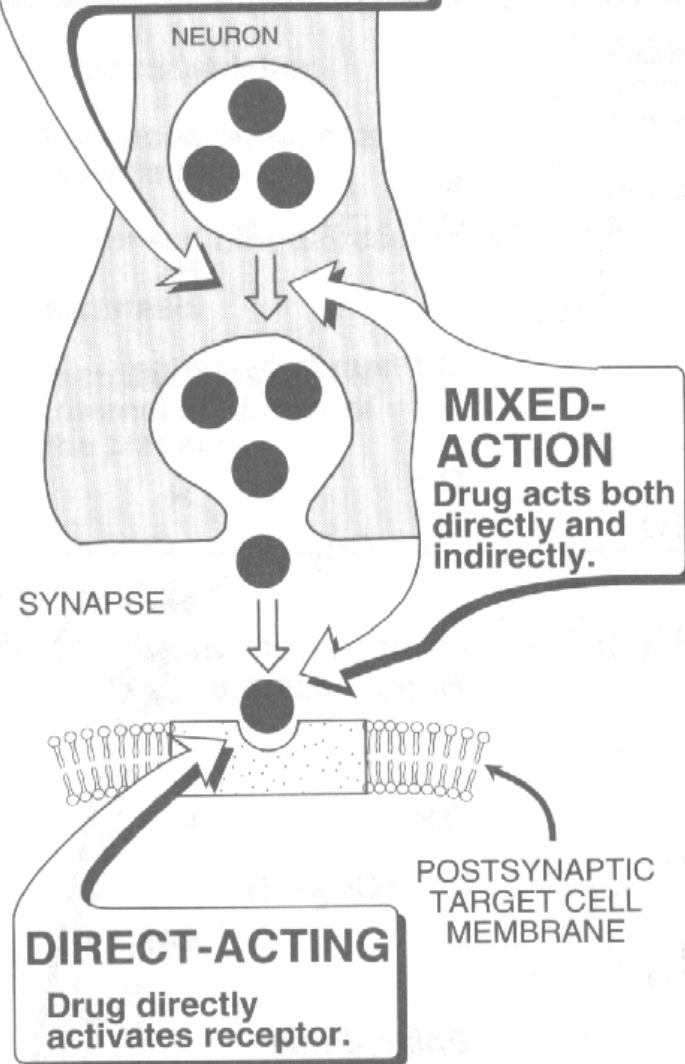
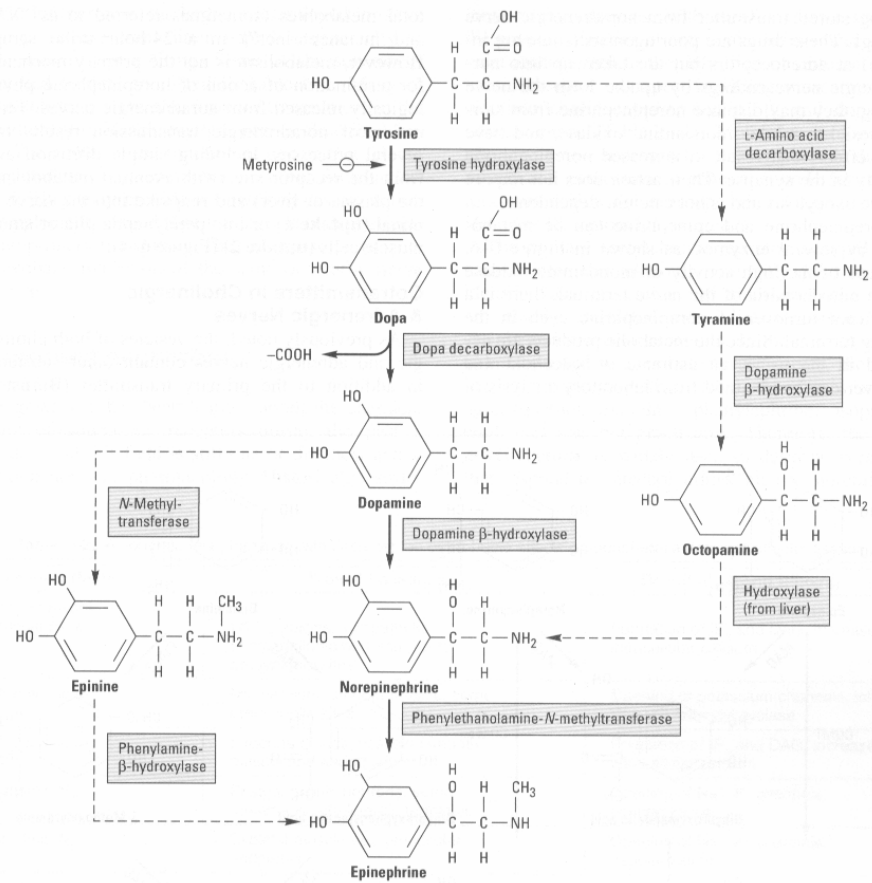
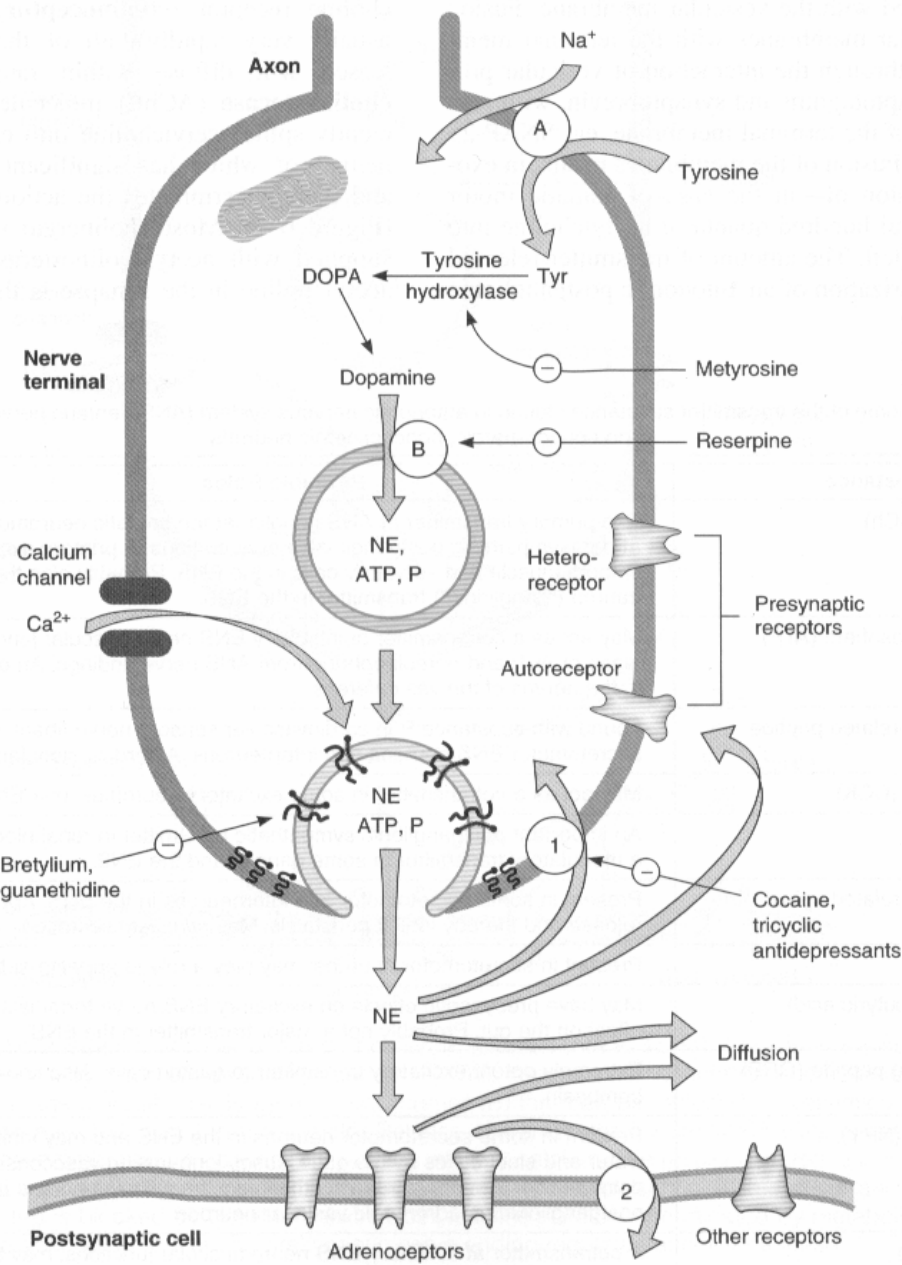


Ativação de Receptores Adrenérgicos (Simpatomiméticos)

INDIRECT-ACTING

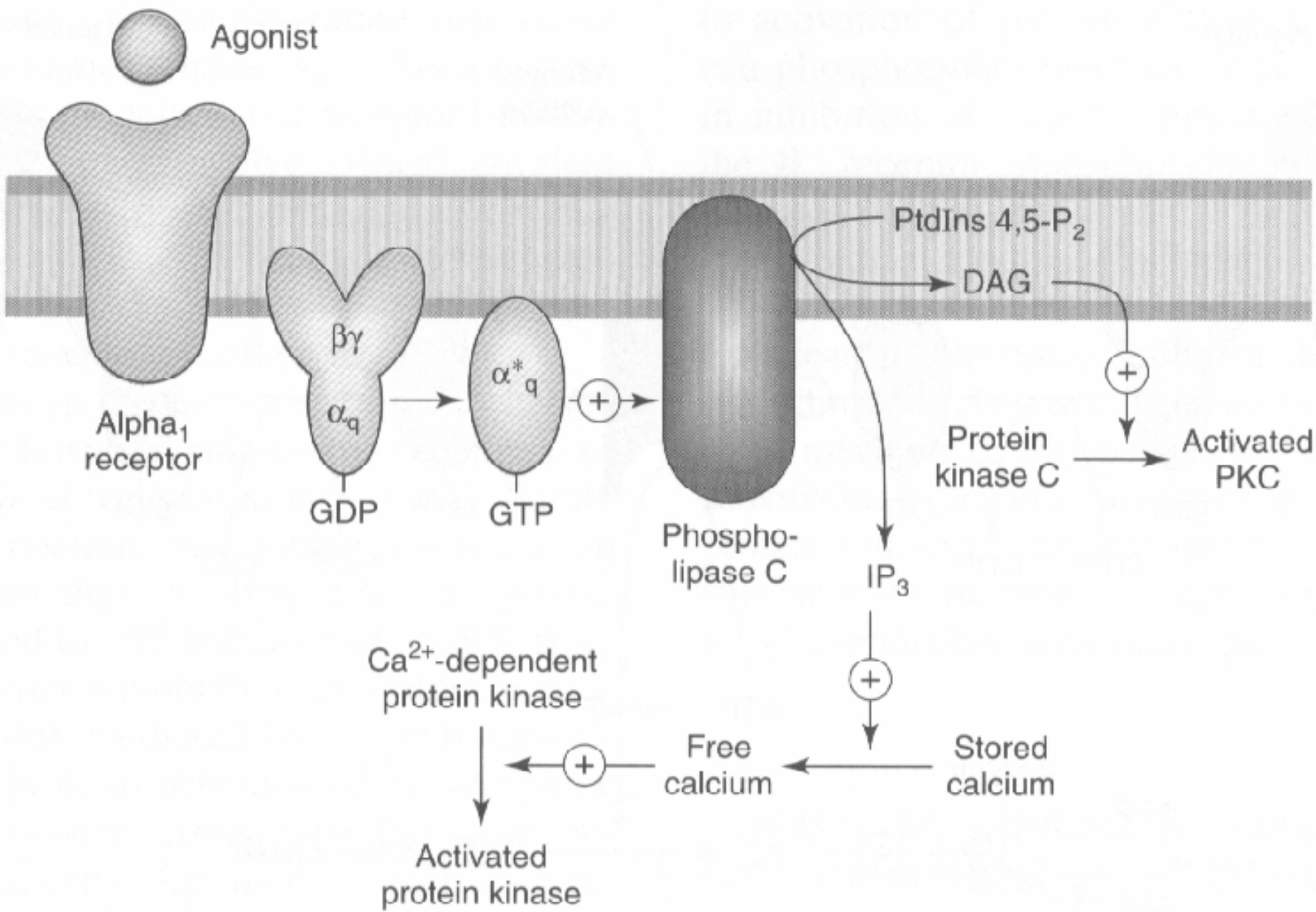
Drug enhances release of norepinephrine from vesicles.

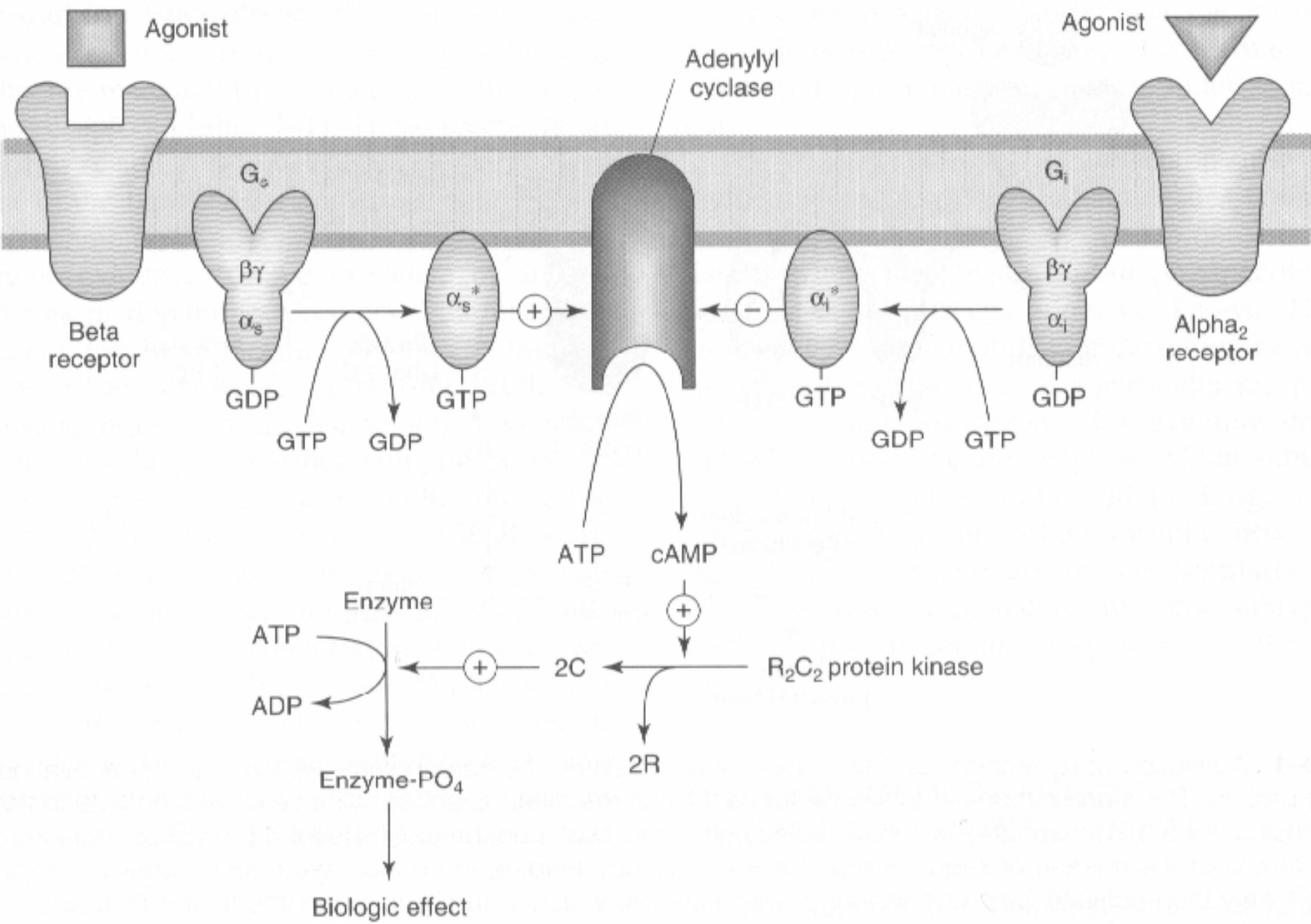


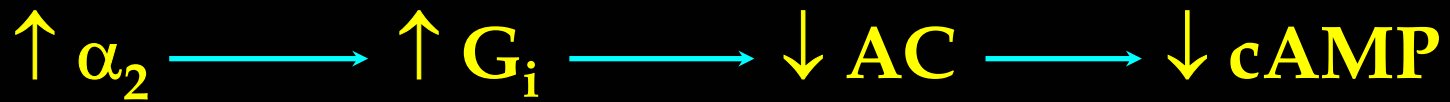


	Agonista	Antagonista	Efeito
Tipo α_1: α_{1A} α_{1B} α_{1D}	Fenilefrina, metoxamina	Prazosin, Corinantina WB4101 Cloroetilclonidina (irrev.) WB4101	Para todos $\uparrow IP_3$, DAG
Tipo α_2: α_{2A} α_{2B} α_{2C}	Clonidina, Oximetazolina	Rauwolscina, Yoimbina Prazosin Prazosin	Para todos: $\downarrow cAMP$ $\uparrow K^+$; $\downarrow Ca^{2+}$ $\downarrow Ca^{2+}$
Tipo β: β_1 β_2 β_3	Isoproterenol Dobutamina Procaterol, Terbutalina BRL37344	Propranolol Betaxolol Butoxamina	Para todos: $\uparrow cAMP$
Dopamina: D_1 D_2 D_3 D_4 D_5	Dopamina Fenoldopam Bromocriptina Quinpirol	 AJ76 Clozapina	$\uparrow cAMP$ $\downarrow cAMP$; $\uparrow K^+$; $\downarrow Ca^{2+}$ $\downarrow cAMP$; $\uparrow K^+$; $\uparrow Ca^{2+}$ $\downarrow cAMP$ $\uparrow cAMP$

	Afinidades relativas
Agonistas α: Fenilefrina, Metoxamina Clonidina, metilnorepinefrina	$\alpha_1 > \alpha_2 >>>> \beta$ $\alpha_2 > \alpha_1 >>>> \beta$
Agonistas mistos α e β: Norepinefrina Epinefrina	$\alpha_1 = \alpha_2 ; \beta_1 >> \beta_2$ $\alpha_1 = \alpha_2 ; \beta_1 = \beta_2$
Agonistas β: Dobutamina Isoproterenol Terbutalina, Metaproterenol, Albuterol, Ritodrina	$\beta_1 > \beta_2 >>> \alpha$ $\beta_1 = \beta_2 >>> \alpha$ $\beta_2 >> \beta_1 >>> \alpha$
Agonistas dopaminérgicos: Dopamina Fenoldopam	$D_1 = D_2 >> \beta >> \alpha$ $D_1 >> D_2$

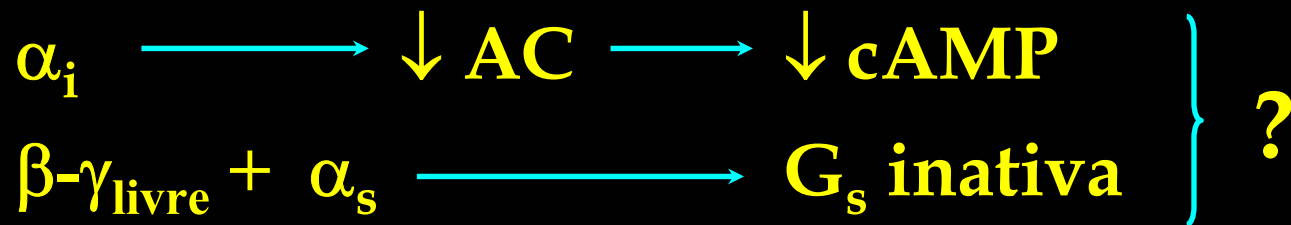




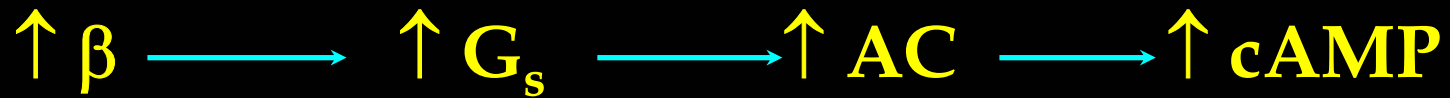


Ex:

Plaquetas $\longrightarrow$ Agregação



Ativação de α_2 : $\left. \begin{array}{l} \uparrow K^+_{\text{ch}} \\ \downarrow Ca^{2+}_{\text{ch}} \end{array} \right\} \begin{array}{l} \text{Independente de } \downarrow AC \\ (G_i / G_0 \text{ ??}) \end{array}$



Ex:

Fígado $\longrightarrow$ $\uparrow$ Glicogênio fosforilase

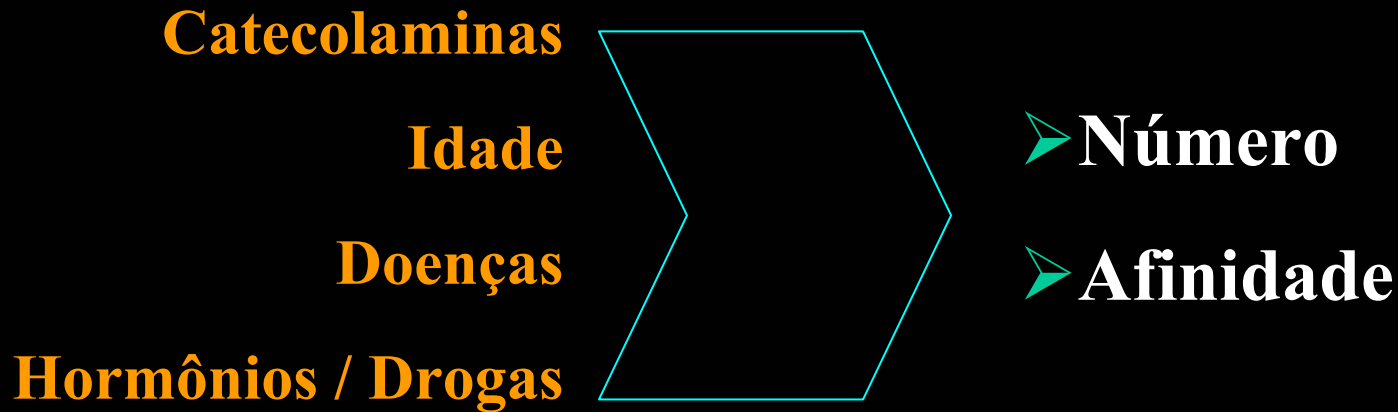
Coração $\longrightarrow$ $\uparrow$ Influxo de Ca^{2+}

Músculo liso $\longrightarrow$ $\uparrow$ Relaxamento



$\uparrow \beta$ cardíacos $\longrightarrow$ $\uparrow$ canais Ca^{2+} voltagem dependentes
 (Dependente de $\uparrow G_s$ / Independente de $\uparrow cAMP$)

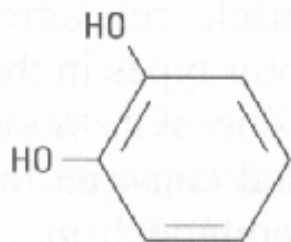
Regulação dos Receptores Adrenérgicos



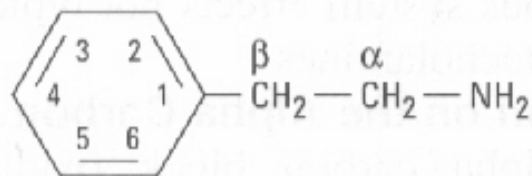
✓ **Desensibilização** (tolerância, taquifilaxia)

❖ **Modificação covalente (fosforilação)**

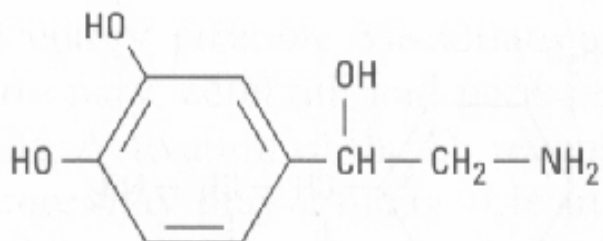
❖ **Internalização**



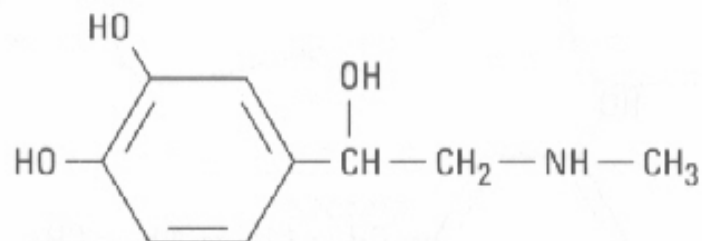
Catechol



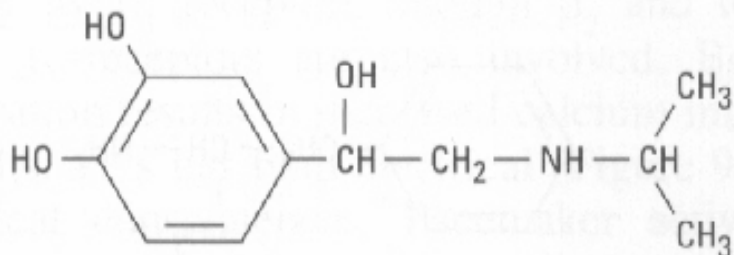
Phenylethylamine



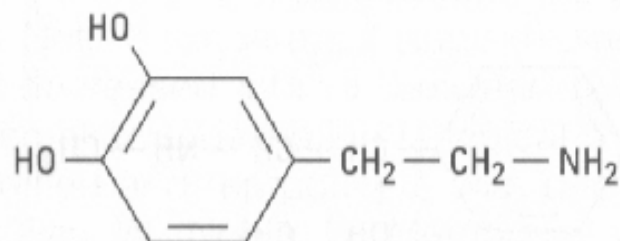
Norepinephrine



Epinephrine

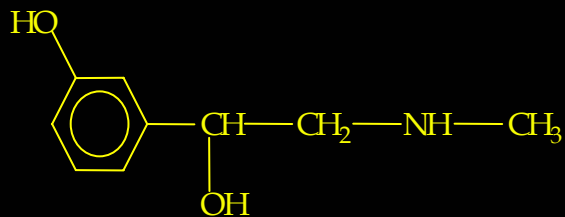


Isoproterenol

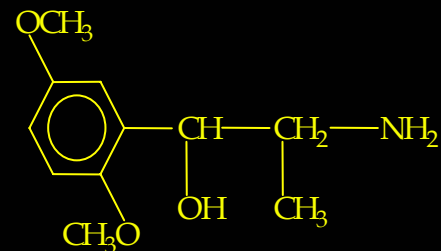


Dopamine

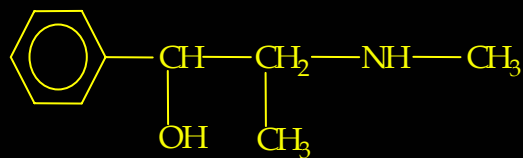
Simpatomiméticos sintéticos



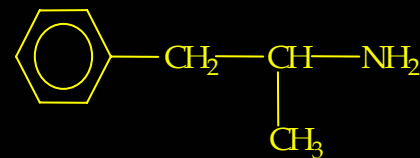
Fenilefrina



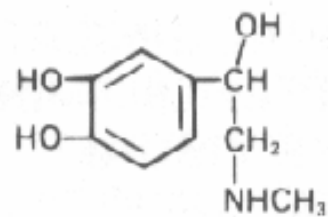
Metoxamina



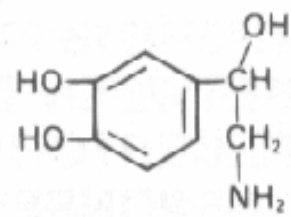
Efedrina



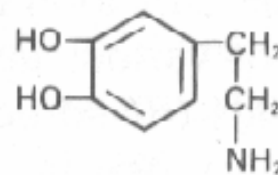
Anfetamina



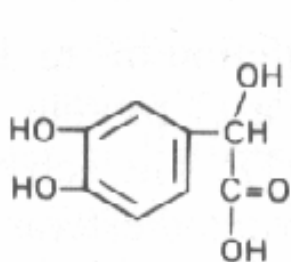
Epinephrine



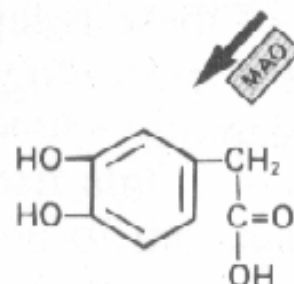
Norepinephrine



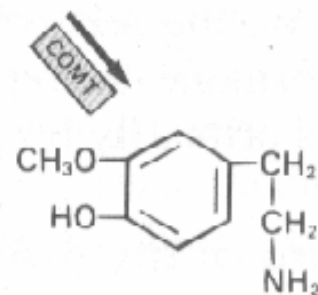
Dopamine



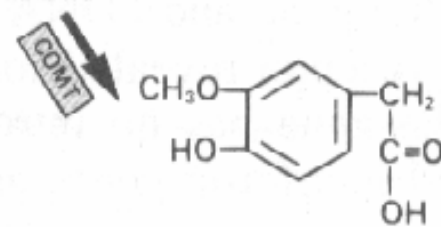
Dihydroxymandelic acid



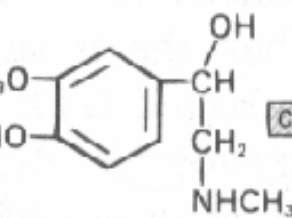
Dihydroxyphenylacetic acid



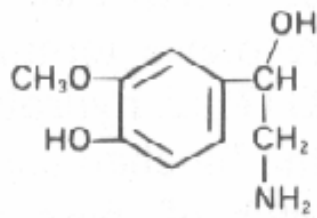
3-Methoxytyramine



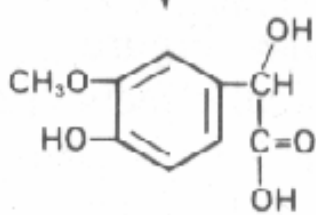
Homovanillic acid



Metanephrine



Normetanephrine

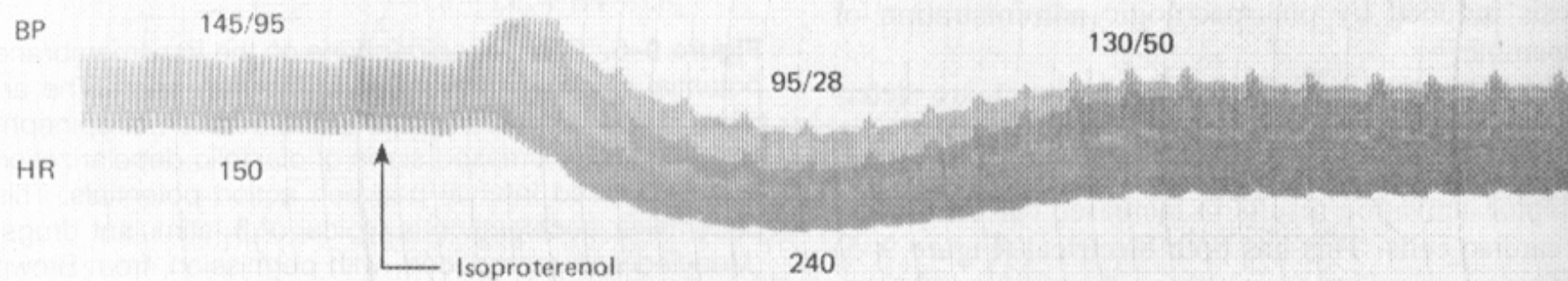
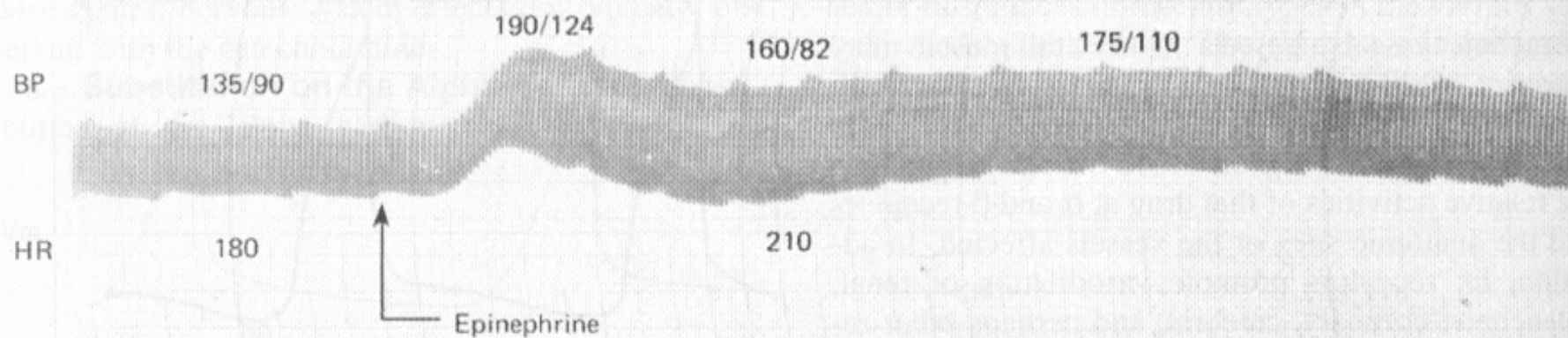
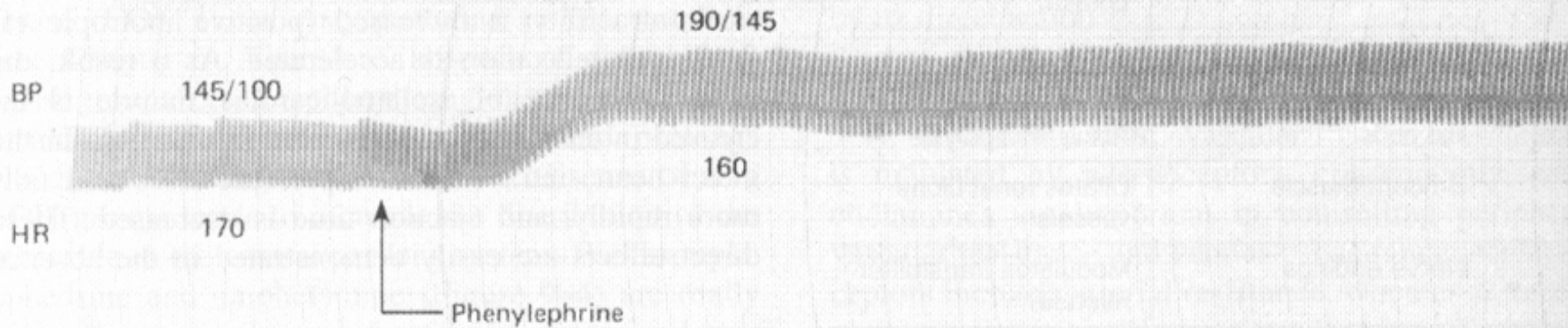


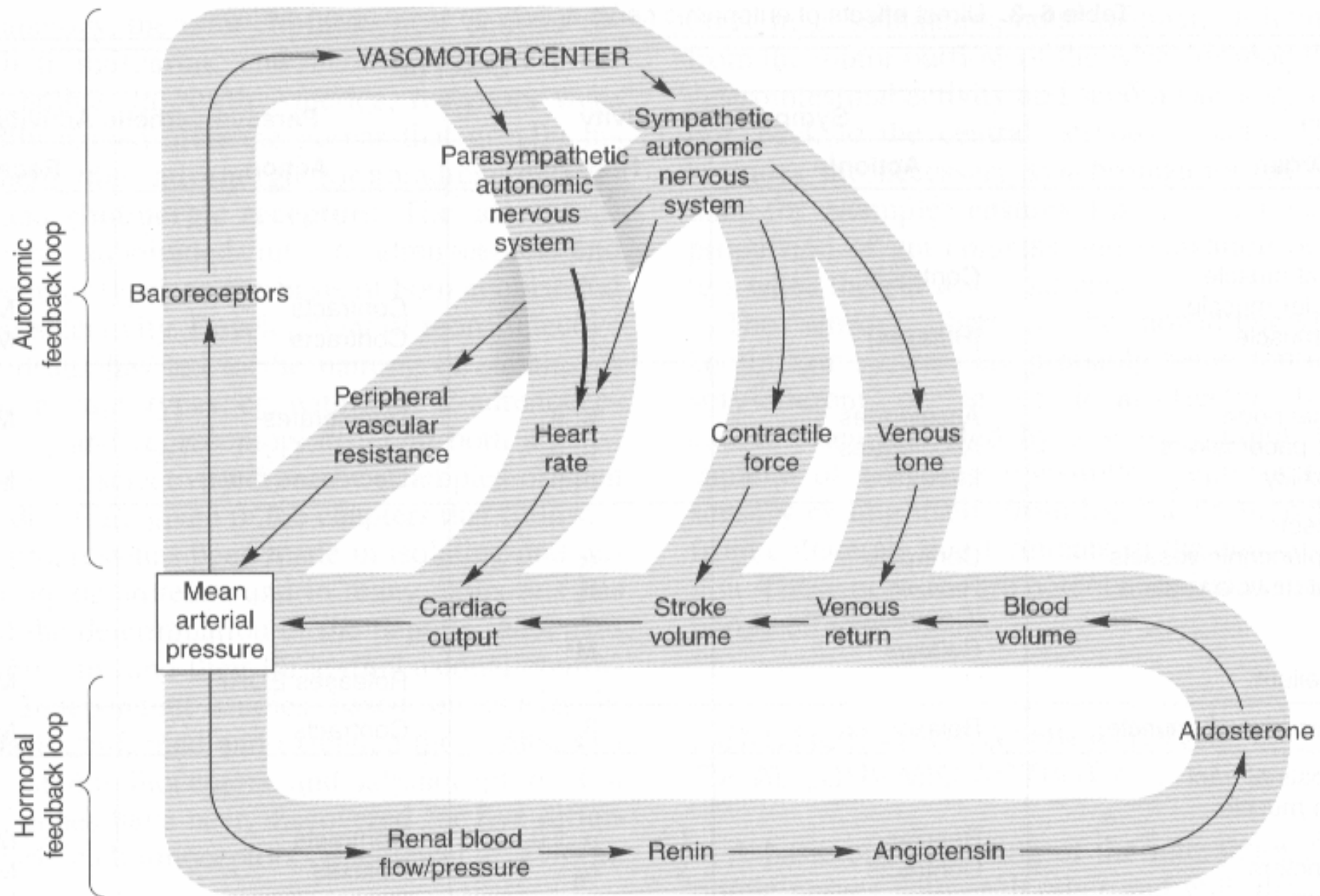
3-Methoxy-4-hydroxy-mandelic acid

Tipo	Tecido	Ações
α_1	Maioria dos músculos lisos vasculares (inervados) Músculo dilatador da pupila Músculo liso pilomotor Próstata Coração	Contração Contração (dilata a pupila) Piloereção Contração ↑Força de contração
α_2	Receptores adrenérgicos pós-sinápticos (SNC) Plaquetas Terminais nervosos adrenérgicos e colinérgicos Alguns músculos lisos vasculares Adipócitos	Múltiplas Agregação Inibição da liberação do transmissor Contração Inibição da lipólise
β_1	Coração	↑Força e velocidade de contração
β_2	Músculo liso vascular (útero, respiratório) Músculo esquelético Fígado (humano)	Relaxamento ↑Entrada (uptake) de K^+ Ativação da glicogenólise
β_3	Adipócitos	Ativação da lipólise
D_1	Músculo liso	Dilatação de vasos sangüíneos renais
D_2	Terminais nervosos	Modulação da liberação de transmissores

	Fenilefrina	Epinefrina	Isoproterenol
Resistência vascular (tônus)			
Cutânea, membranas muscosas (α)	↑ ↑	↑ ↑	0
Músculo esquelético (β_2 , α)	↑	↓ ou ↑	↓ ↓
Renal (α , β)	↑	↑	↓
Esplâncnico (α)	↑ ↑	↓ ou ↑ *	↓
Resistência total periférica	↑ ↑ ↑	↓ ou ↑ *	↓ ↓
Tônus venoso (α , β)	↑	↑	↓
Cardíaca			
Contratilidade (β_1)	0 ou ↑	↑ ↑ ↑	↑ ↑ ↑
Frequência (predominante β_1)	↓ ↓ (reflexo vagal)	↑ ou ↓	↑ ↑ ↑
Débito cardíaco	↓	↑	↑ ↑
Pressão arterial			
Média	↑ ↑	↑	↓
Diastólica	↑ ↑	↓ ou ↑ *	↓ ↓
Sistólica	↑ ↑	↑ ↑	0 ou ↓

*: baixas doses: ↓ / altas doses: ↑





Olhos (α e β):

$\uparrow\alpha \longrightarrow$ Midriase

$\uparrow\alpha \longrightarrow \uparrow$ Fluxo de Saída de Humor aquoso

$\downarrow\beta \longrightarrow \downarrow$ Humor aquoso $\longrightarrow$ Tratamento de Glaucoma

Respiratório:

Bronquios $\longrightarrow \beta$

Vasos $\longrightarrow \alpha$

Gastrointestinal:

$\uparrow\beta \longrightarrow$ Relaxamento ML (*hiperpolarização; direto*)

$\uparrow\alpha_2 \longrightarrow$ Relaxamento ML ($\downarrow$ Ach; *indireto*)

Útero (α e β):

$\uparrow\beta_2 \longrightarrow$ Relaxamento $\longrightarrow$ Trabalho prematuro

Bexiga, esfíncter urinário, próstata (α):

$\uparrow\alpha \longrightarrow$ Contração $\longrightarrow$ Continência urinária

$\uparrow\beta \longrightarrow$ Relaxamento bexiga

Glândulas exócrinas:

Salivares: $\uparrow$ Amilase, agua (Clonidina ?)

Sudoríparas (não termo-regulatórias)



Sudoríparas (termo-regulatórias): Simpático ACh (M)

Metabolismo:

↑ Lipólise:

↑ β_3

↓ Lipólise:

↑ α_2 (↓cAMP)

Glicogenólise:

↑ β_2

↑↑ [catecolaminas]:

Acidose

↓ K⁺ plasmático:

↑ β_2

(↑ captação de K⁺)

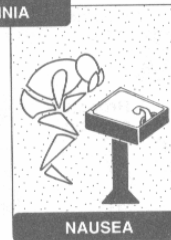
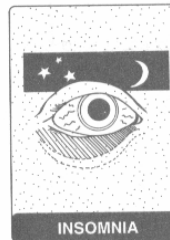
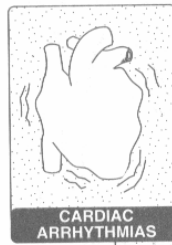
Proteção no exercício)

Insulina (↑ β ; ↓ α_2)

Renina (↑ β ; ↓ α_2)

PTH , **Calcitonina** , **T₄** , **Gastrina**,

↑↑ [Epi]: Leucocitose



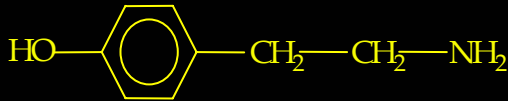
- **Fenoldopam (D_1):** Hipertensão severa
- **Dobutamina (β_1)**
- **Fenilefrina (α):** Midriático, descongestionante
- **Metoxamina (α_1)**
- **Midodrina (α_1):** Hipotensão postural
- **Efedrina (liberação de catecolaminas; ~Epi):**
Descongestionante nasal
- **Anfetamina (Metanfetamina, Fenmetrazina, Pemoline):**
(liberação de catecolaminas)
- **Fenilpropanolamina:** Anorexígeno, descongestionante
- **Clonidina, Metildopa, Guanfacina, Guanabenz (α_2):**
Hipertensão arterial
- **Cocaina:** Recaptação de catecolaminas (dopamina)

- **Tiramina:**

Metabolismo da tirosina

MAO

Liberação de catecolaminas



Cerveja

Leguminosas (fava, feijão)

Queijos

Fígado de frango

Chocolate

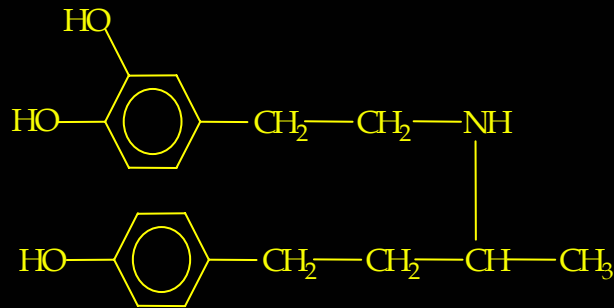
Embutidos (salsichas, salames, lingüiças)

Peixes

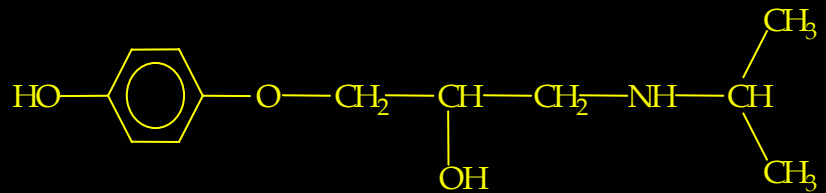
Vinhos

Leveduras (fermentos)

Agonistas β_1 seletivos

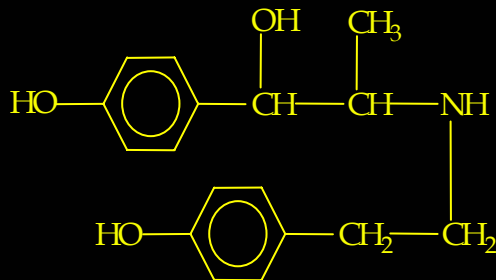


Dobutamina

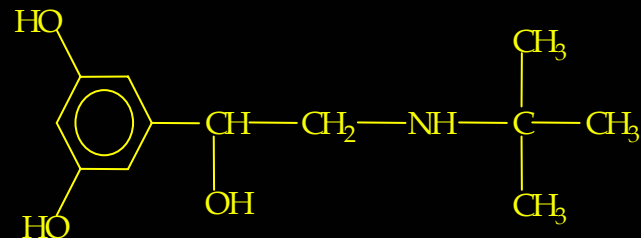


Prenalterol

Agonistas β_2 seletivos



Ritodrina

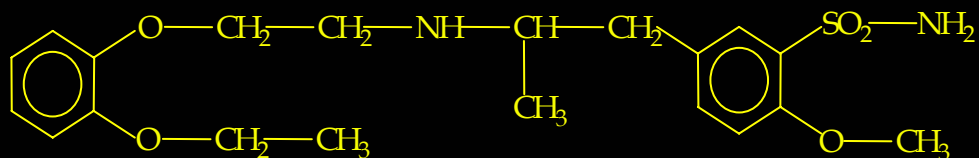
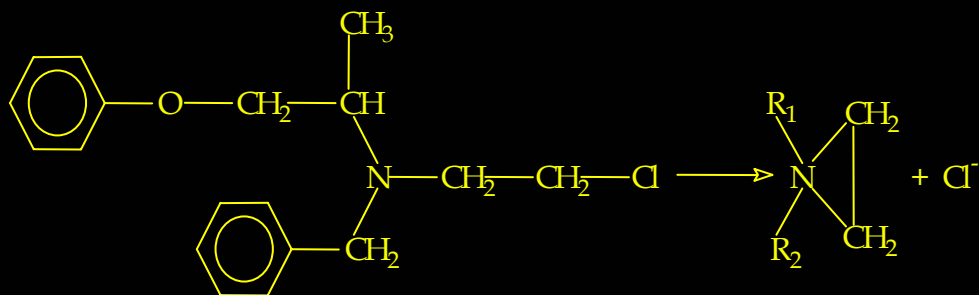
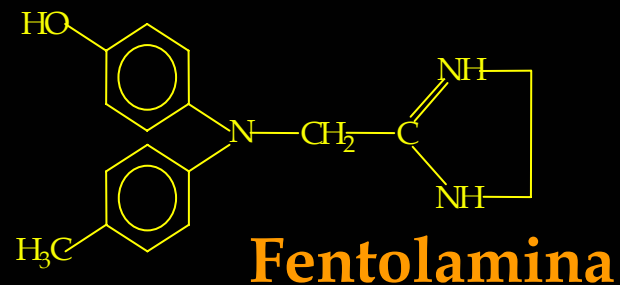
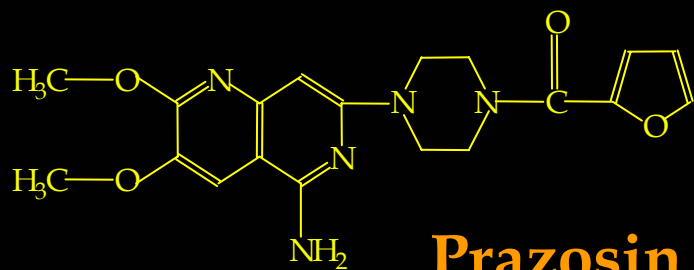


Terbutalina

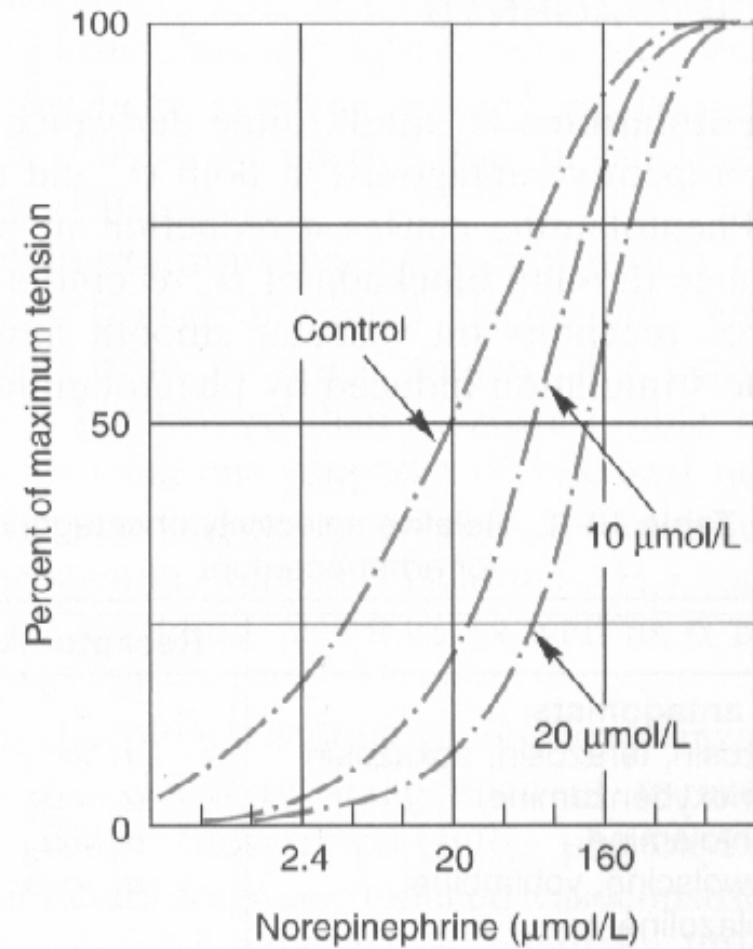
Bloqueadores de Receptores Adrenérgicos

	Afinidade
Prazosin, terazosin, doxazosin	$\alpha_1 \gg \gg \gg \alpha_2$
Fenoxibenzamina	$\alpha_1 > \alpha_2$
Fentolamina	$\alpha_1 = \alpha_2$
Rawolscina, yoimbina, tolazolina	$\alpha_2 \gg \alpha_1$

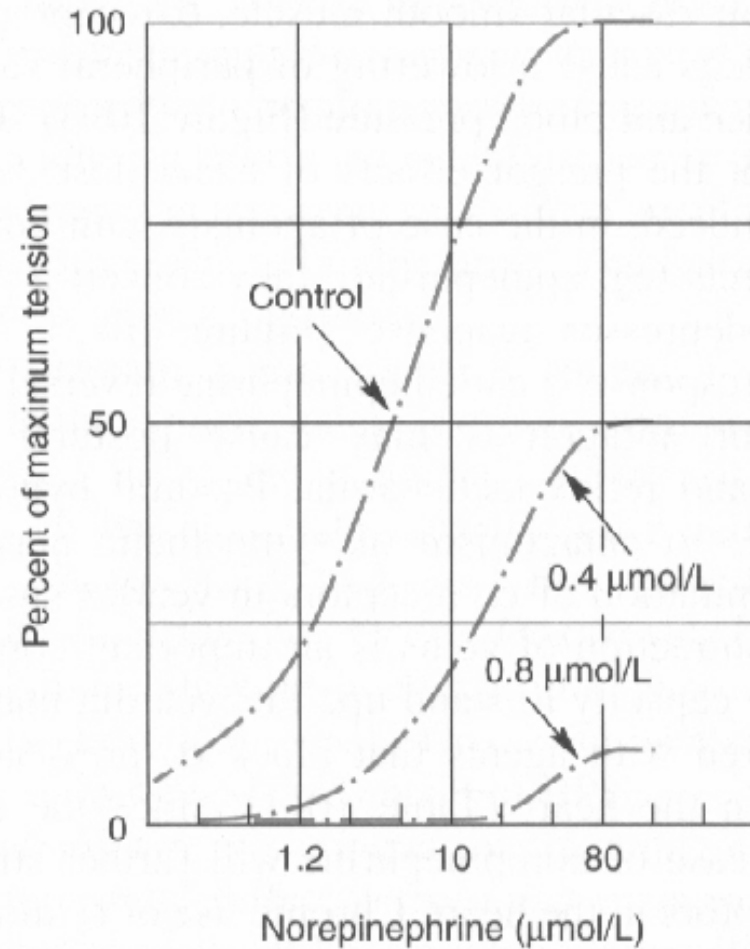
Antagonistas α

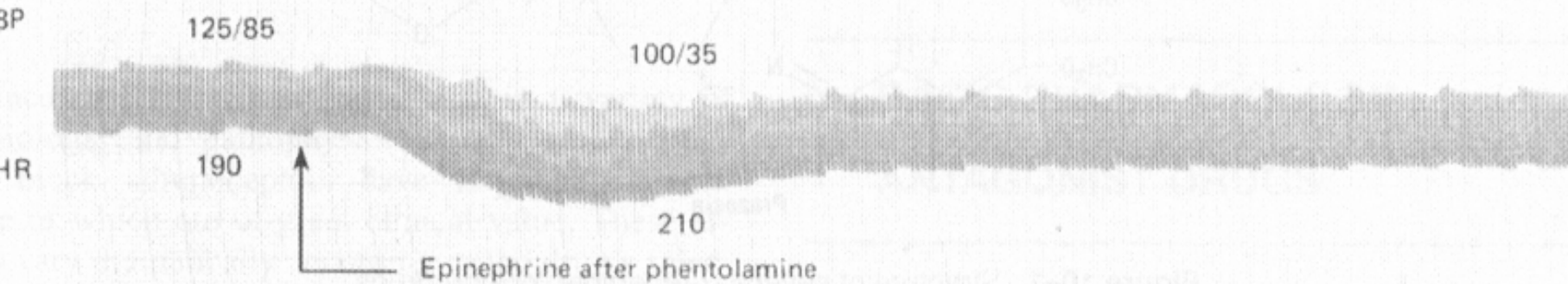
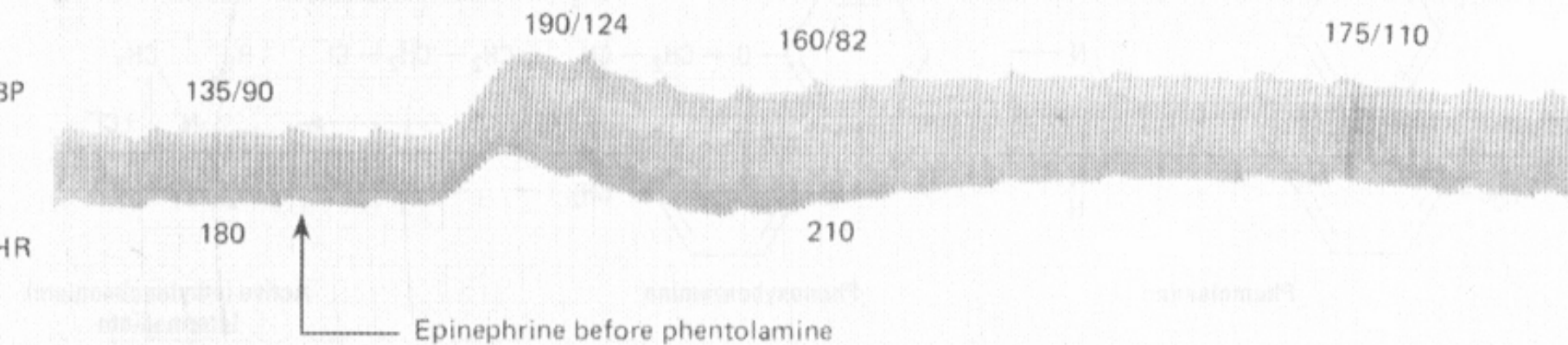
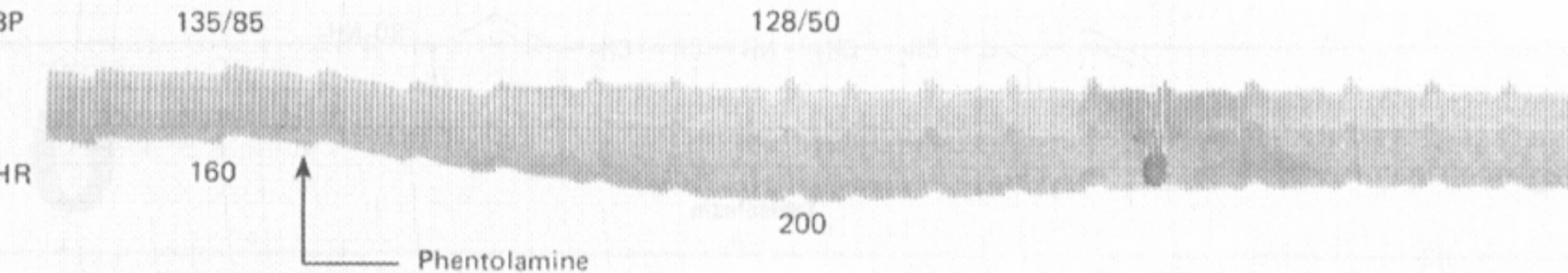


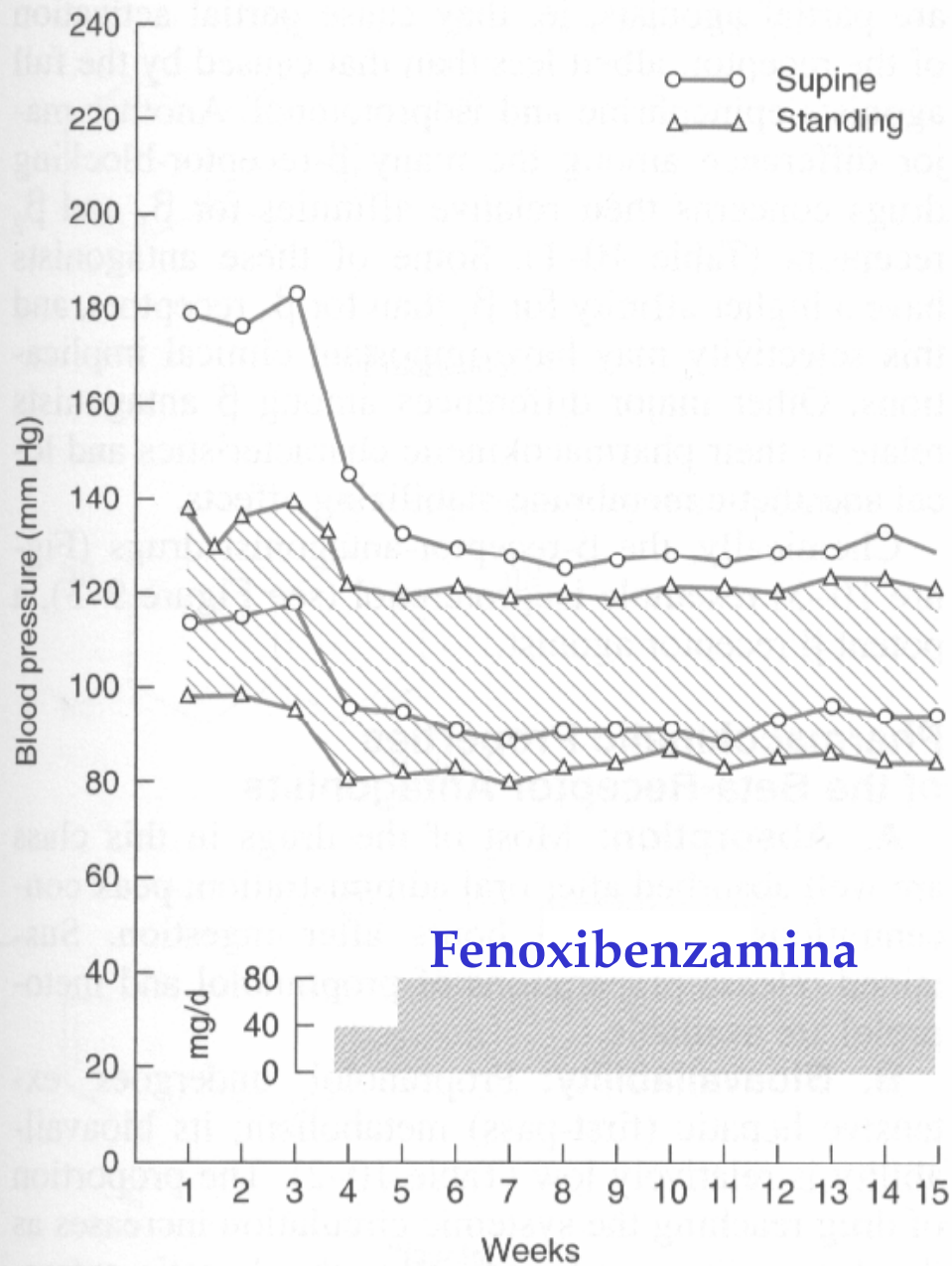
Tolazolina



Dibenamina

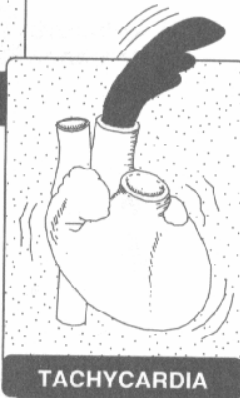
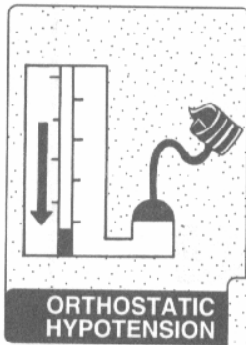






Aplicações clínicas:

- Feocromocitoma (Fenoxibenzamina / + Metil-tirosina)
- Hipertensão crônica (Prazosin)
- Exceso de vasoconstritor local
- Hiperplasia benigna de próstata (Tamsulosin, α_{1A})
- Disfunção sexual masculina (Fentolamina / + Papaverina)

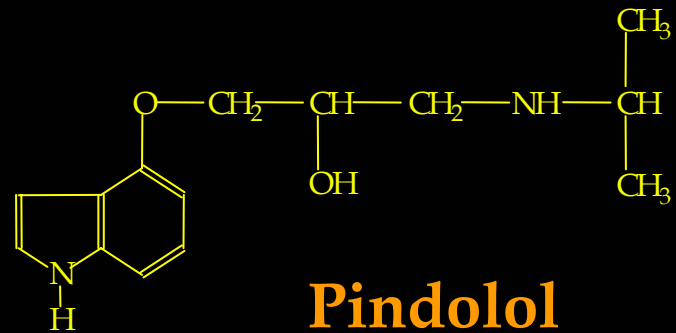
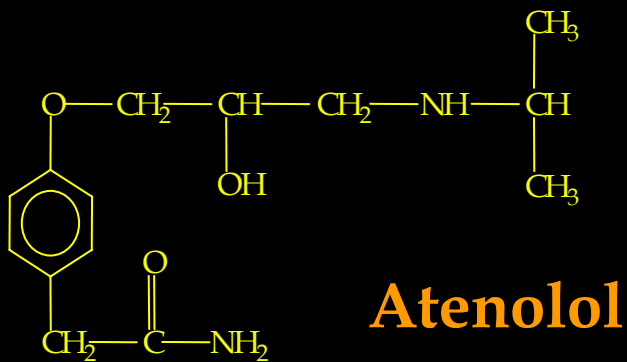
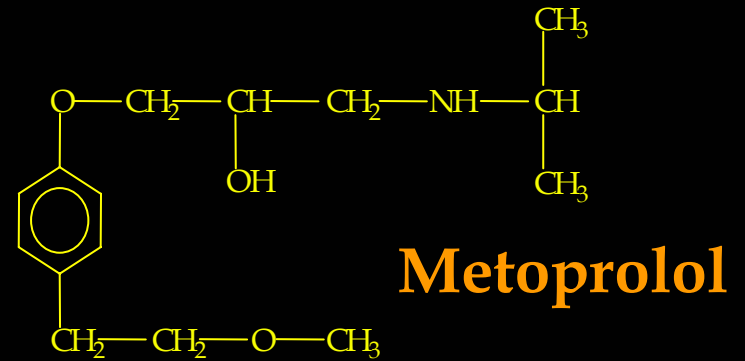
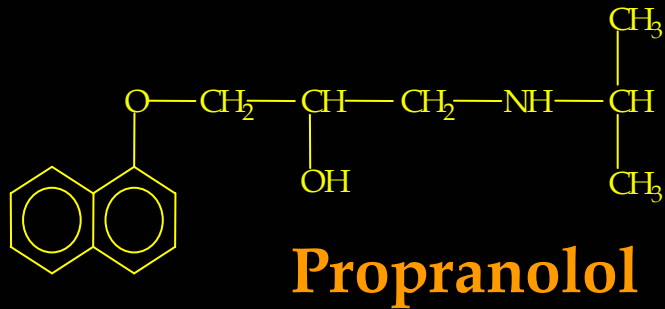


➤ Miose

➤ Congestão nasal

➤ ↑ Hipervolemia (uso crônico)

Antagonistas β



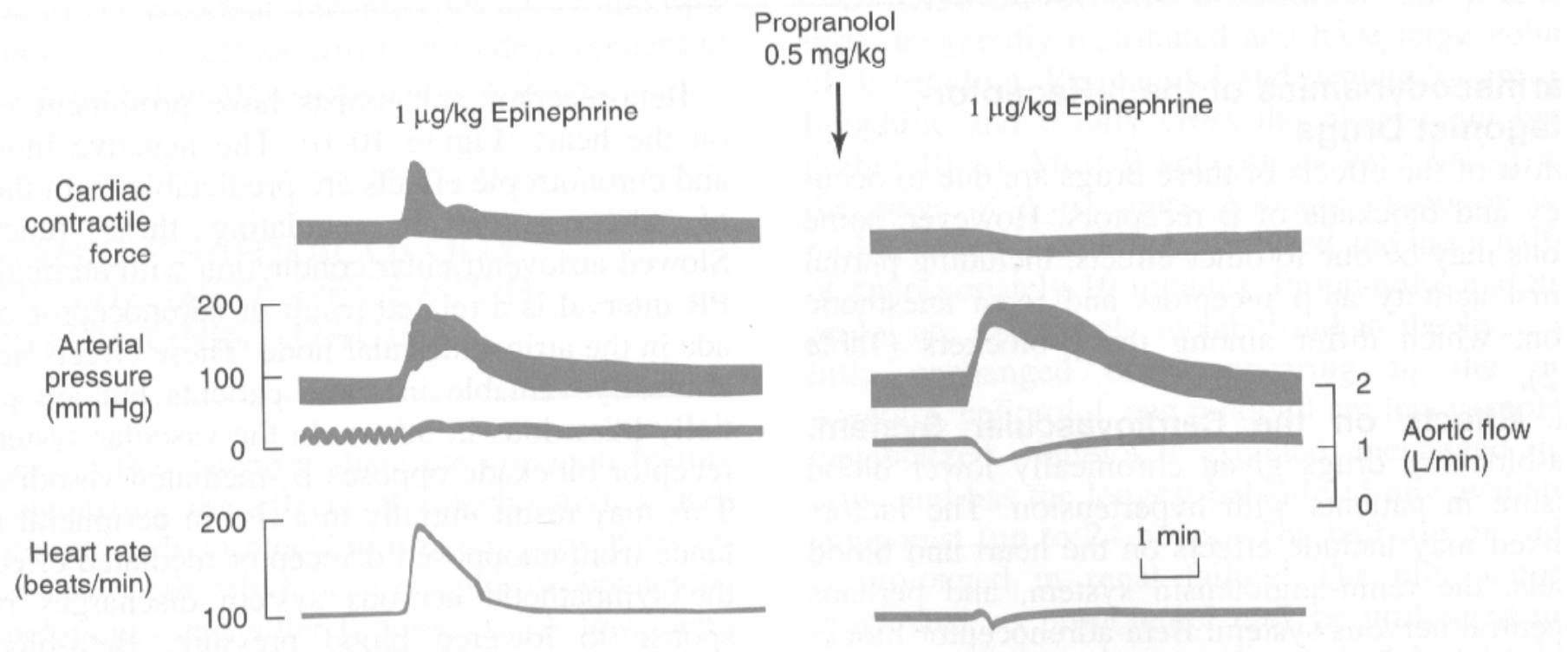
	Afinidade
Metoprolol, acebutolol, alprenolol, atenolol, betaxolol, celiprolol, esmolol	$\beta_1 \gg \beta_2$
Propranolol, carteolol, penbutolol, pindolol, timolol	$\beta_1 = \beta_2$
Butoxamina	$\beta_2 \gg \beta_1$
Mistos (Labetalol, carvedilol)	$\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$

- **Cardiovascular (coração, vasos, renina, SNC)**
- **Trato respiratório**
- **Olhos (Timolol)**
- **Inibição da lipólise**
- **↑ VLDL / ↓ HDL Colesterol**

	Seletividade	Agonista parcial?	Anestésico local?	Lipossolubilidade	T _{1/2}	F (%)
Acebutolol	β_1	Sim	Sim	Baixa	3 – 4 h	50
Atenolol	β_1	Não	Não	Baixa	6 – 9 h	40
Betaxolol	β_1	Não	Leve	Baixa	14 – 22 h	90
Bisoprolol	β_1	Não	Não	Baixa	9 – 12 h	80
Carteolol	Nenhuma	Sim	Não	Baixa	6 h	85
Carvedilol ¹	Nenhuma	Não	Não	?	6 – 8 h	25 - 35
Celiprolol	β_1	Sim ²	Não	?	4 – 5 h	70
Esmolol	β_1	Não	Não	Baixa	10 min	~0
Labetalol ¹	Nenhuma	Sim	Sim	Média	5 h	30
Metoprolol	β_1	Não	Sim	Média	3 – 4 h	50
Nadolol	Nenhuma	Não	Não	Baixa	14 – 24 h	33
Penbutolol	Nenhuma	Sim	Não	Alta	5 h	>90
Pindolol	Nenhuma	Sim	Sim	Média	3 – 4 h	90
Propranolol	Nenhuma	Não	Sim	Alta	3.5 – 6 h	30 ³
Sotalol	Nenhuma	Não	Não	Baixa	12 h	90
Timolol	Nenhuma	Não	Não	Média	4 – 5 h	50

¹Carvedilol e Labetalol também bloqueiam α_1 ; ²Atividade agonista parcial β_2 ;

³Biodisponibilidade dependente da dose.



Heart rate

Drama

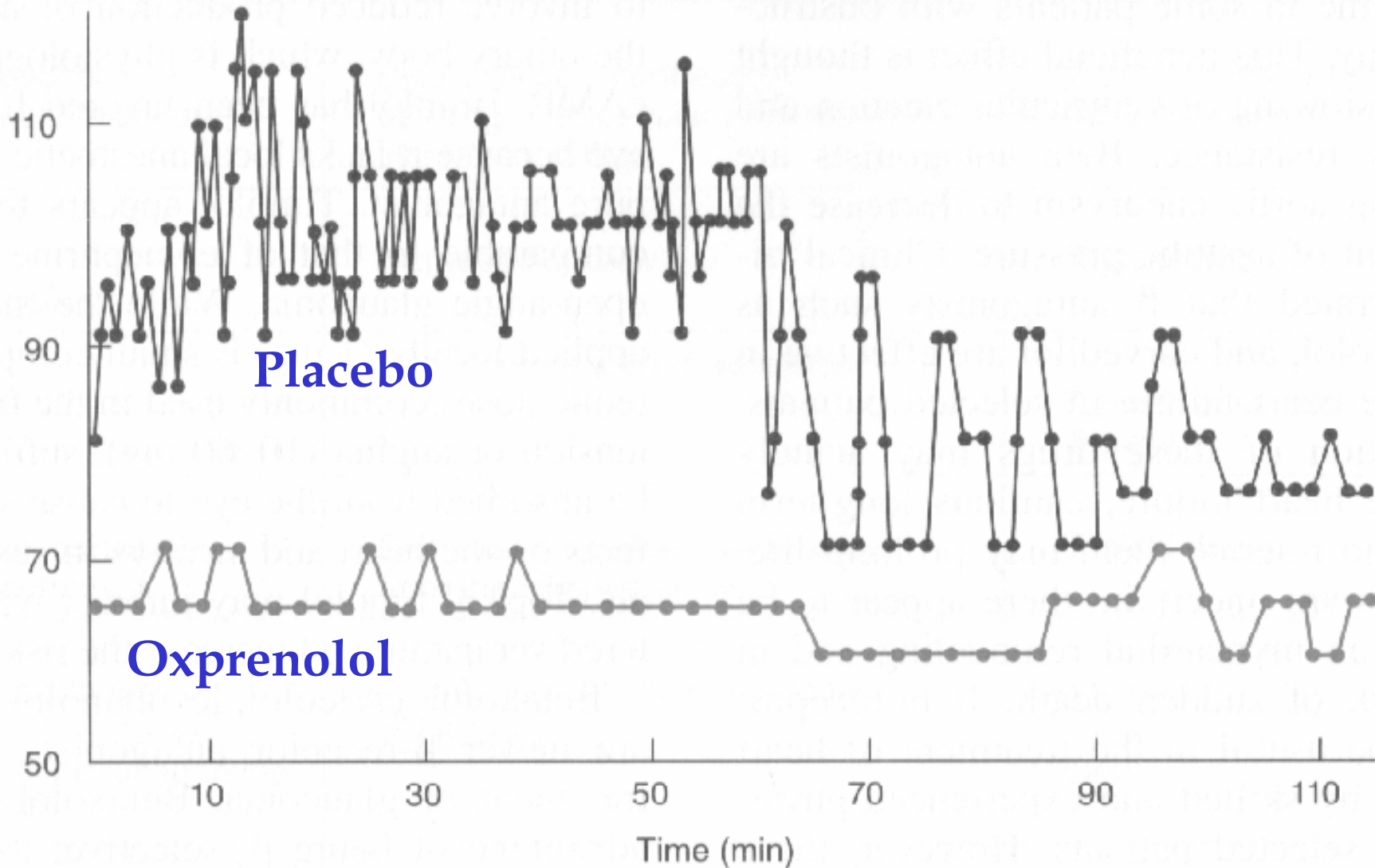
Comedy

Documentary

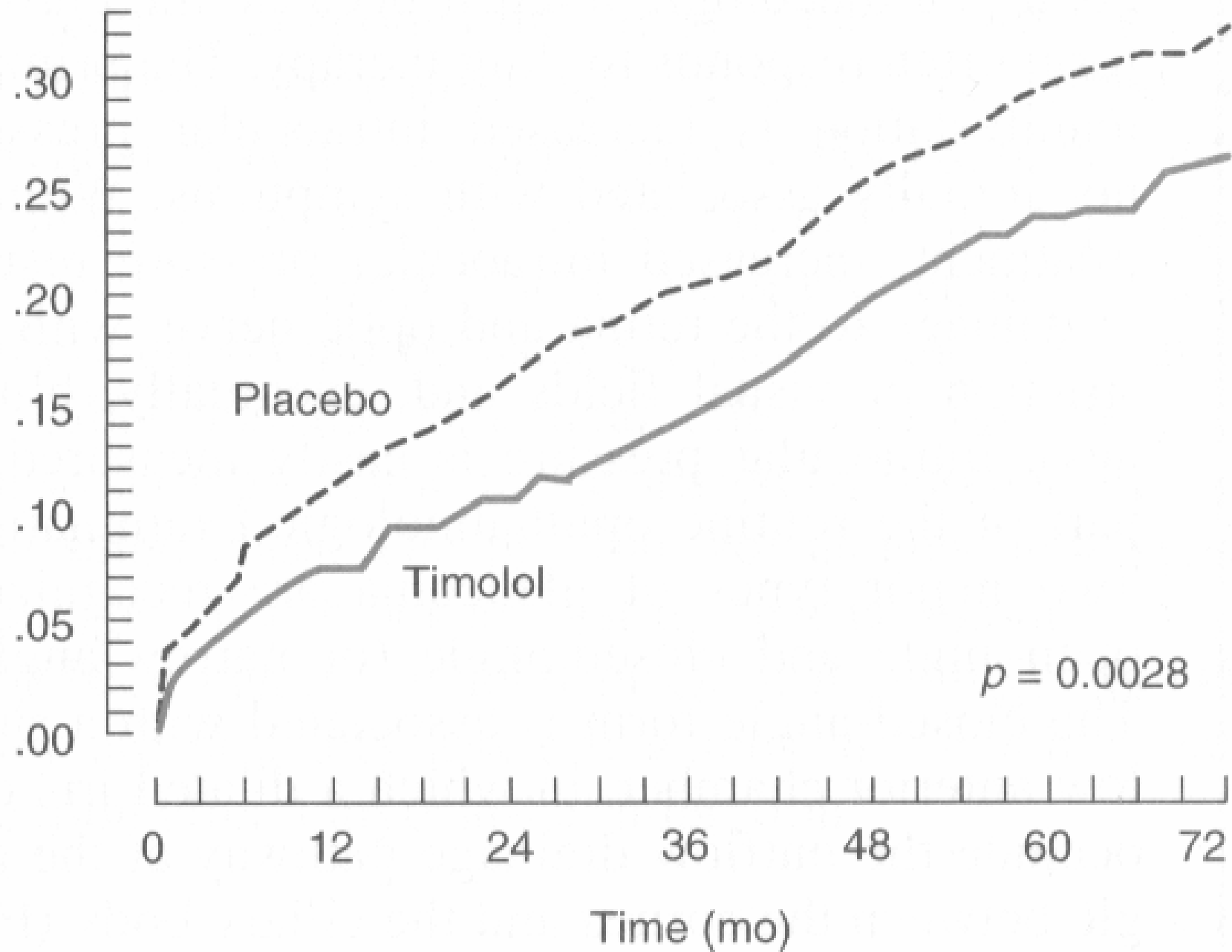
Placebo

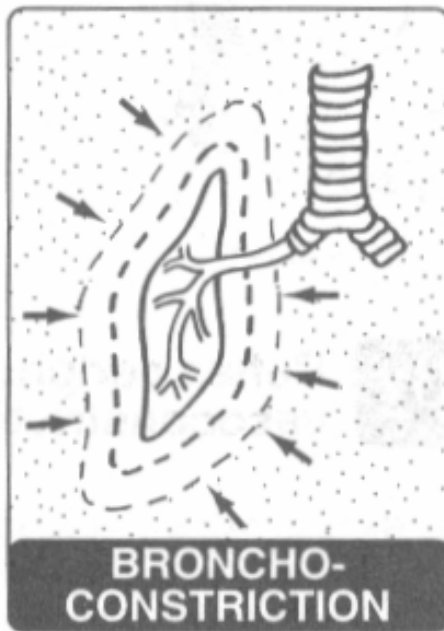
Oxprenolol

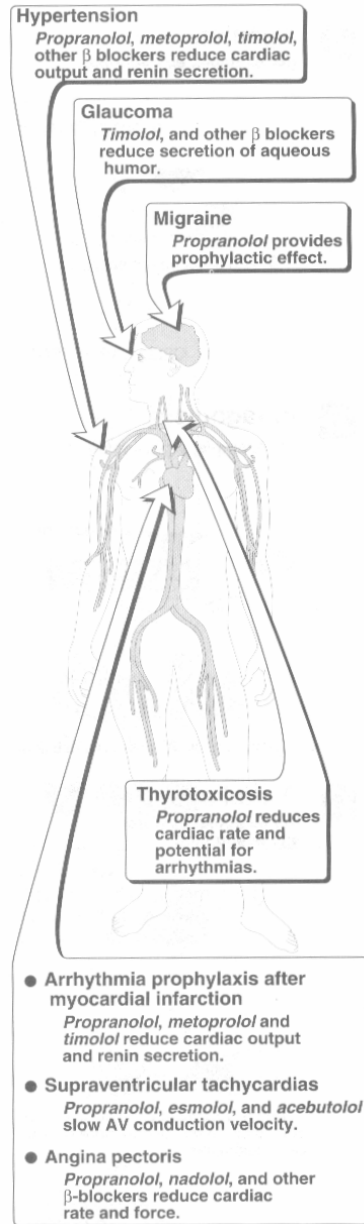
Time (min)



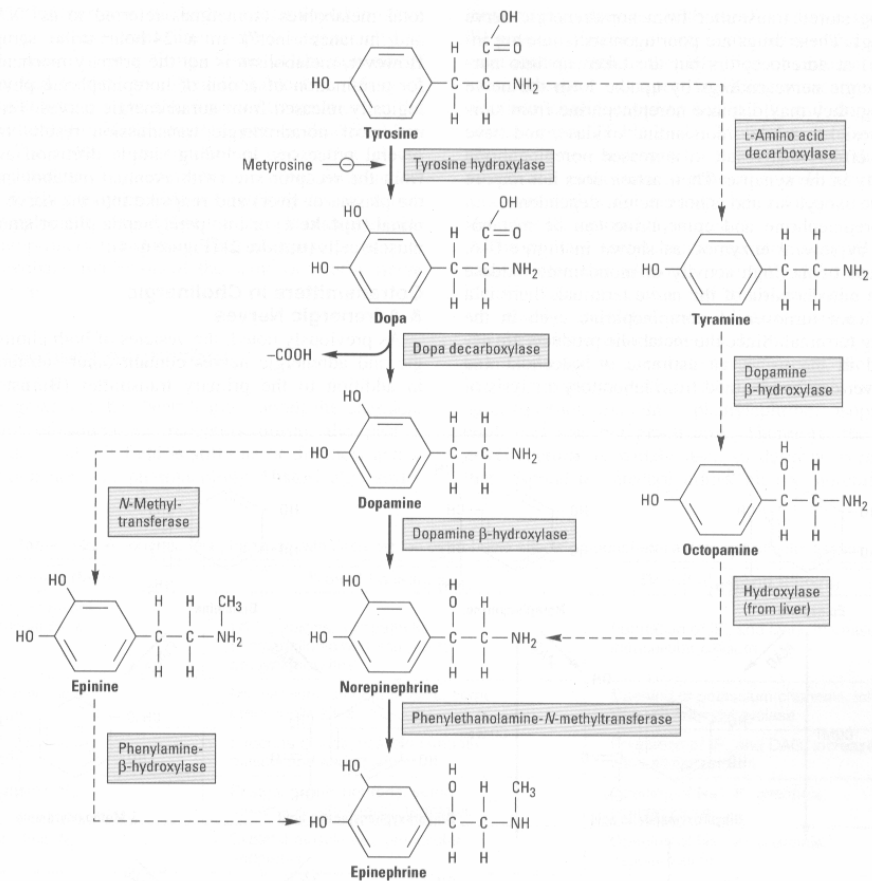
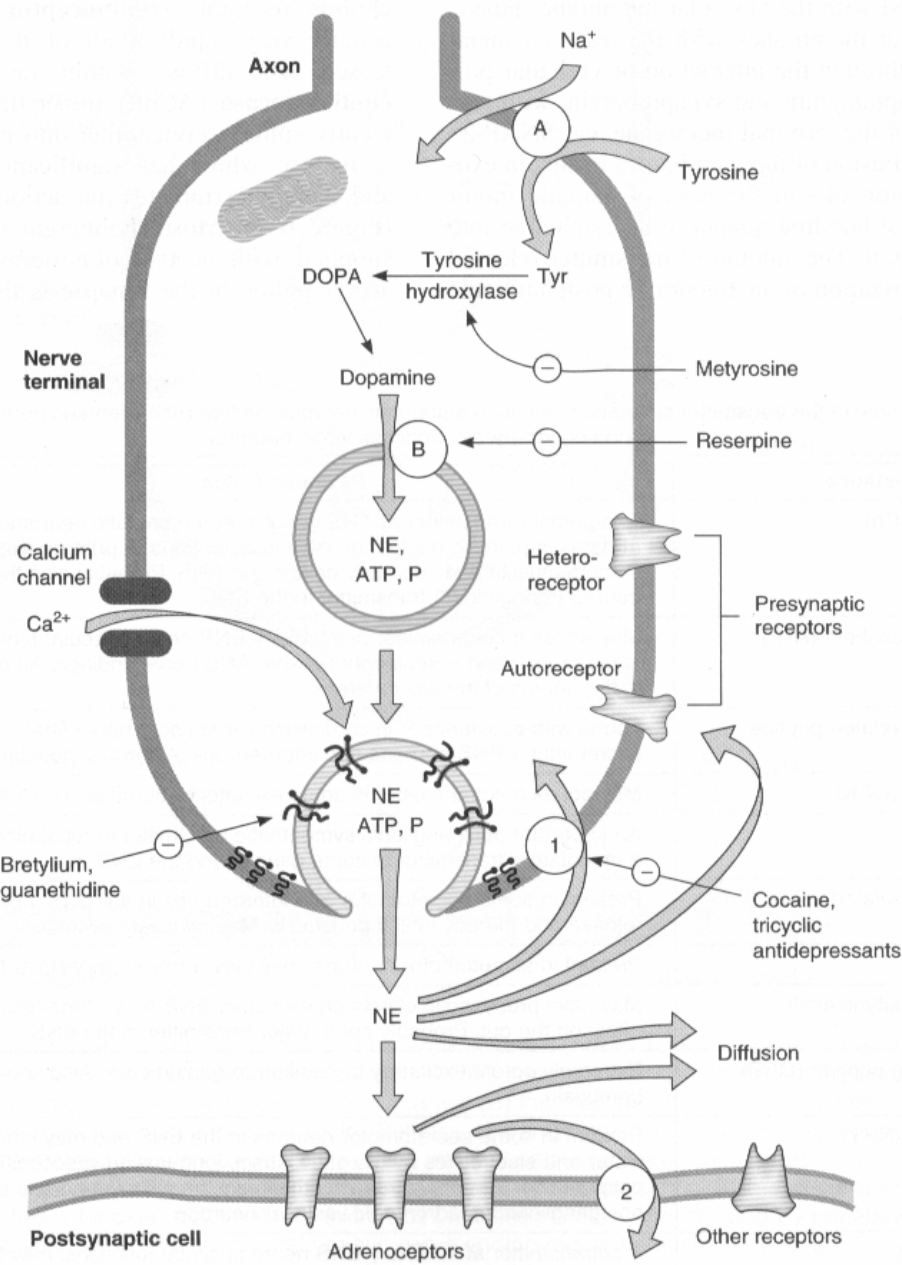
Cumulative mortality rate







Drogas que interagem com Neurônios Adrenérgicos



Síntese:

Metildopa

Carbidopa

α -Metiltirosina

6-OH-Dopamina

Estocagem:

Reserpina

Inibidores da MAO

Liberção:

Exocitose (bloqueadores neuronais)

Guanetidina

Bretílio

Simpatomiméticos de ação indireta

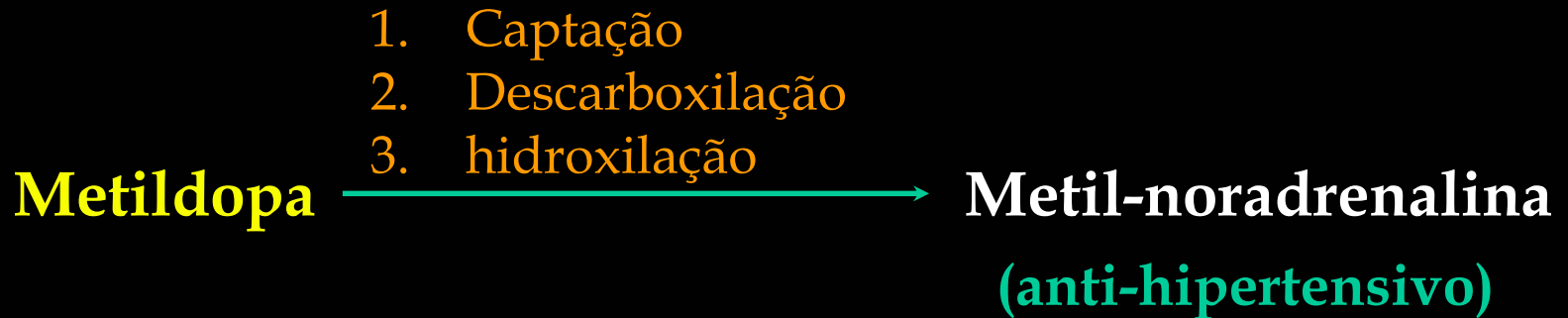
Tiramina

Anfetamina

Efedrina

α_2 pré-sinápticos

agonistas α_2 , AII, Dopamina, PGs



- resistente à MAO
- < potência que NA (α_1)
- > potência que NA (α_2)



α -Metiltirosina
(feocromocitoma)



~~Tirosina hidroxilase~~

Carbidopa
(Parkinson)



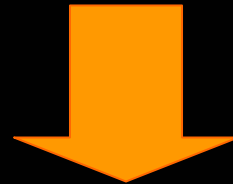
~~Dopa descarboxilase~~

Reserpina:
(anti-hipertensivo)

Ligação c/proteína transportadora



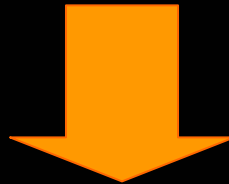
~~Estocagem de NE~~



Acúmulo de NE citoplasmática $\xrightarrow{\text{MAO}}$ ~~NE~~

Guanetidina:

Internalização / Acúmulo
(Uptake 1)

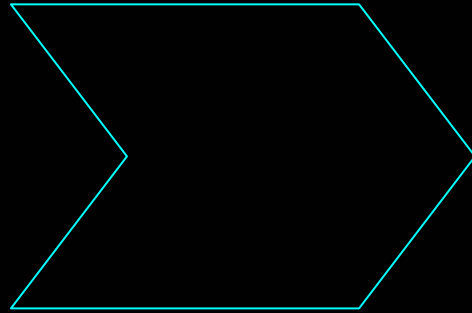


Vesículas → Dislocamento de NE



Acúmulo de NE citoplasmática $\xrightarrow{\text{MAO}}$ ~~NE~~

Anfetamina
Imipramina
Cocaina



~~Uptake 1~~



↑↑ **Catecolaminas na fenda sináptica**