents (hydrochlorothiazide, chlorthalidone, *etc.*)
2. Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid)
3. $K^+$-sparing diuretics (amiloride, triamterene, spironolactone)

*Sympatholytic drugs* (Chapters 9, 10, and 33)

1. b Adrenergic antagonists (metoprolol, atenolol, *etc.*)
2. a Adrenergic antagonists (prazosin, terazosin, doxazosin, phenoxybenzamine, phentolamine)
3. Mixed adrenergic antagonists (labetalol, carvedilol)
4. Centrally acting agents (methyldopa, clonidine, guanabenz, guanfacine)
5. Adrenergic neuron blocking agents (guanadrel, reserpine)

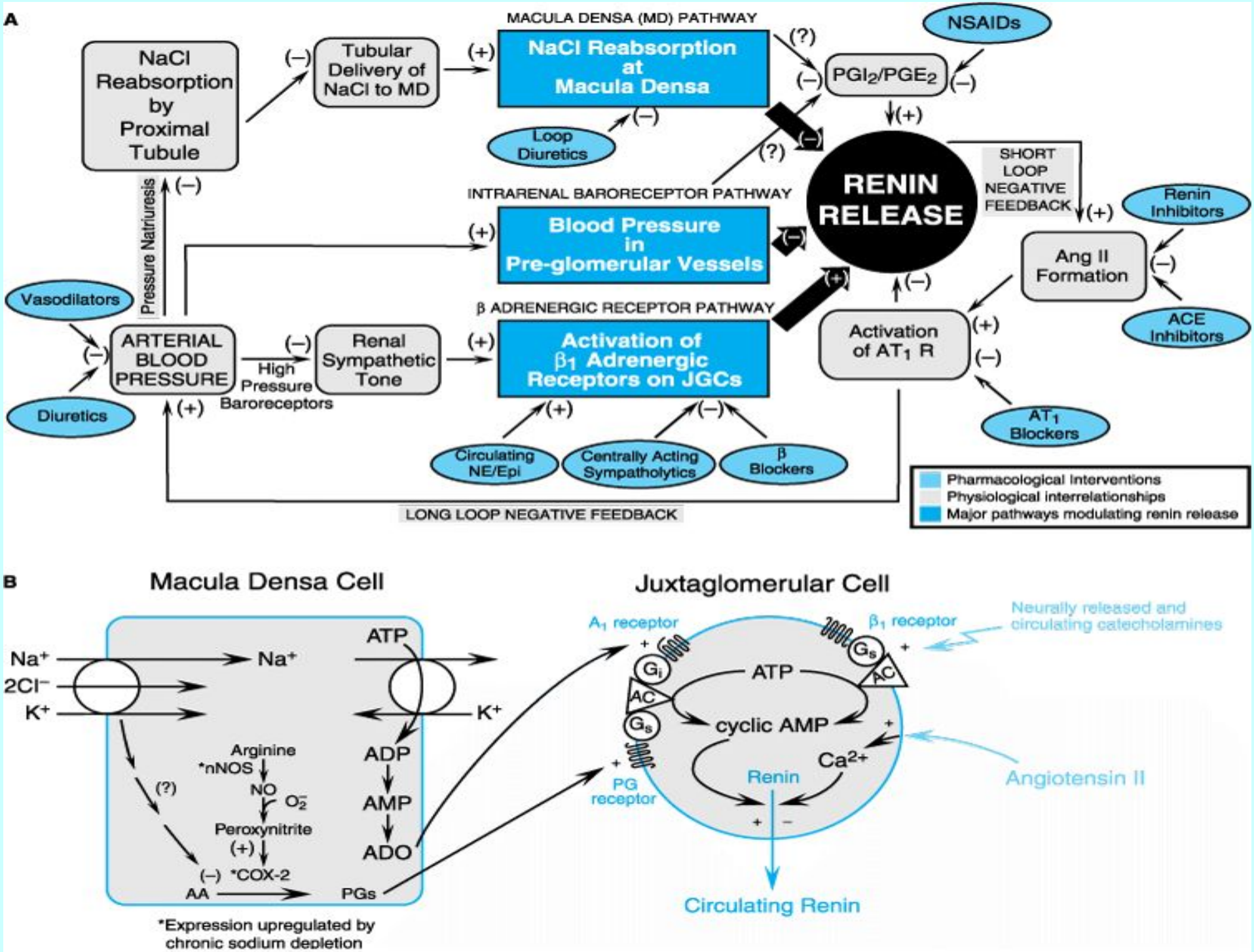
*$Ca^{2+}$ channel blockers* (Chapters 31, 32, 33, and 34) (verapamil, diltiazem, nimodipine, felodipine, nicardipine, isradipine, amlodipine)

*Angiotensin-converting enzyme inhibitors* (Chapters 30 and 31), (captopril, enalapril, lisinopril, quinapril, ramipril, benazepril, fosinopril, moexipril, perindopril, trandolapril)

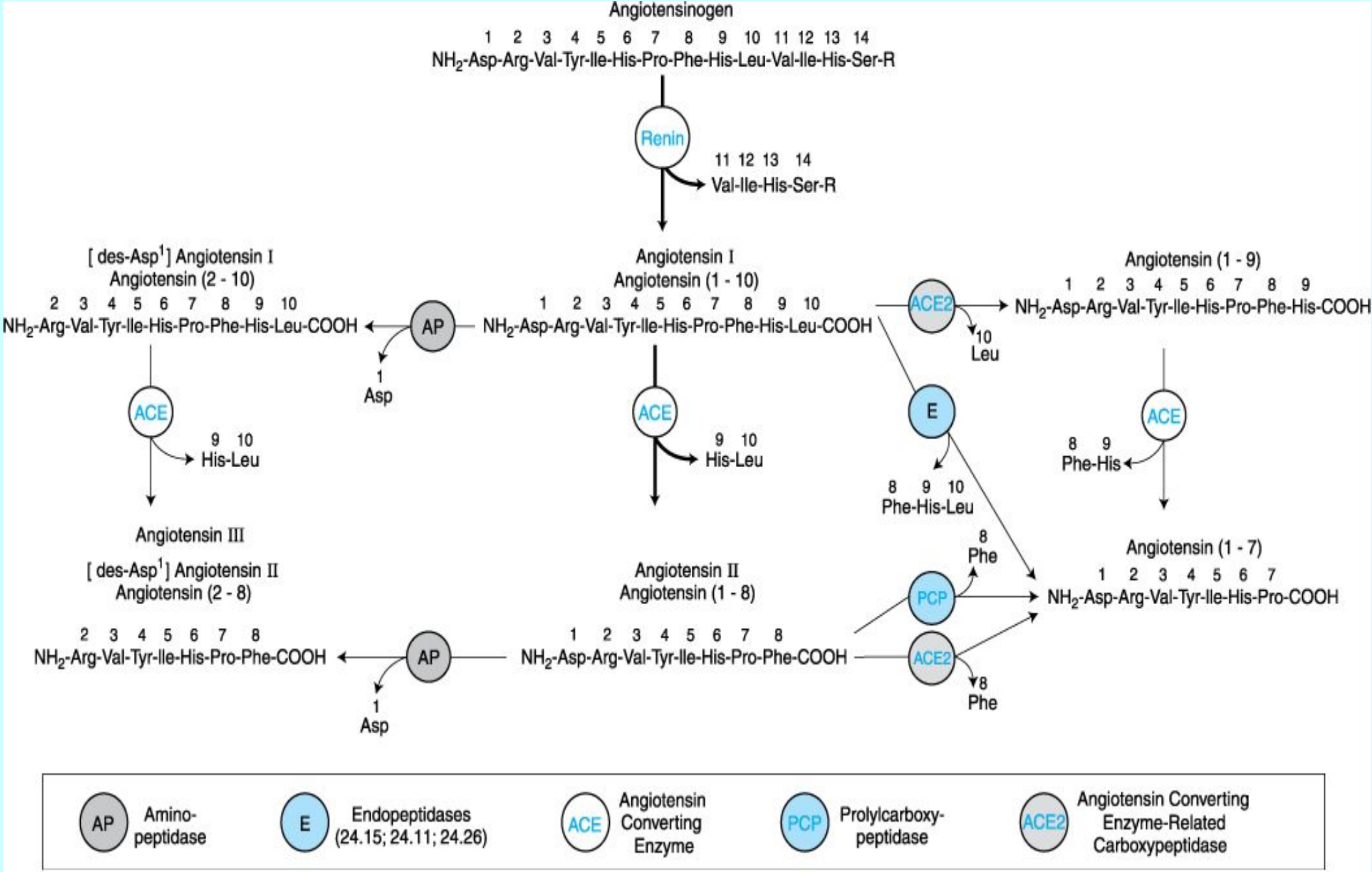
*Angiotensin II receptor antagonists* (Chapters 30 and 33) (losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan)

*Vasodilators* (Chapter 33)

1. Arterial (hydralazine, minoxidil, diazoxide, fenoldopam)
2. Arterial and venous (nitroprusside)

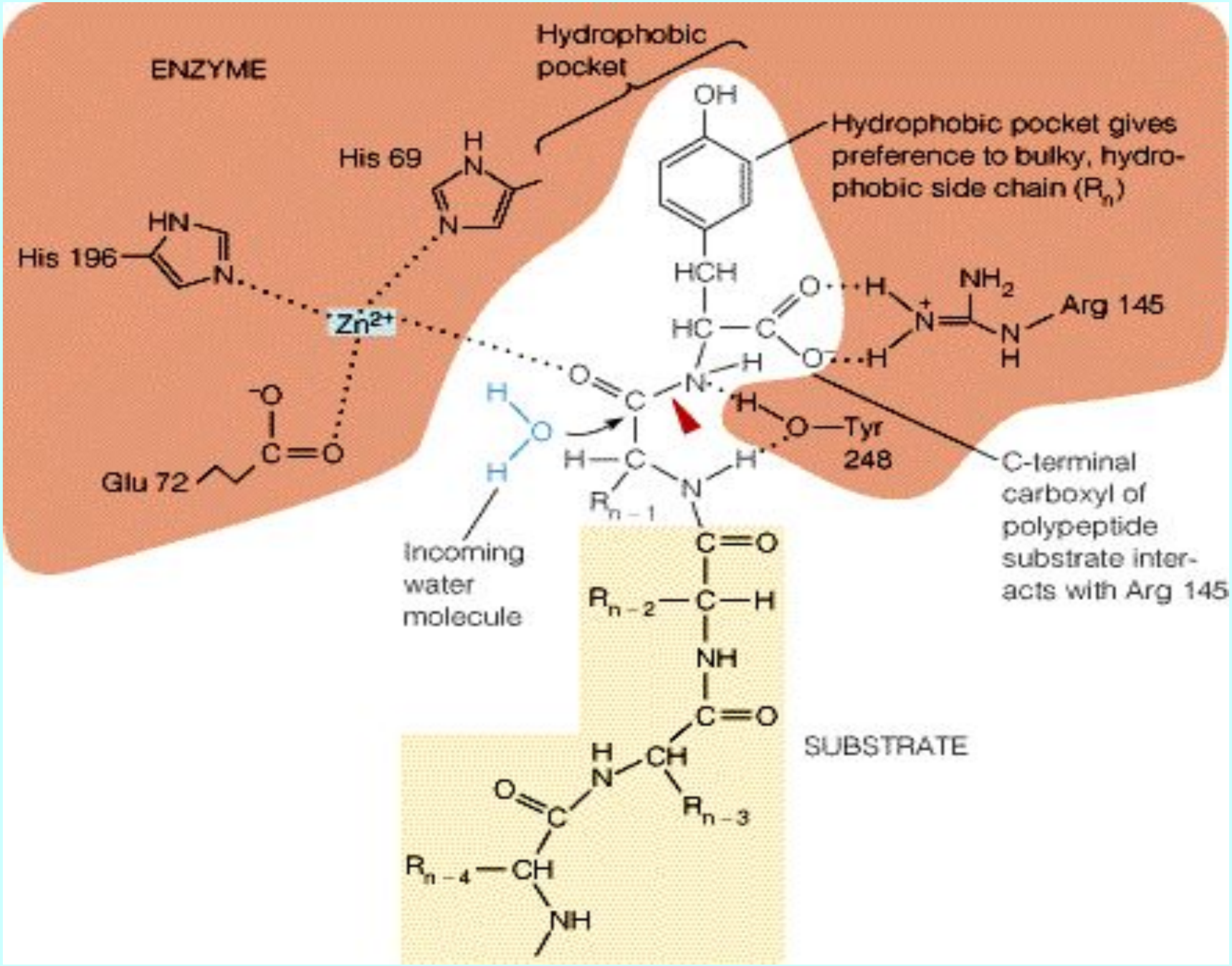



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com



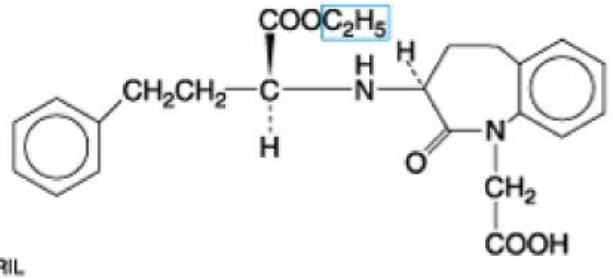

Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

# SITO ATTIVO DI PROTEASE METALLICA

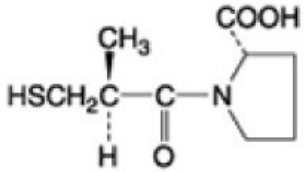


# INIBITORI ACE

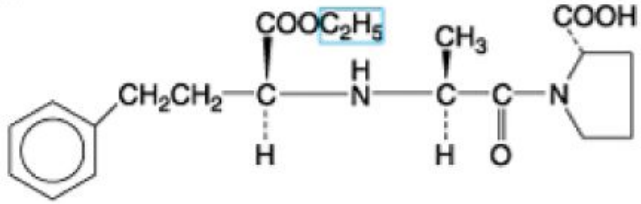
BENAZEPRIL



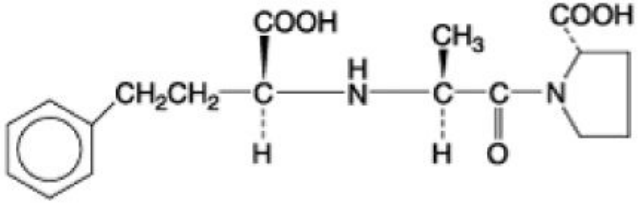
CAPTOPRIL



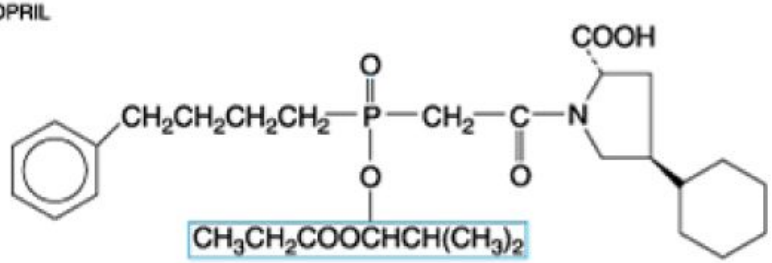
ENALAPRIL



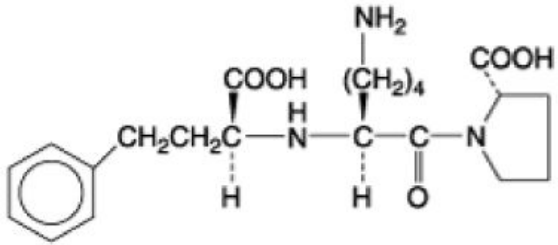
ENALAPRILAT



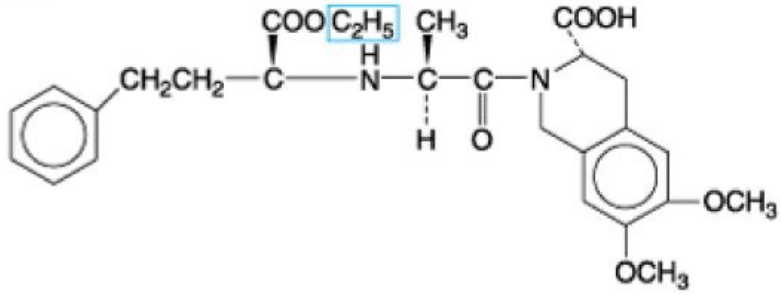
FOSINOPRIL



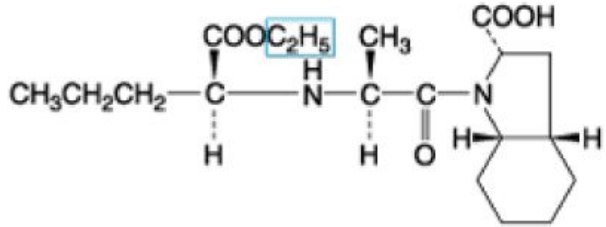
LISINOPRIL



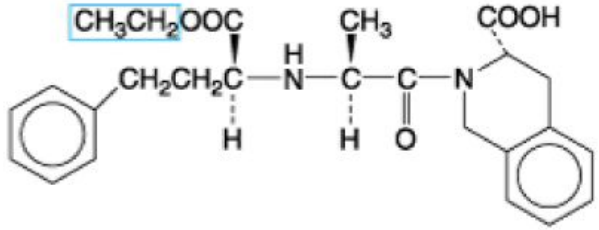
MOEXIPRIL



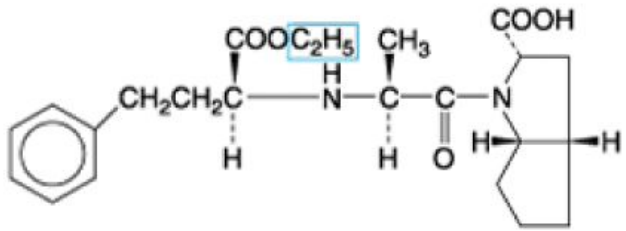
PERINDOPRIL



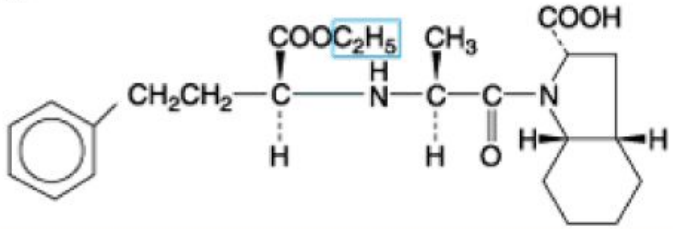
QUINAPRIL



RAMIPRIL

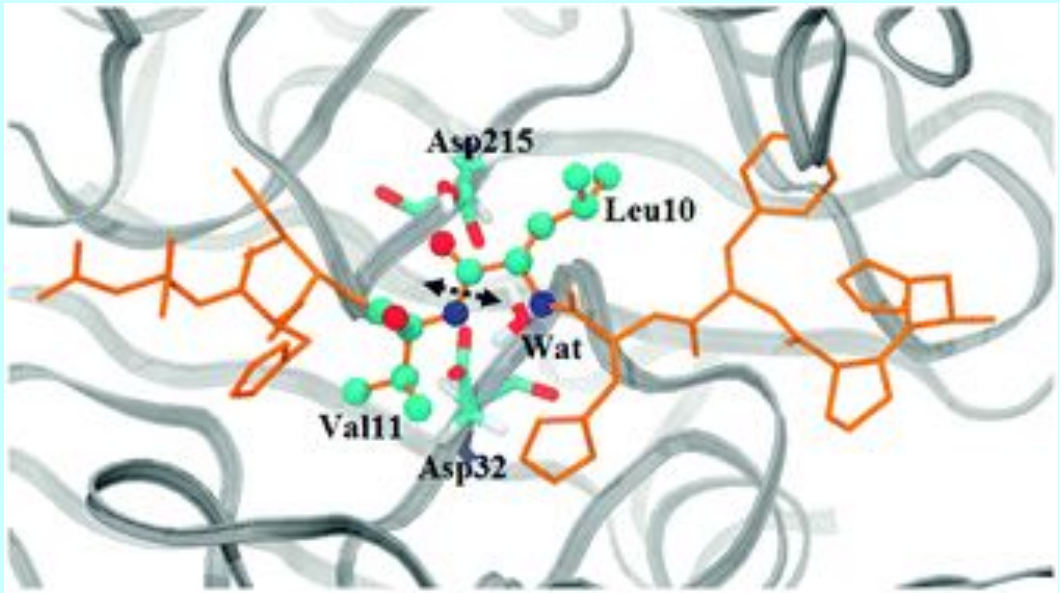


TRANDOLAPRIL



# INIBITORI RENINA

L'inibizione della renina (Aliskiren) è notevolmente potente (Ki 0.6 nM per la renina umana), reversibile e selettiva (scarsa è infatti l'inibizione di pepsina, catepsina D, catepsina E e retropepsina HIV-1).




a

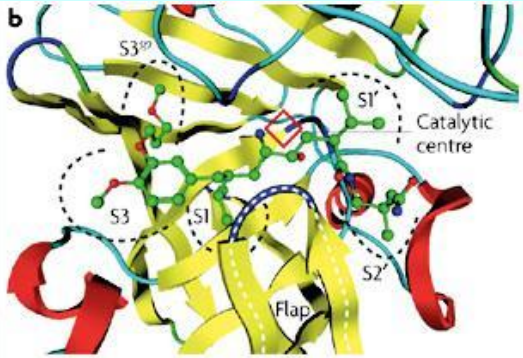
H - Pro - His - Pro — Ile - His - Lys - OH

**H-142** ($IC_{50}$ = 10 nM)

**Remikiren** ($IC_{50}$ = 0.7 nM)

**Aliskiren** ($IC_{50}$ = 0.6 nM)

b

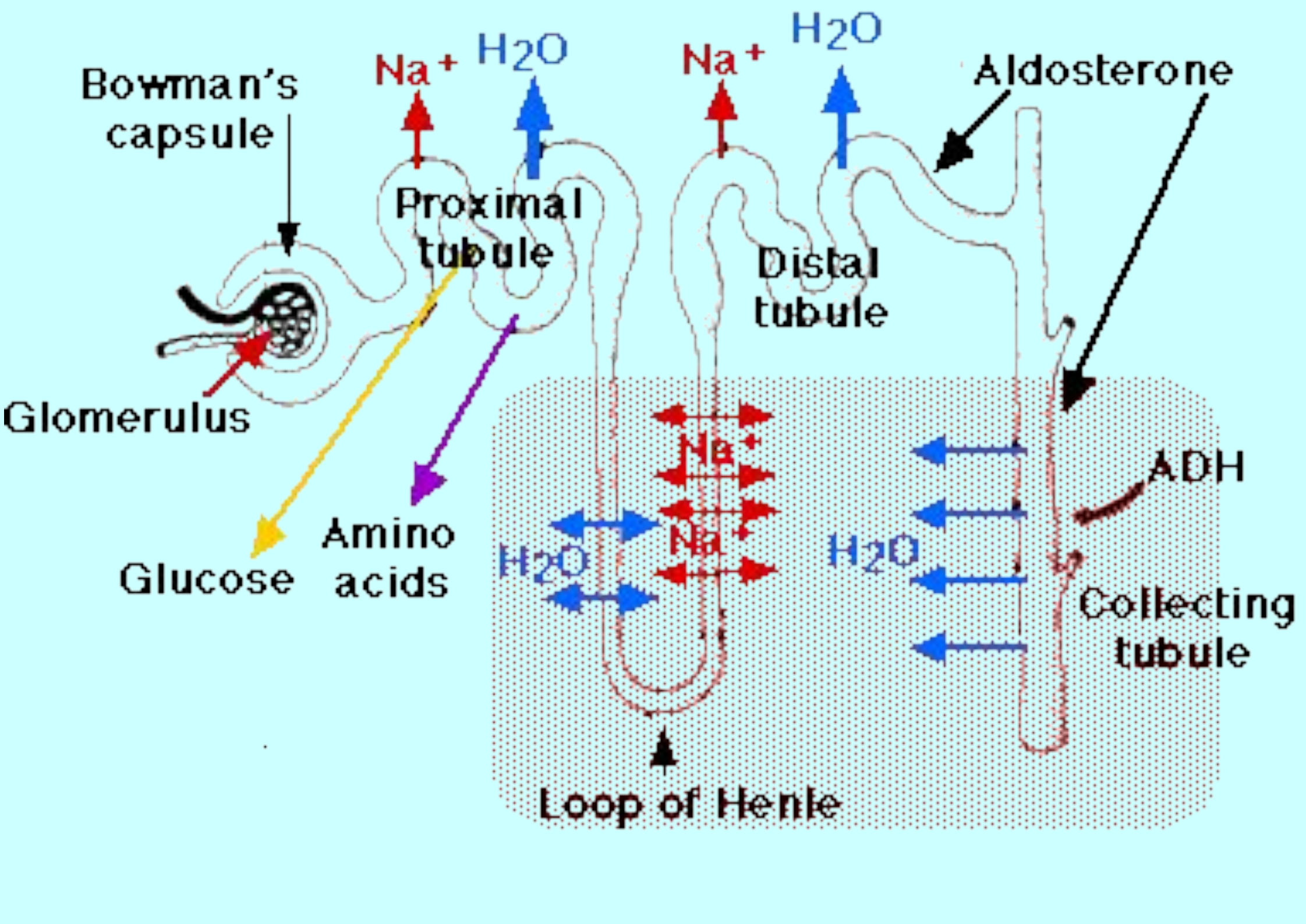



c

| Enzyme | $IC_{50}$ (nM) |
|---|---|
| Renin | 0.7 |
| Cathepsin D | 5,000 |
| Cathepsin E | >10,000 |
| Pepsin | >10,000 |
| HIV-1 proteinase | >10,000 |

| Species (renin) | $IC_{50}$ (nM) |
|---|---|
| Human | 0.6 |
| Marmoset | 2 |
| Dog | 7 |
| Rabbit | 11 |
| Guinea pig | 63 |
| Rat | 80 |
| Pig | 150 |
| Cat | 8,500 |

Nature Reviews | Drug Discovery


Bowman's capsule
Na+
H2O
Na+
H2O
Aldosterone
Proximal tubule
Distal tubule
Glomerulus
Glucose
Amino acids
Na+
Na+
H2O
H2O
ADH
Collecting tubule
Loop of Henle

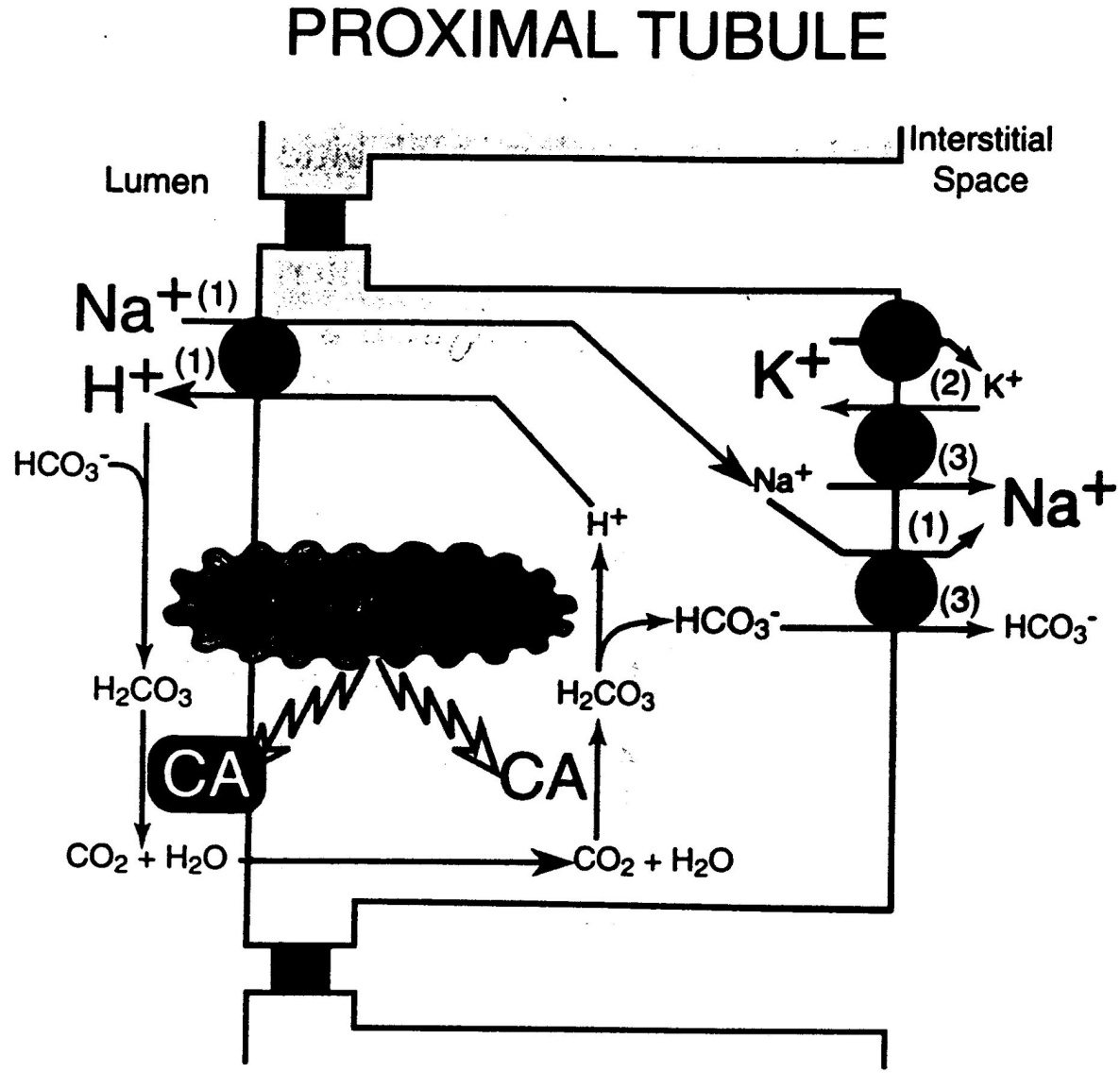
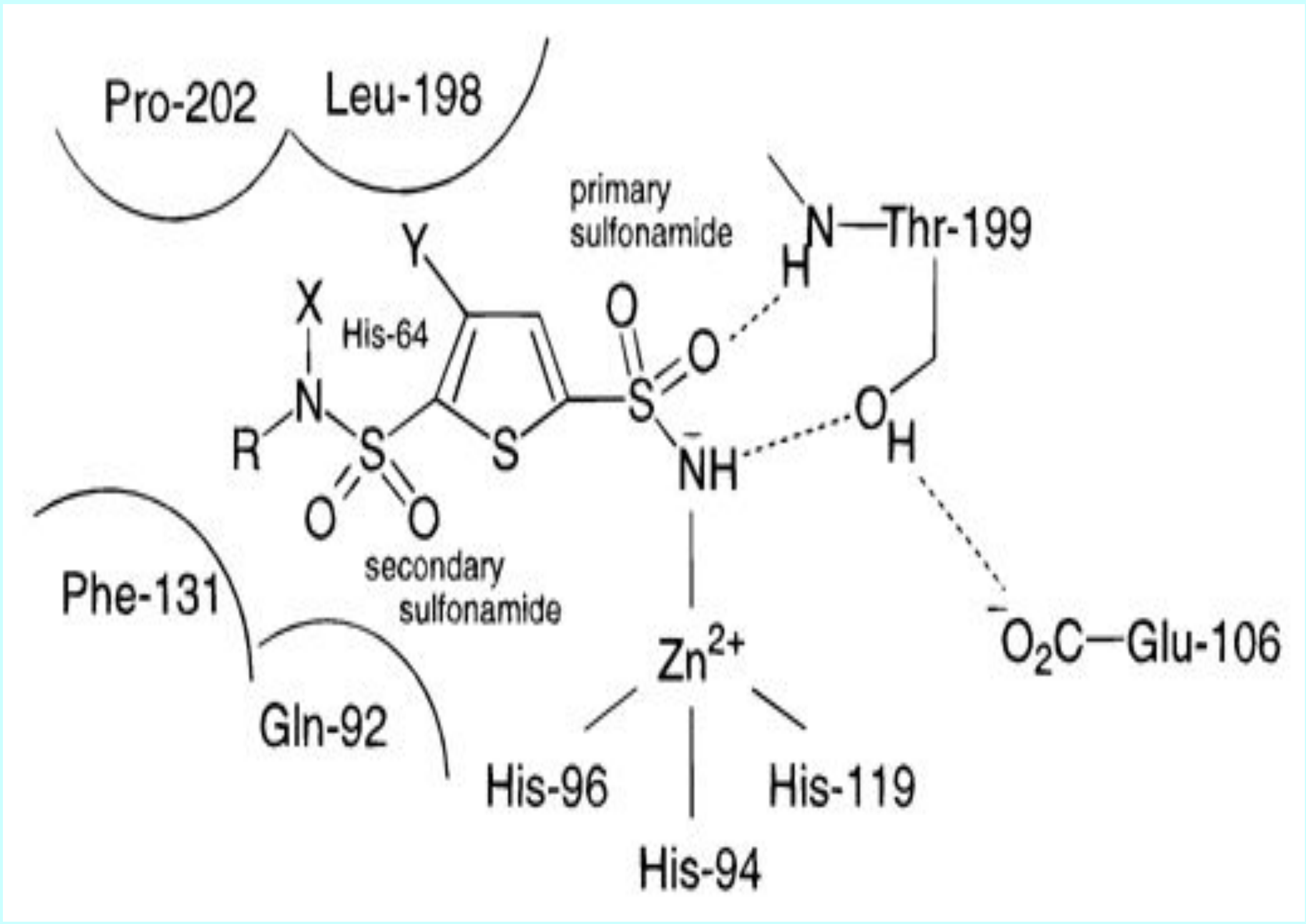
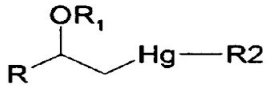



***Figure 29–5. $NaHCO_3$ reabsorption in proximal tubule and mechanism of diuretic action of carbonic anhydrase (CA) inhibitors.***

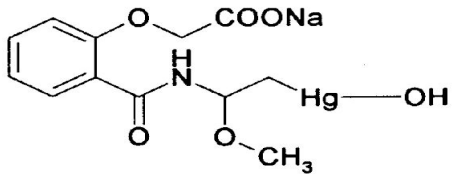

Pro-202
Leu-198
primary
sulfonamide
N—Thr-199
H
Y
X
His-64
O
O
S
N
R
S
S
NH
O
H
O
O
secondary
sulfonamide
Phe-131
Zn2+
O2C—Glu-106
Gln-92
His-96
His-119
His-94

# DIURETICI

**Mercuriali**




Formula generale

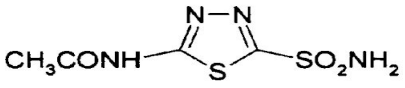



Meroalile

Inibiscono il trasporto attivo del sodio

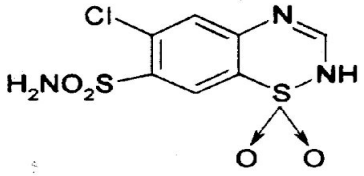
---

**Sulfonammidici**

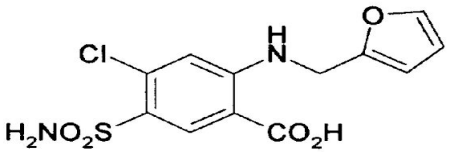



Acetazolamide

**Inibitori dell'anidrasi carbonica**

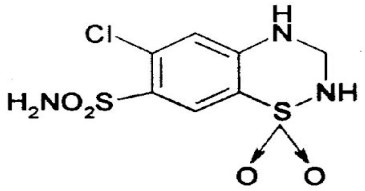



Clortiazide



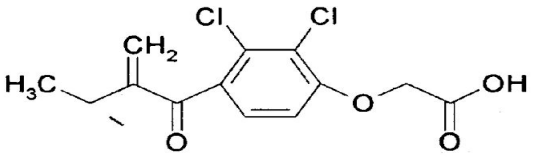

Furosemide

(*high cieling*)

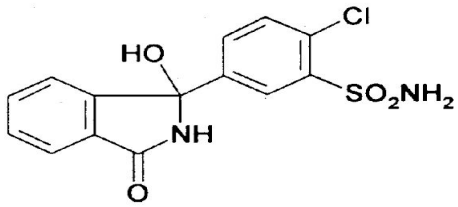



Idroclortiazide

(*Low ceiling*)




Acido etacrinico




Clortalidone

**Maggior effetto saliuretico**

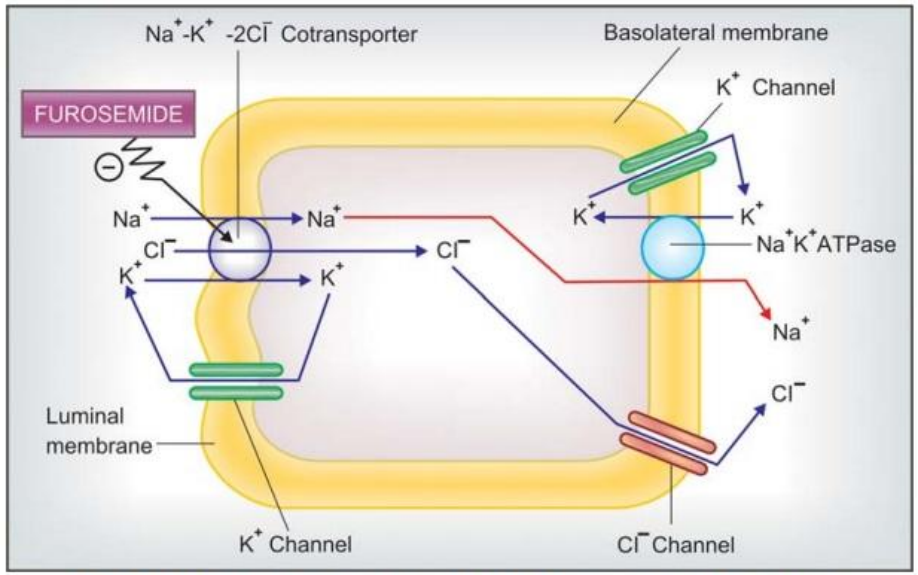



**Fig. 41.1:** Mechanism of salt reabsorption in the thick ascending limb of loop of Henle (AscLH) cell, and site of action of furosemide on the $Na^+$-$K^+$-$2Cl^-$ cotransporter

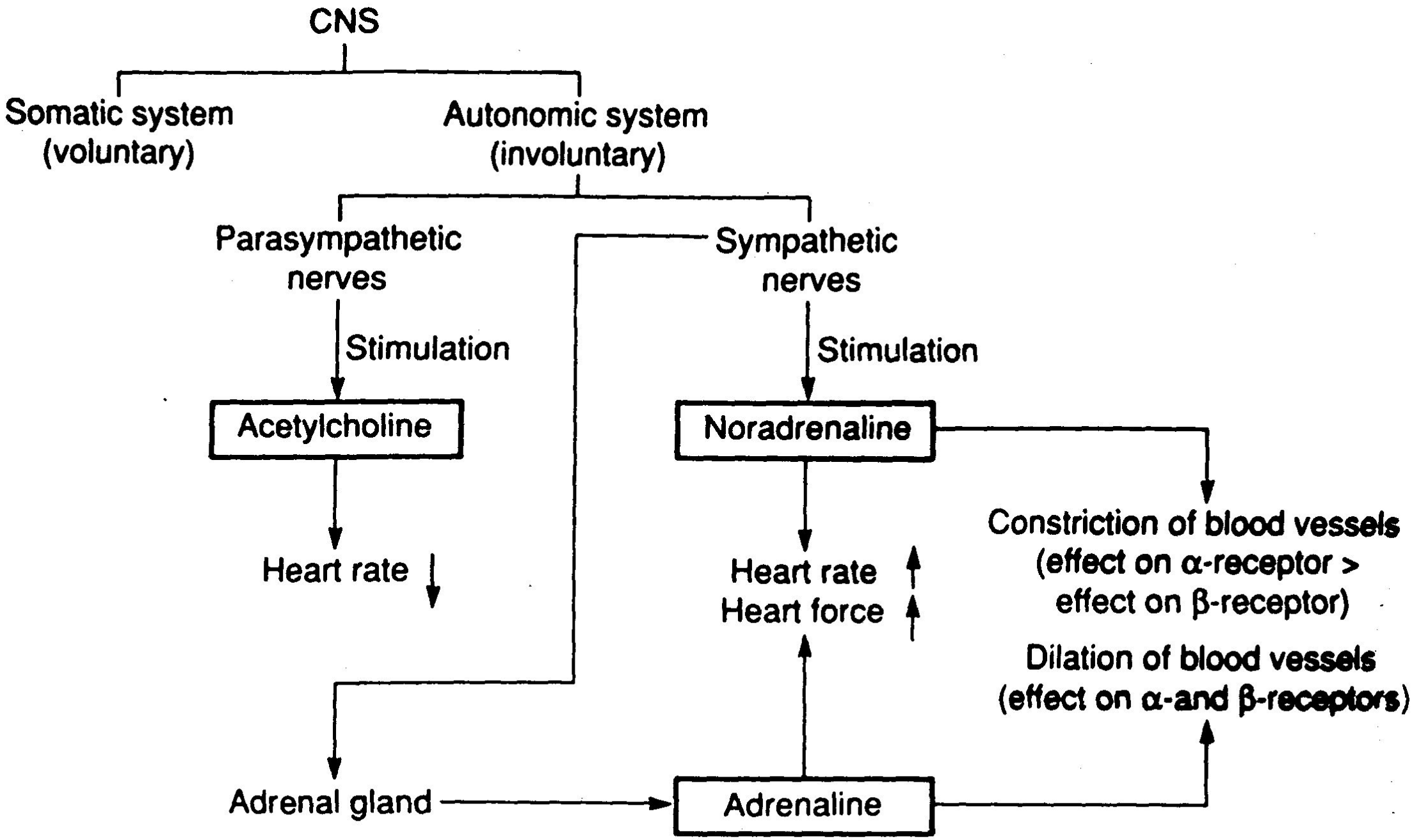
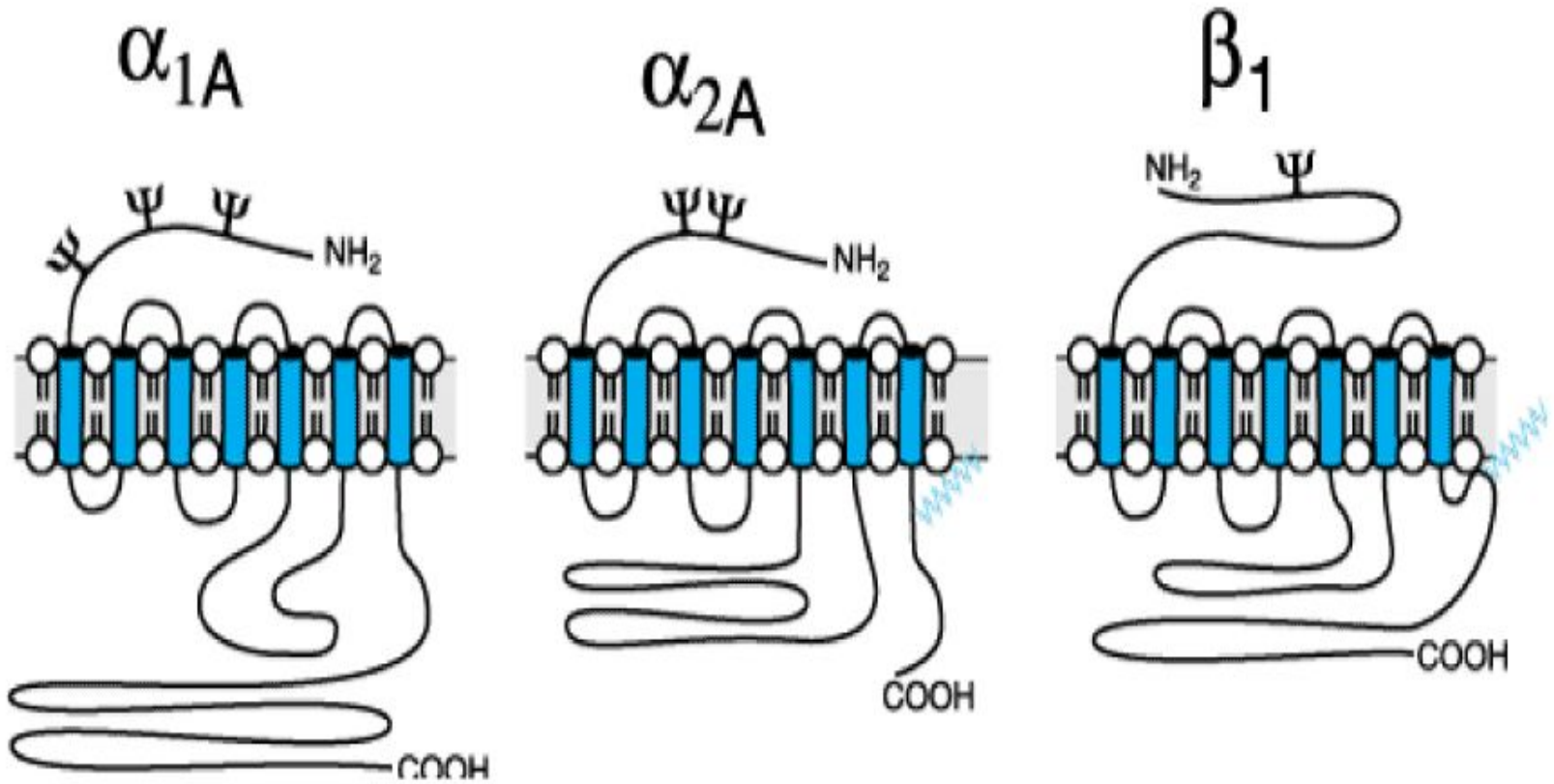



Fig. 10.1 Factors contributing to the control of heart rate and blood vessels.



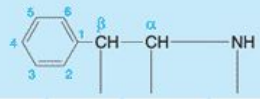

Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com



***Subtypes of adrenergic receptors.***

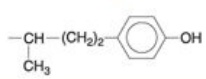
All of the adrenergic receptors are heptaspanning GPCRs. A representative of each type is shown; each type has three subtypes: $\alpha_{1A}$, 1B, and 1D, $\alpha_{2A}$, 2B, and 2C, and $\beta_{1, 2, \text{and } 3}$. All $\beta$ receptor subtypes are coupled to stimulation of adenylyl cyclase activity; similarly, all $\alpha_2$ adrenergic receptor subtypes affect the same effector systems (*i.e.*, inhibition of adenylyl cyclase, activation of receptor-operated $K^+$ channels, and inhibition of $Ca^{2+}$ channels). In contrast, there is evidence that different $\alpha_1$ adrenergic receptor subpopulations couple to different effector systems, the $G_q$-PLC-$IP_3$ pathway being a major effector. Ψ indicates a site for *N*-glycosylation. ⁄⁄⁄⁄ indicates a site for thio-acetylation.

## Table 10–1 Chemical Structures and Main Clinical Uses of Important Sympathomimetic Drugs[†]




| | | | | | MAIN CLINICAL USES | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | α Receptor | | | | β Receptor | | | |
| | | | | | A | N | P | V | B | C | U | CNS, 0 |
| Phenylethylamine | | H | H | H | | | | | | | | |
| Epinephrine | 3-OH,4-OH | OH | H | $CH_3$ | A | | P | V | B | C | | |
| Norepinephrine | 3-OH,4-OH | OH | H | H | | | P | | | | | |
| Dopamine | 3-OH,4-OH | H | H | H | | | P | | | | | |
| Dobutamine | 3-OH,4-OH | H | H | 1* | | | | | | C | | |
| Colterol | 3-OH,4-OH | OH | H | $C(CH_3)_3$ | | | | | B | | | |
| Ethylnorepinephrine | 3-OH,4-OH | OH | $CH_2CH_3$ | H | | | | | B | | | |
| Isoproterenol | 3-OH,4-OH | OH | H | $CH(CH_3)_2$ | | | | | B | C | | |
| Isoetharine | 3-OH,4-OH | OH | $CH_2CH_3$ | $CH(CH_3)_2$ | | | | | B | | | |
| Metaproterenol | 3-OH,5-OH | OH | H | $CH(CH_3)_2$ | | | | | B | | | |
| Terbutaline | 3-OH,5-OH | OH | H | $C(CH_3)_3$ | | | | | B | | U | |
| Metaraminol | 3-OH | OH | $CH_3$ | H | | | P | | | | | |
| Phenylephrine | 3-OH | OH | H | $CH_3$ | | N | P | | | | | |
| Tyramine | 4-OH | H | H | H | | | | | | | | |
| Hydroxyamphetamine | 4-OH | H | $CH_3$ | H | | | | | | | | |
| Ritodrine | 4-OH | OH | $CH_3$ | 2* | | | | | | | U | |
| Prenalterol | 4-OH | OH‡ | H | $-CH(CH_3)_2$ | | | | | | C | | |
| Methoxamine | 2-$OCH_3$,5-$OCH_3$ | OH | $CH_3$ | H | | | P | | | | | |
| Albuterol | 3-$CH_2OH$,4-OH | OH | H | $C(CH_3)_3$ | | | | | B | | U | |
| Amphetamine | | H | $CH_3$ | H | | | | | | | | CNS, 0 |
| Methamphetamine | | H | $CH_3$ | $CH_3$ | | | | | | | | CNS, 0 |
| Benzphetamine | | H | $CH_3$ | 3* | | | | | | | | 0 |
| Ephedrine | | OH | $CH_3$ | $CH_3$ | | N | P | | B | C | | |
| Phenylpropanolamine | | OH | $CH_3$ | H | | N | | | | | | 0 |
| Mephentermine | | H | 4* | $CH_3$ | | N | P | | | | | |
| Phentermine | | H | 4* | H | | | | | | | | 0 |
| Propylhexedrine | 5* | H | $CH_3$ | $CH_3$ | | N | | | | | | |
| Diethylpropion | | | 6* | | | | | | | | | 0 |
| Phenmetrazine | | | 7* | | | | | | | | | 0 |
| Phendimetrazine | | | 8* | | | | | | | | | 0 |

1

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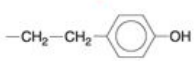


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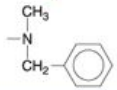


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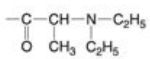


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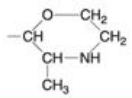


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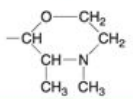



*α Activity*
A = Allergic reactions (includes β action)
N = Nasal decongestion
P = Pressor (may include β action)
V = Other local vasoconstriction (*e.g.*, in local anesthesia)

*β Activity*
B = Bronchodilator
C = Cardiac
U = Uterus

CNS = Central nervous system
0 = Anorectic

*Numbers bearing an asterisk refer to the substituents numbered in the bottom rows of the table; substituent 3 replaces the N atom, substituent 5 replaces the phenyl ring, and 6, 7, and 8 are attached directly to the phenyl ring, replacing the ethylamine side chain.

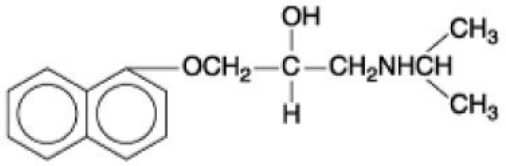
[†]The α and β in the prototypical formula refer to positions of the C atoms in the ethylamine side chain.

[‡]Prenalterol has $—OCH_2—$ between the aromatic ring and the carbon atom designated as β in the prototypical formula.

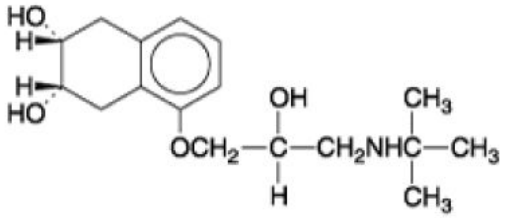
# ANTAGONISTI DEI β-ADRENORECETTORI

- Diminuzione del rilascio della Renina dalle cellule juxtaglomerulari (blocco degli adrenorecettori $\beta_1$)
- Diminuzione della frequenza cardiaca (blocco degli adrenorecettori $\beta_1$ nel nodo sinoatriale)
- Vasodilatazione (diminuzione del tono simpatico centrale)
- Vasodilatazione (aumento del rilascio di noradrenalina mediato dal blocco degli adrenorecettori $\beta_1$)

*Nonselective antagonists*



PROPRANOLOL



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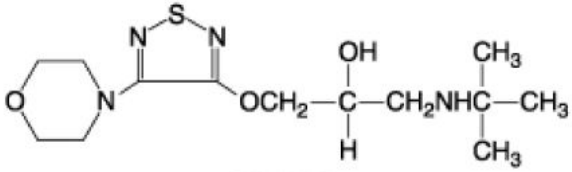
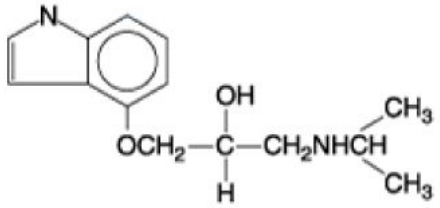
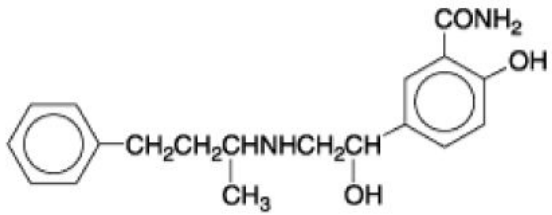


TIMOLOL

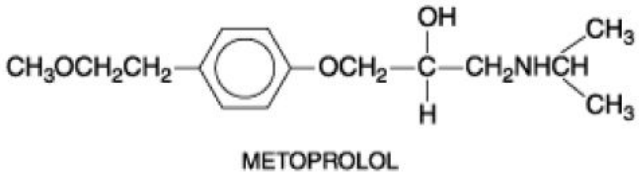


PINDOLOL

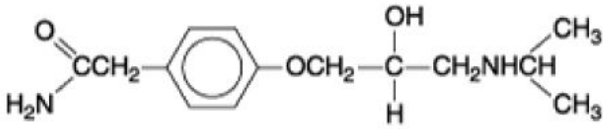


LABETALOL

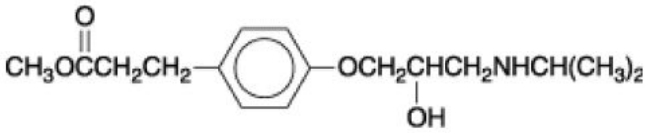
*$\beta_1$-selective antagonists*



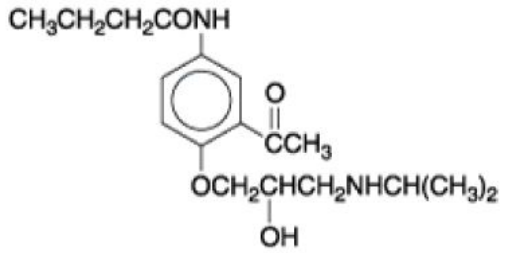
METOPROLOL



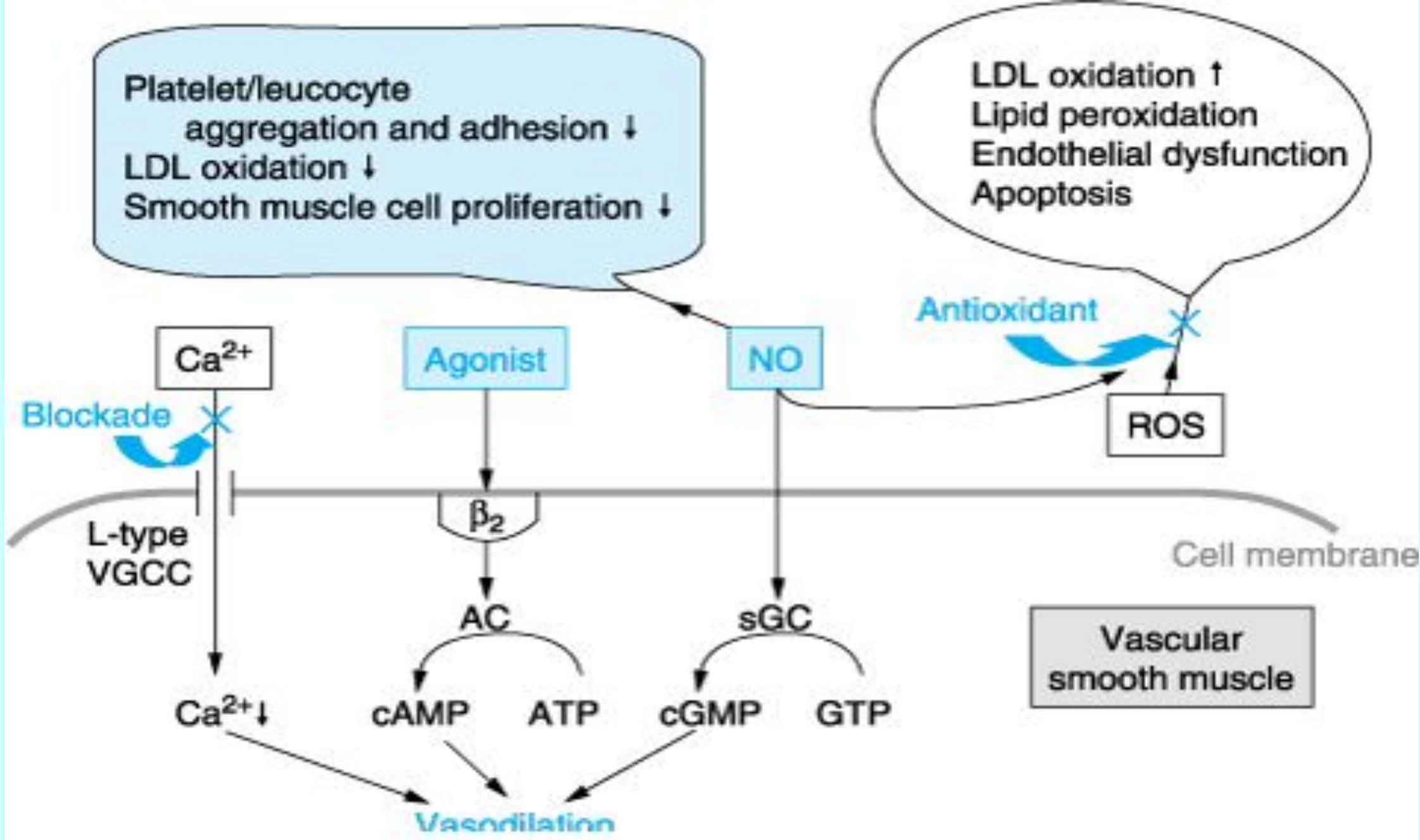
ATENOLOL



ESMOLOL



ACEBUTOLOL




Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

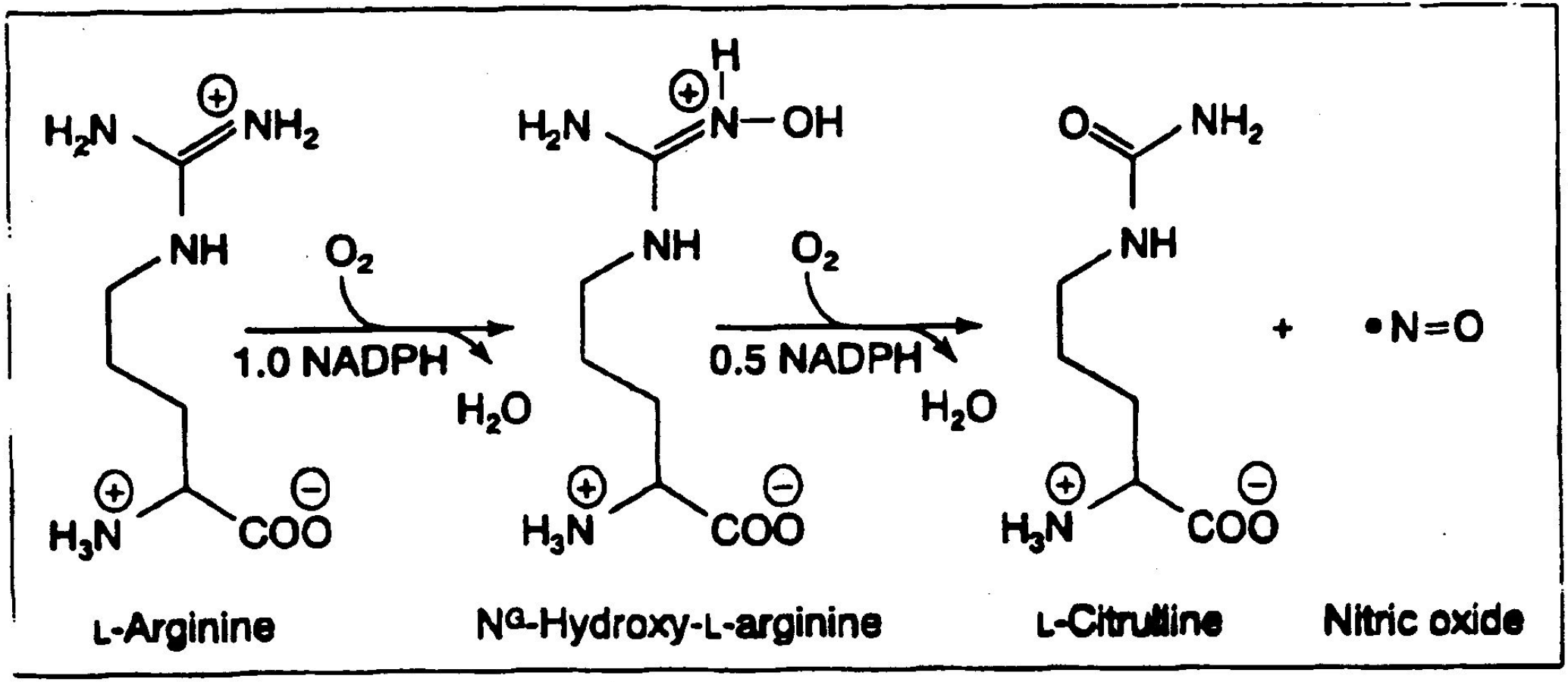



**Figure 1**
The nitric oxide synthase reaction.