



Centro Stampa

ATTENZIONE QUESTI APPUNTI SONO OPERA DI STUDENTI , NON SONO STATI VISIONATI DAL DOCENTE. IL NOME DEL PROFESSORE, SERVE SOLO PER IDENTIFICARE IL CORSO.

N° 3821

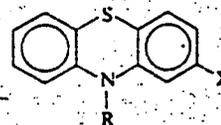
**CHIMICA FARMACEUTICA E TOSSICOLOGICA 1
(SECONDA PARTE)**

DI PEILA EMANUELA

b) DA antagonisti (neurolettici o antipsicotici)

64

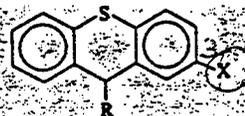
Phenothiazines



Drug name	(X)	(R)	average p.o. dose (man) (mg/kg/d)
Chlorpromazine	Cl	$\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	25-50
Trifluorpromazine	CF_3	$\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	10-25
Prochlorperazine	Cl	$\text{CH}_2\text{CH}_2\text{CH}_2\text{-N}$ (piperazine ring) -N-CH_3	5-10
Trifluoperazine	CF_3	$\text{CH}_2\text{CH}_2\text{CH}_2\text{-N}$ (piperazine ring) -N-CH_3	2-10
Fluphenazine	CF_3	$\text{CH}_2\text{CH}_2\text{CH}_2\text{-N}$ (piperazine ring) $\text{-N-CH}_2\text{CH}_2\text{OH}$	0.25-0.5
Thioridazine	SCH_3	$\text{CH}_2\text{CH}_2\text{-}$ (piperidine ring) -N-CH_3	25-100

Drug name	X	R	average p.o. dose (man) (mg/kg/d)
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Thioxanthenes



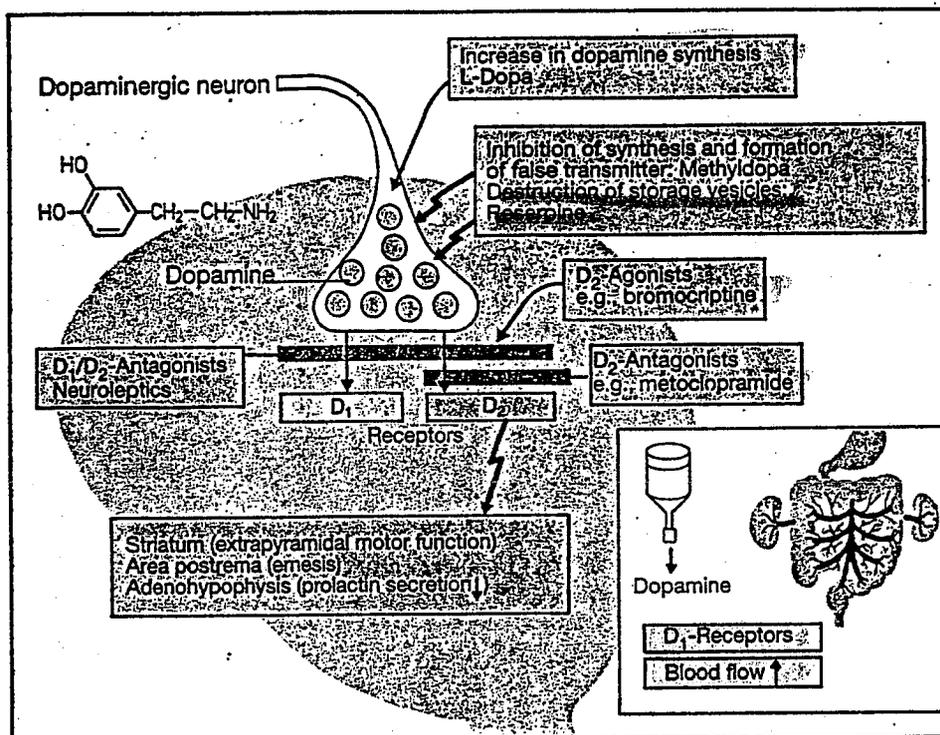
Chlorprothixene (cis)	Cl	$=\text{CH-CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	200-300
Flupenthixol	CF_3	$=\text{CH-CH}_2\text{CH}_2\text{-N}$ (piperazine ring) $\text{-N-CH}_2\text{CH}_2\text{OH}$	10-20
Pifuthixol (6-F)	CF_3	$=\text{CH-CH}_2\text{CH}_2\text{-N}$ (piperazine ring) $\text{-N-CH}_2\text{CH}_2\text{OH}$	5-6

Butyrophenones

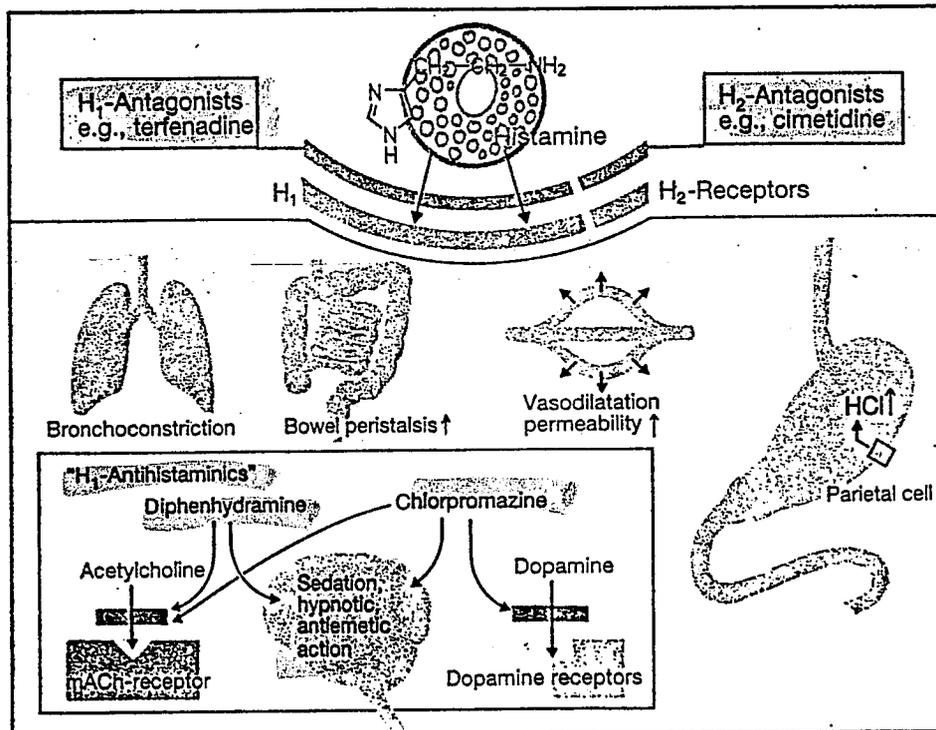
Haloperidol		2-5
Spiroperidon		0.02-0.05
Benperidol		0.05-0.1

252

65



A. Dopamine actions as influenced by drugs



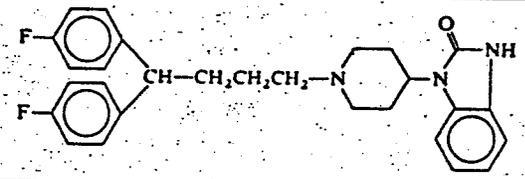
B. Histamine actions as influenced by drugs

.(continued)

Diphenylbutylpiperidines

Pimozide

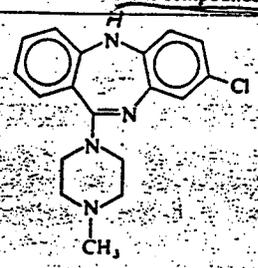
↓ panchi



0.05-0.1

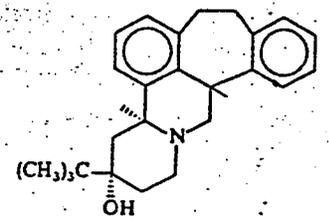
Other compounds

Clozapine



10-20

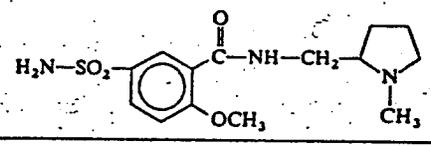
Butaclamol



1-2

Sulpiride

↓ panchi

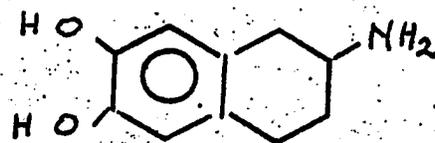
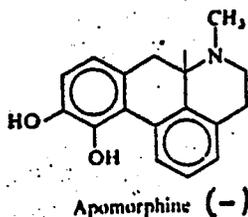


11a from A. Goth, *Medical Pharmacology*, 9th ed. Mosby, St. Louis, 1978. p. 219; L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, semilAn, 1970

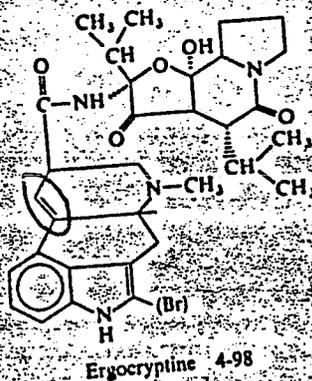
do
guardare

Farmaci con effetti
post-sinaptici

α / DA agonisti



Amintetralina



(Vaso dilatatore)
diidro derivato } D₂
Br derivato } agonisti
(inibisce le recettori di
prolattina)

α-antagonista

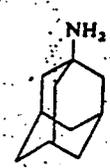
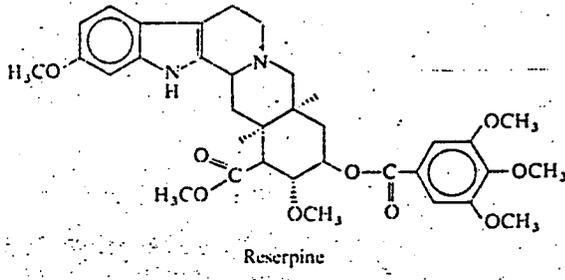
Dopaminergic Agents Related to Ergolines



Fig. 7. This figure outlines the portions of the tetracyclic ergoline nucleus that have been proposed by various investigators to be the dopaminergic fragment.

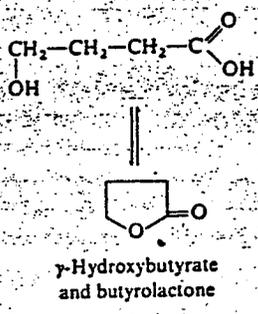
c) Farmaci che interferiscono con l'impegno e il rilascio delle dopamine

1) Farmaci che nuotano le terminazioni nervose di DA

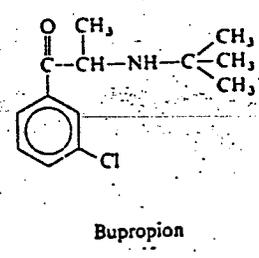
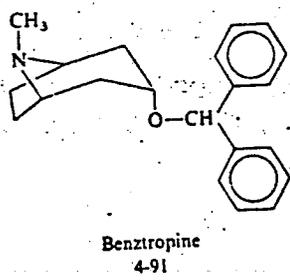


Amantadine
(facilita il rilascio)

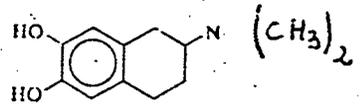
2) Farmaci che impediscono il rilascio



d) Inibitori del reuptake

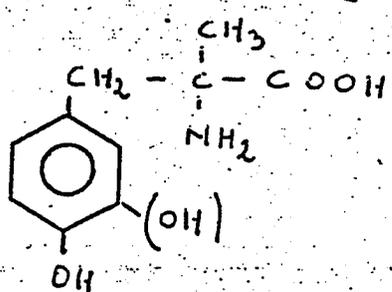


e) Agenti presinaptici (agonisti)



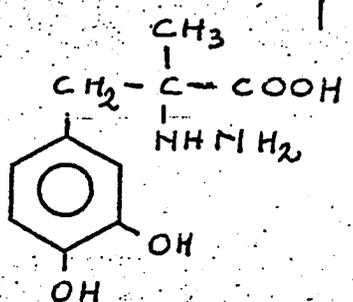
~~Si~~ Farmaci con effetti presinaptici

a) Inibitori della sintesi delle dopamine

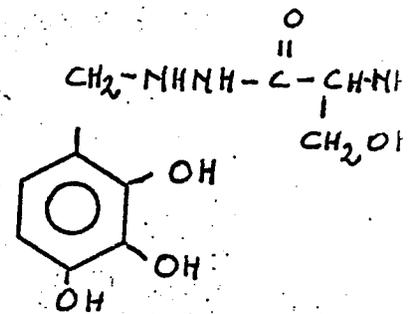


α-metil DOPA

(H) α-metil tirosine

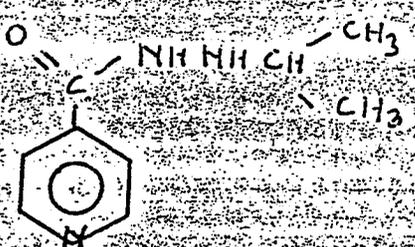


Carbidopa



Serazide

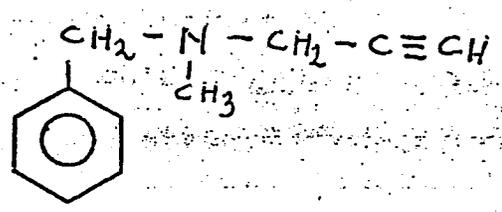
b) Inibitori del metabolismo delle dopamine



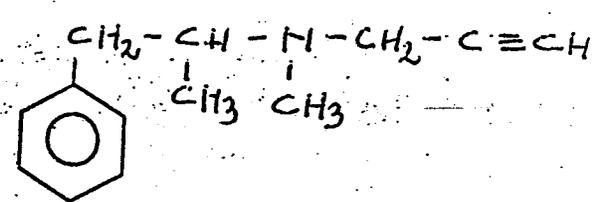
Iponezide



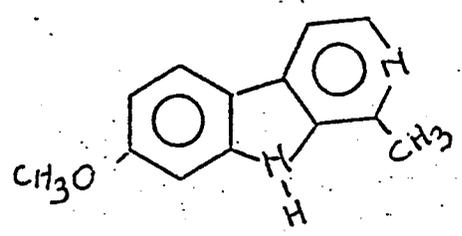
Tramylcypamina



Pargiline



Deprenile



Armina

250

Farmaci che influenzano la trasmissione dopaminergica tramite meccanismi non recettoriali

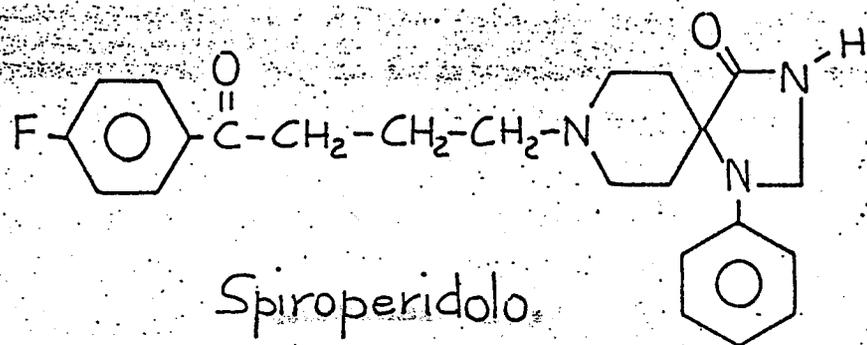
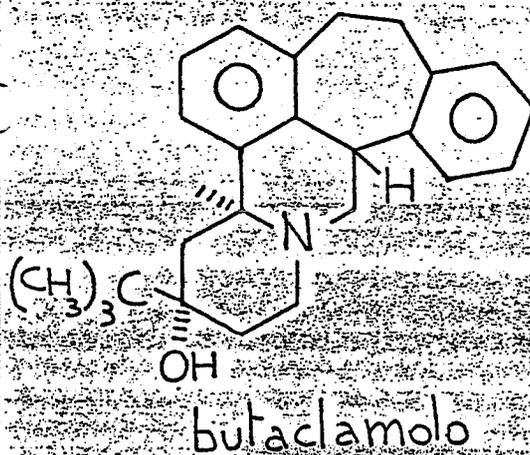
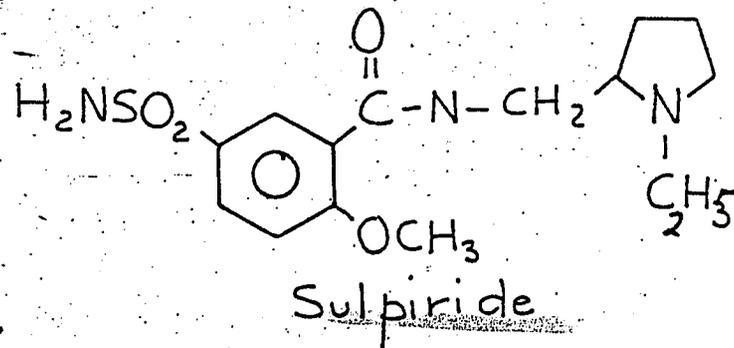
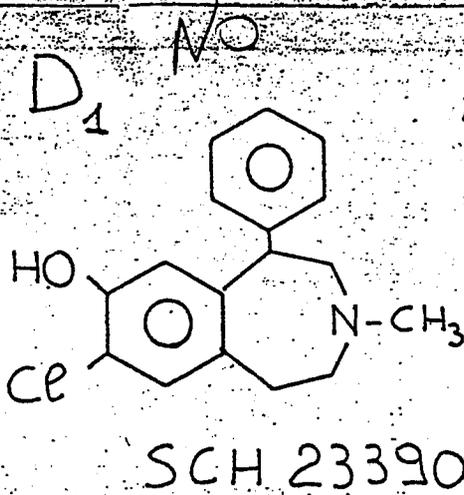
1) Inibitori delle biosintesi

2) Inibitori del metabolismo

3) Farmaci che influenzano l'accumulo

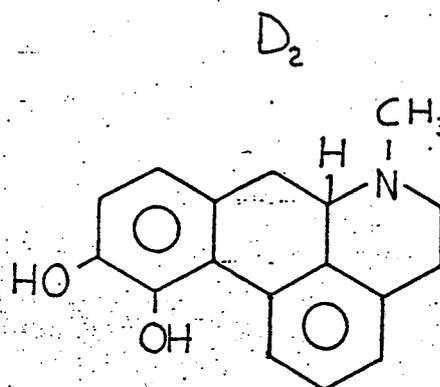
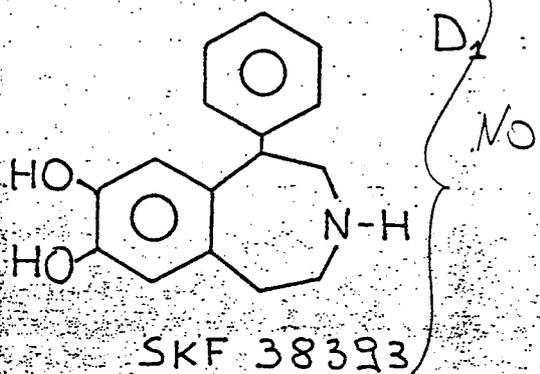
4) Farmaci che influenzano il riassorbimento

Antagonisti

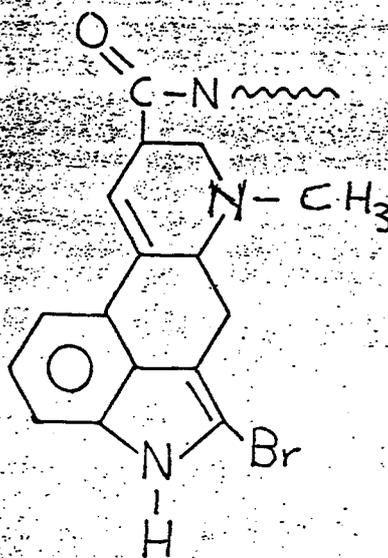


249

Agonisti



Apomorfina



Bromocriptina

Dopamine Receptors

277

55

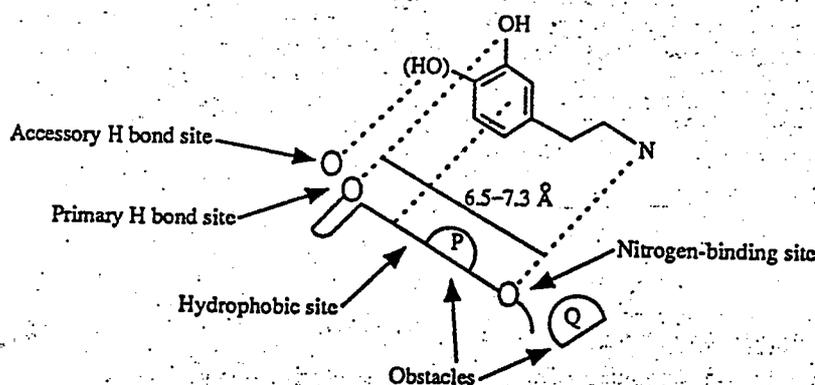


Figure 5 Topographical model for DA receptors:⁶⁵ Seeman's model (1980)

the vascular DA receptor. It was envisaged that the amino group interacts with the receptor *via* hydrogen bonding through the nitrogen lone pair or the hydrogens of the amine. Two sites were postulated for the binding of the catechol group and, in addition, for the A ring of the aporphines, a hydrophobic region. In 1979, McDermed *et al.*⁹⁴ postulated their model accounting for enantioselectivity, which was mentioned in Section 12.3.13.1.

A detailed model of D-2 receptors was postulated in 1980 by Seeman in an extensive review²¹ on brain DA receptors (Figure 5). The essential features were: (i) a hydrogen-bonding group corresponding to the *m*-hydroxy group, and possibly an accessory hydrogen-bonding site corresponding to the *p*-hydroxy group in DA; (ii) high fat solubility, obtained by expansion of the carbon framework of DA analogues or introduction of *N*-alkyl substituents, which is considered to be helpful but not essential; (iii) a nitrogen atom positioned about 0.6 Å above the plane of the aromatic ring bearing the hydrogen-bonding groups; (iv) a distance of less than 7.3 Å between the *m*-hydroxy group and the nitrogen atom; and (v) avoidance of steric hindrance factors in the form of an « obstacle Q » located near the binding site for the nitrogen atom, which would account for the inactivity of octahydrobenzo[*g*]quinolines and norapomorphines with substituents on the nitrogen larger than propyl. A second region of bulk intolerance, called « obstacle P », rationalized the inactivity of octahydrobenzo[*h*]quinolines and isoapomorphine.

Seiler and Markstein¹⁰² (1982) examined the binding of phenolic aminotetralins to the striatal D-1 receptor. Their model, which was similar to McDermed's, has two major binding sites complementary to the *m*-hydroxy and the nitrogen of the 7-OH(+)-(2*R*)- and 5-OH(-)-(2*S*)-ATN series. In the 5-OH series, but not the 7-OH series, an accessory binding site could accommodate the *N,N*-dipropyl substituents. According to this model, DA would interact with the receptor in the β rotameric form, and the *N,N*-dipropyl groups would force the α rotamer to become the preferred conformation. A year later (1983), Nichols⁴ described a model similar to that of McDermed's, which included enantioselective-stereoselective nitrogen and *m*-OH sites, a steric boundary and a hydrophobic site or a region of bulk tolerance. It was suggested that the latter site was of importance for D-2 or DA₂ receptors.

Following their extensive studies on aporphine derivatives, Neumeyer *et al.*⁸ suggested a model for the DA receptor having the following elements (Figure 6): (i) putative binding sites, M₁ and M₂, on the receptor surface, complementary to the hydroxyl groups of the *meta* and *para* positions of the DA element in the aporphines; a binding site (M₃) for hydroxyl groups at position 2 of the aporphines which diminishes affinity; (ii) an electronegative site, B, complementary to the nitrogen of agonist molecules; the distance between the *m*-hydroxy group and the nitrogen atom was calculated to be 6.9 ± 0.4 Å; (iii) an obstacle that inhibits the binding of aporphines with a (6*aS*) configuration; and (iv) an explanation of enantioselectivity in terms similar to those of McDermed.

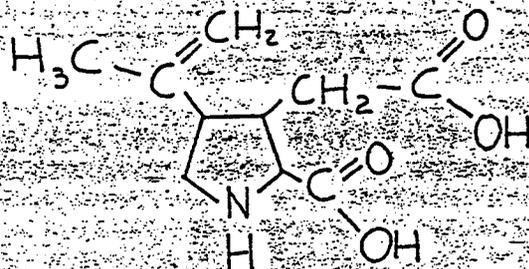
The topography of the renal DA receptor (Figure 7) has been investigated by Erhardt (1983).⁴ Cartesian coordinates were used to indicate the recognition sites of the receptor, which are: (i) a single *x, y* plane containing the amine (A) and catechol recognition sites (H_{*m*} and H_{*p*}); the distance between A and H_{*m*} or H_{*p*} approximates 7 Å; (ii) a steric parameter, S₁, in agreement with McDermed's model; (iii) a second steric parameter, S₂ ('ceiling'), located approximately 2 Å above the *x, y* plane; and (iv) an auxiliary lipophilic-binding site, B, located opposite the steric parameter, S₁.

248

No

Table 4.6. Dopamine receptor classification

Receptor type	D ₁ (CNS) DA ₁ (vascular) high aff. $\frac{GTP}{Ca^{2+}}$ low aff. (D ₃) activation	D ₂ (CNS) DA ₂ (neuronal) high aff. $\frac{GTP+Na^+}{Ca^{2+}}$ low aff. (D ₄ , auto) deactivation
Selective agonist	SK&F 38393 (4-103)	quinpirole (4-106) bromocriptine (4-108) (-) apomorphine (4-101)
Selective antagonist	SCH 23390 (4-104) butaclamol (4-126)	sulpiride (4-127) spiroperidol (4-122)



Acido Kainico

NO

34

Dopamine Receptors

279

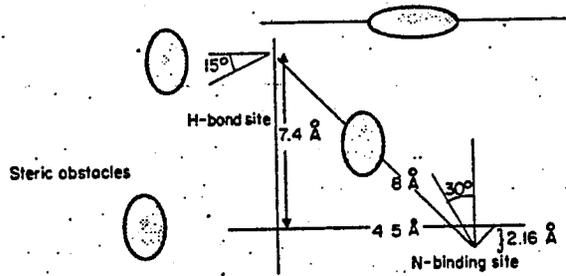


Figure 9 Topographical model for DA receptors:⁶⁵ Seeman's model (1985)

binding sites for hydrogen bonds with the *m*-OH and the nitrogen, the extremities of which are separated by 8 Å; (ii) hydrogen-bonding receptor groups which are directed between 15° and 30° orthogonal to the surface of the receptor; and (iii) a series of obstacles at 7, 10 and 1 o'clock, which account for the inactivity of certain analogues. The 'bottom' of the receptor and the 'back wall' are assumed to be hydrophobic surfaces. This model has many advantages, one of which is that it is able to explain the activity of the aminoindans.

Kaiser^{4,5} has also been responsible for proposing various models of the DA receptor, beginning in 1984 and the latest of which appeared in 1986. This model consists of nine possible binding sites (Figure 10), which together account for features of both the D-1 and D-2 receptors. The essential features of this model are: (i) an electronegative amine site complementary to the side chain nitrogen of the dopaminergic pharmacophore (i.e. the *m*-hydroxyphenethylamine unit); (ii) a site, M, complementary to the OH *meta* to the ethylamine chain; (iii) a site, N, interacting with the aromatic nitrogen of the pyrroethylamine pharmacophore of the dopaminergic ergot-like compounds; this primary nitrogen-binding site is located 2.0 Å away from a secondary binding site, P, for the *p*-OH group; (iv) accessory binding sites are proposed for (v) the aromatic ring of the pharmacophore (II₁); (vi) the 1-phenyl substituent of 3-benzazepines (II₂); and (vii) the benzo-fused A ring of aporphines (II₃). Additional sites which are tentatively suggested are: (viii) a lipophilic cavity in the area of steric intolerance, which maximally fits a properly 'downwards'-orientated *n*-propyl group; and (ix) a site in a properly oriented 'upward' direction that may accept lipophilic groups exceeding the size of an *n*-propyl substituent. Present in both D-1 and D-2 subtypes are sites (i), (ii), (iv) and (v). Sites (iii) and (viii) are related with D-2 activity, whereas (vi) and (ix) are present in D-1 receptors. Grof *et al.*¹⁰⁵ (1985) postulated two binding sites, P and M (Figure 11), complementary to the *p*-OH and *m*-OH

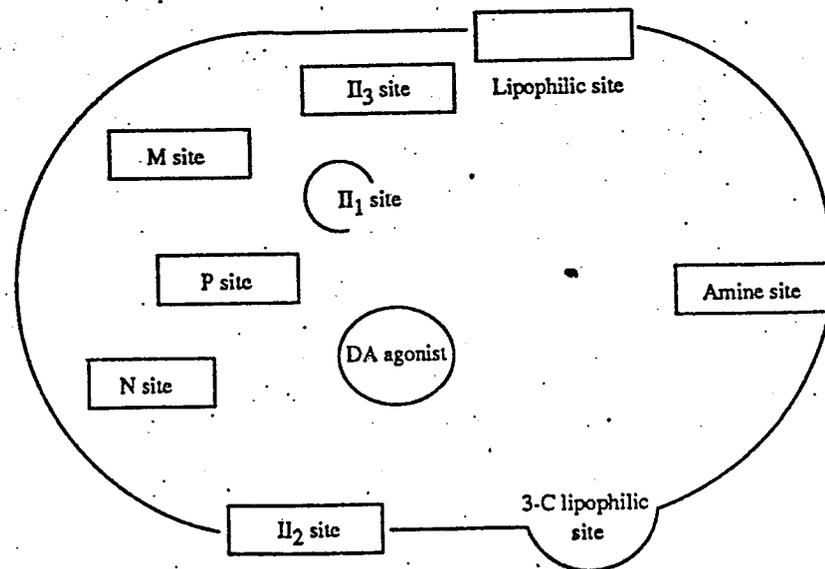
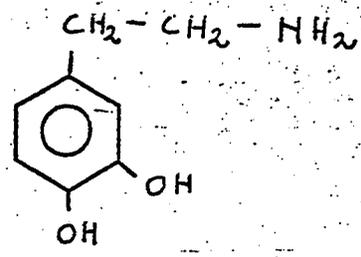


Figure 10 Topographical model for DA receptors:⁶⁵ Kaiser and Jain model (1986)

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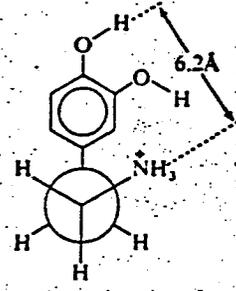
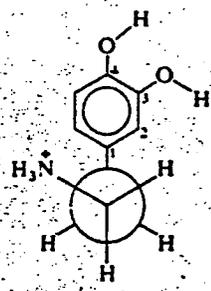
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(i) two

52 (21)

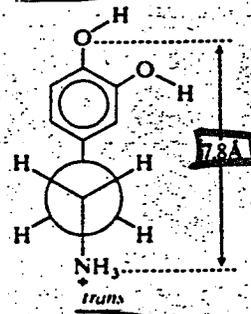


Dopemina

Non ha
centri chirali
(ma ha ≠
configurazioni)

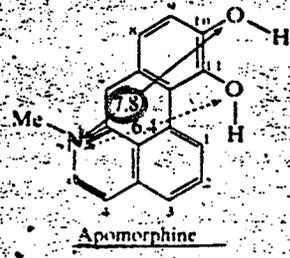


Dopamine conformers

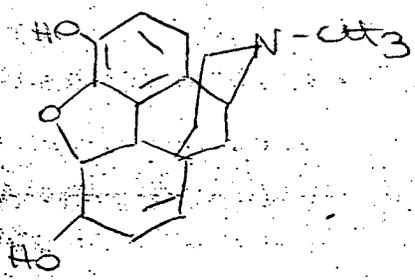


2 gauche +
trans
x 2 = 4
catena con
di C e un solo
legge sostituiti

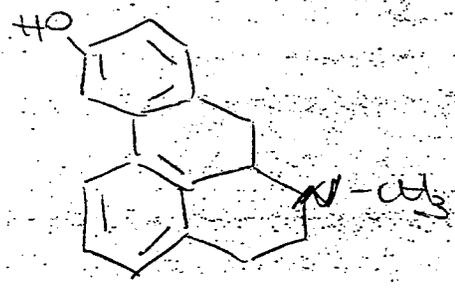
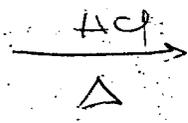
Tutte
posizioni
di
sostituiti



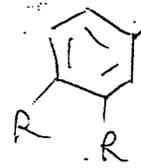
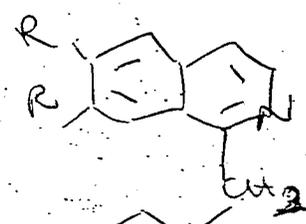
Apomorphine



morfino



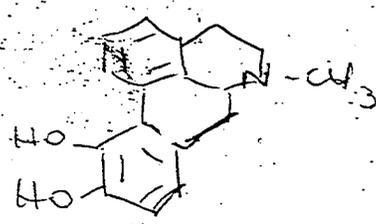
apomorfina
(si rimuove la
funzione maestra della
DO)



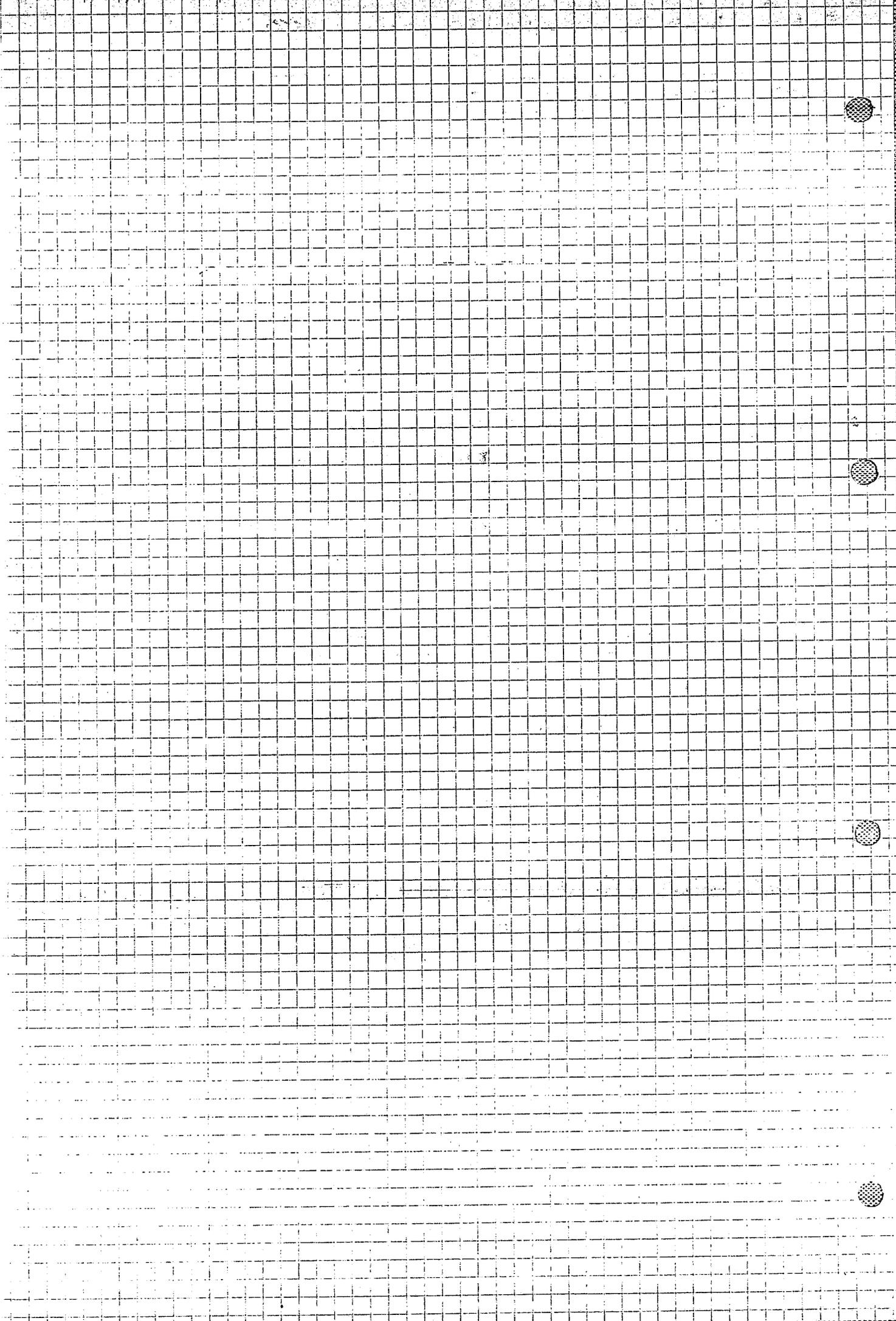
R = OCH₃

papaverina

collegato



246



Neurotrasmettitori e struttura catecolica:

● loc 52

7,8 A₁ ritrova in un f. ossista dei D₂ Recettori: apomorfina

↓ si ottiene dalla morfina x riscaldamento in HCl

Biosintesi e metabolismo di D₂
(andare a vedere)

● E' nei posti dove c'è NA, A₁; neuroni adrenergici, midollo della ghiandola SNC (messaggero)

Classi di recettori:

α proteina → AD → cAMP

D₁ ↑ cAMP (ecitatorio)

D₂ ↓ cAMP

D₃, D₄, D₅

loc 65

● Perifericamente: provoca dilatazione delle arterie renali, ipertensione (costo x shock).

Provoca ... vasodilataz. (gole ... αβ_{1,2})

Tessolo - ceramico, centralmente: regola funzioni motorie e la attività psico-motrice (quando c'è del livello renale si fa psizofrenia; si usano neurolettici)

controllo e avers e inibisce la recet. di prolattina

Funzioni mediate da D₂

244

Attività psicomotorie (D_1 e D_2)
 eucinetica e prolativa (D_2)

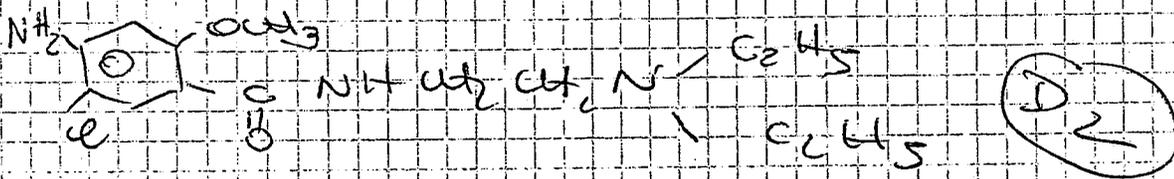
D_2 - agonisti : luc 66

Bromocriptina : funz. eccitatoria e blocco
del recettore extrapiramidale

E_{D_2} : induce eucinetica e blocco
prolattina

Usata nel trattamento del Parkinson o nella
 soppressione della gattazione

antagonisti della D_0
 - antidromici : metoclopramide



- mevedetici luc 64
 fenotiazine

non distinguo D_1 da D_5

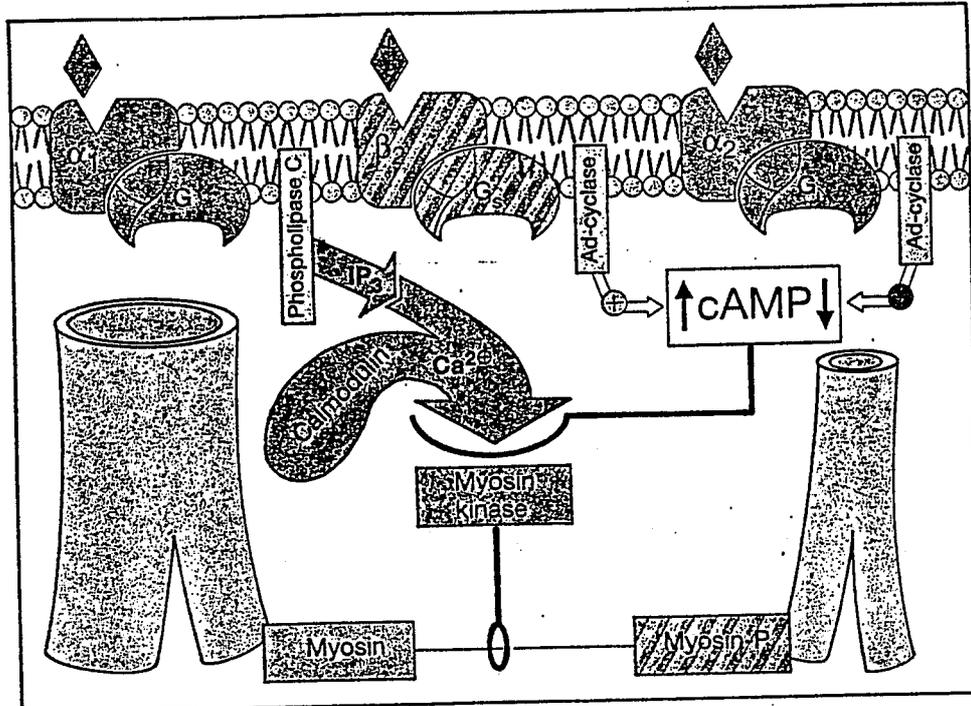
- derivati del tioxantene (D_1 e D_2)
- butirofenoni : D_2 (direttamente
 combatti nessa scalogrenia)
 derivano dal fenilpropilcarotene

luc 63

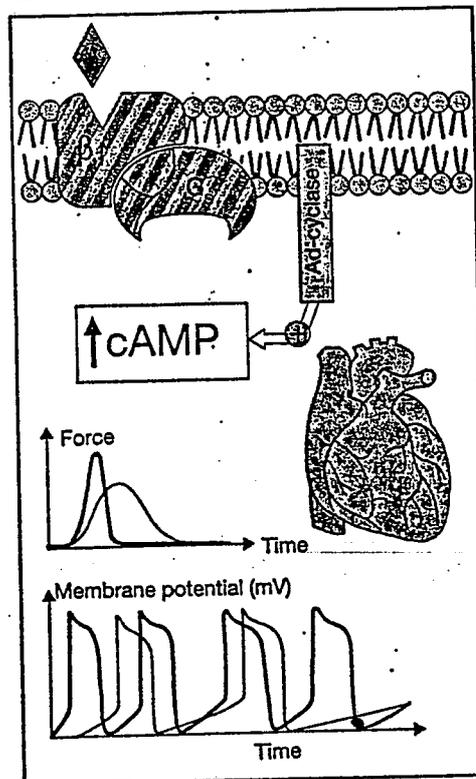
- di fenilbutilpiperidine

83

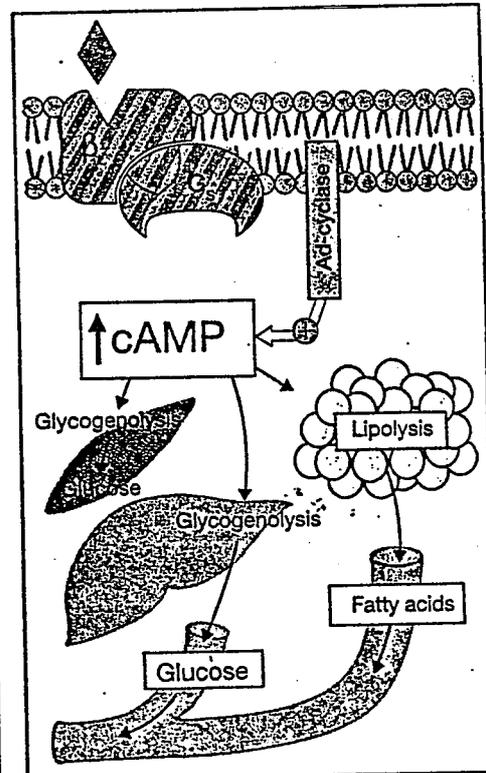
stimu-
MP pro-
ment all
systolic
velocity
tropism),
ronotro-
(positive
ility (po-
cemaker
n is has-
hould for
d sooner
, B). The
mpatho-
re is ex-
rdiac ar-
netics in
cardiac
with a
ood pres-
hycardia
t activat-
eptors.
• β_2 -Re-
nversion
ogenoly-
etal mus-
released
ssue, tri-
fatty ac-
 β_3 -recep-
e blood.
catechol-
herapeu-



A. Vasomotor effects of catecholamines



B. Cardiac effects of catecholamines

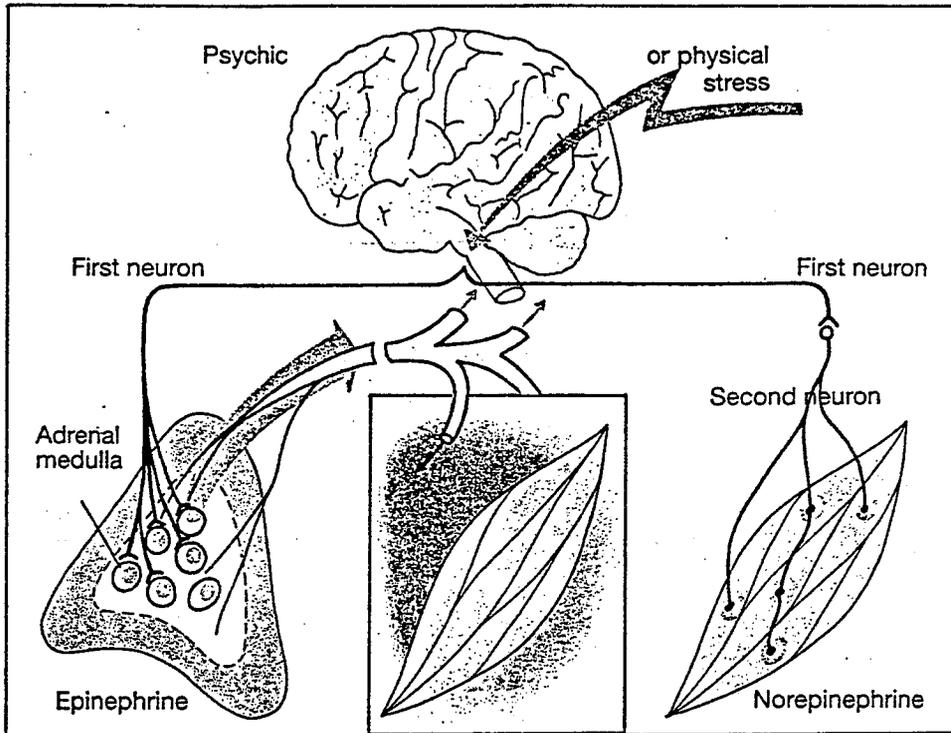


C. Metabolic effects of catecholamines

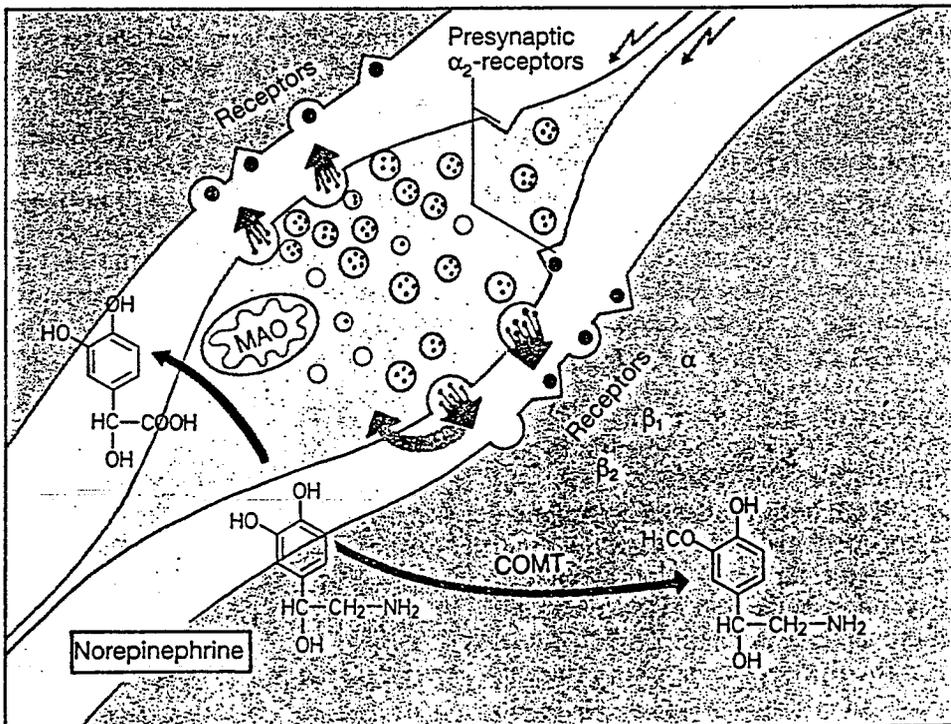
243

82

epineph-
rane-en-
05 to 0.2
plasm, L-
interme-
ich is ta-
here con-
by dop-
n stimu-
pathetic
ts of part
epineph-
ace. Lib-
cts with
junction-
tor cells
embrane
presyn-
norepi-
negative
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norepi-
ause ap-
nsported
into stor-
uptake).
rine are
catechol-
(COMT,
ostjunc-
oxidase
ondria of
l cells).
ved with
ore con-
degrada-
ine and
ct of the
AO and
cid.



A. Epinephrine as hormone, norepinephrine as transmitter



B. Second neuron of sympathetic system, varicosity, norepinephrine release

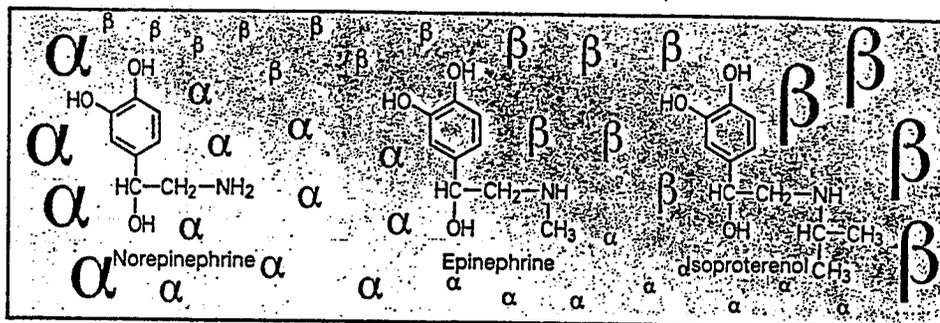
81

catecholamine
usually and can
however, this
is a loss in af-

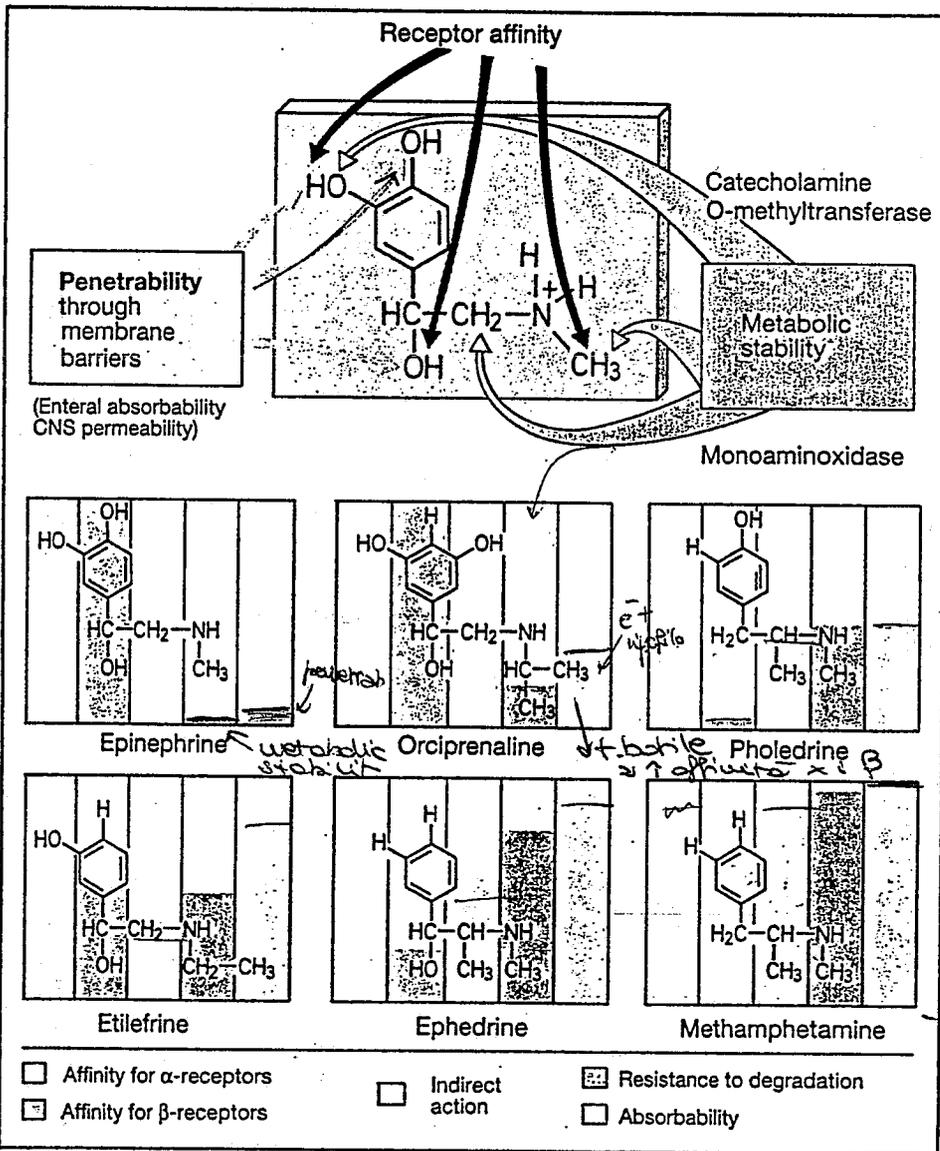
both aromatic
substituted with an
sympathomimetic
the ability of
epinephrine
without ex-
tending the adreno-

of aromatic
metaproterenol
substitution
against in-
(2). Introduc-
tion at the car-
bamino group
methamphetamine
to degradation
replaces the
groups of the
parent substituent
(ne). Accord-
ing to subject to

requirements for
hand, and for
other, do not
sympathomimetic
e. If the high
is to be ex-
amined the inter-
epinephrine,
availability
is desired,
must be ac-



A. Chemical structure of catecholamines and affinity for α - and β -receptors



B. Structur-activity relationship of epinephrine derivatives

affinita
k α e β
bassa
x met
pro
tolo
gli - ott

Notate azioni
indirette
Alta resist.
alla degradazione
(rotazione - att.
prede delle
coste)

262

27

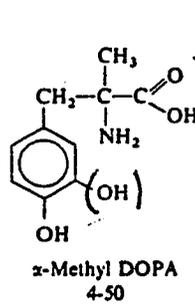
Farmaci che influenzano la trasmissione dell'impulso adrenergico tramite meccanismi non recettoriali

- a) Farmaci che agiscono sulle sintesi delle catecolamine (es. reserpina come autogolici)
- b) Farmaci che agiscono sul metabolismo delle catecolamine (es. MAO e COMT)
inibiscono il metabolismo; effetto simile agli agonisti
- c) Farmaci che agiscono sull'accumulo delle catecolamine (immagazzinamento e rilascio)
- d) Farmaci che agiscono sul riassorbimento di catecolamine

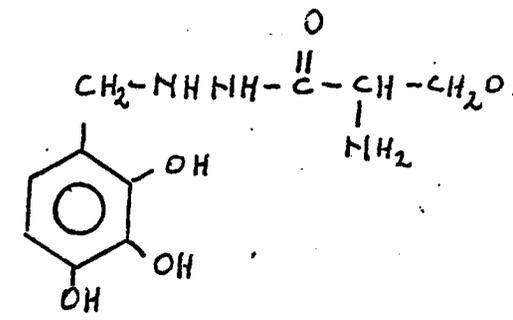
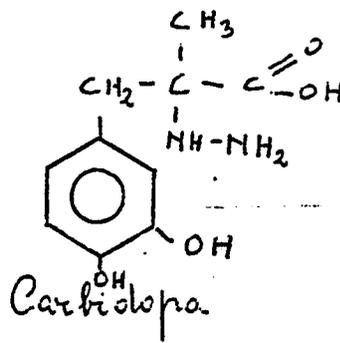
Sintesi di farmaci indolati

28

a) Inibitori della sintesi delle catecolamine

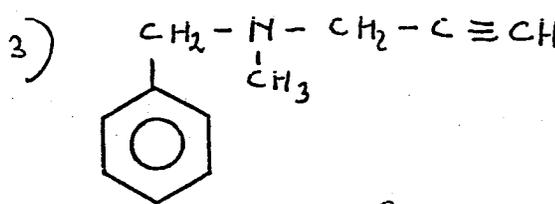
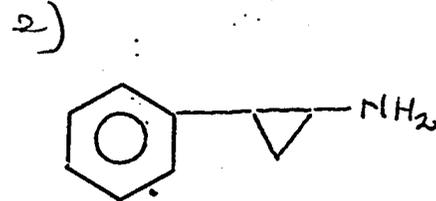
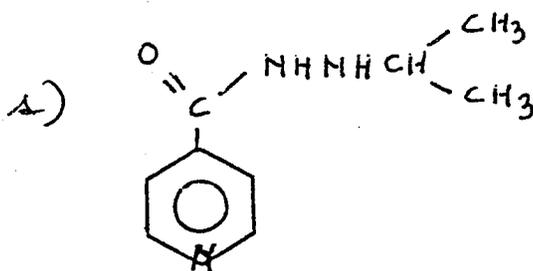


(H) α -metiltirosina



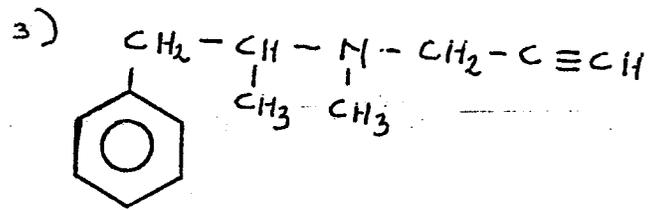
b) Inibitori delle MAO

(Fanno N-decarbossilazione ossidativa)
impiego come antidepressivi

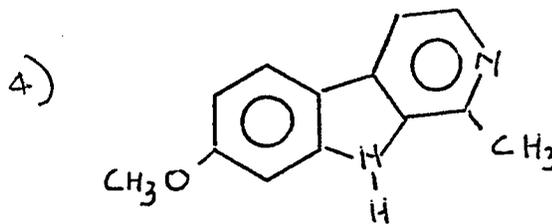


Pargiline

(ricordare solo 1)



Deprenile



Atemine

80

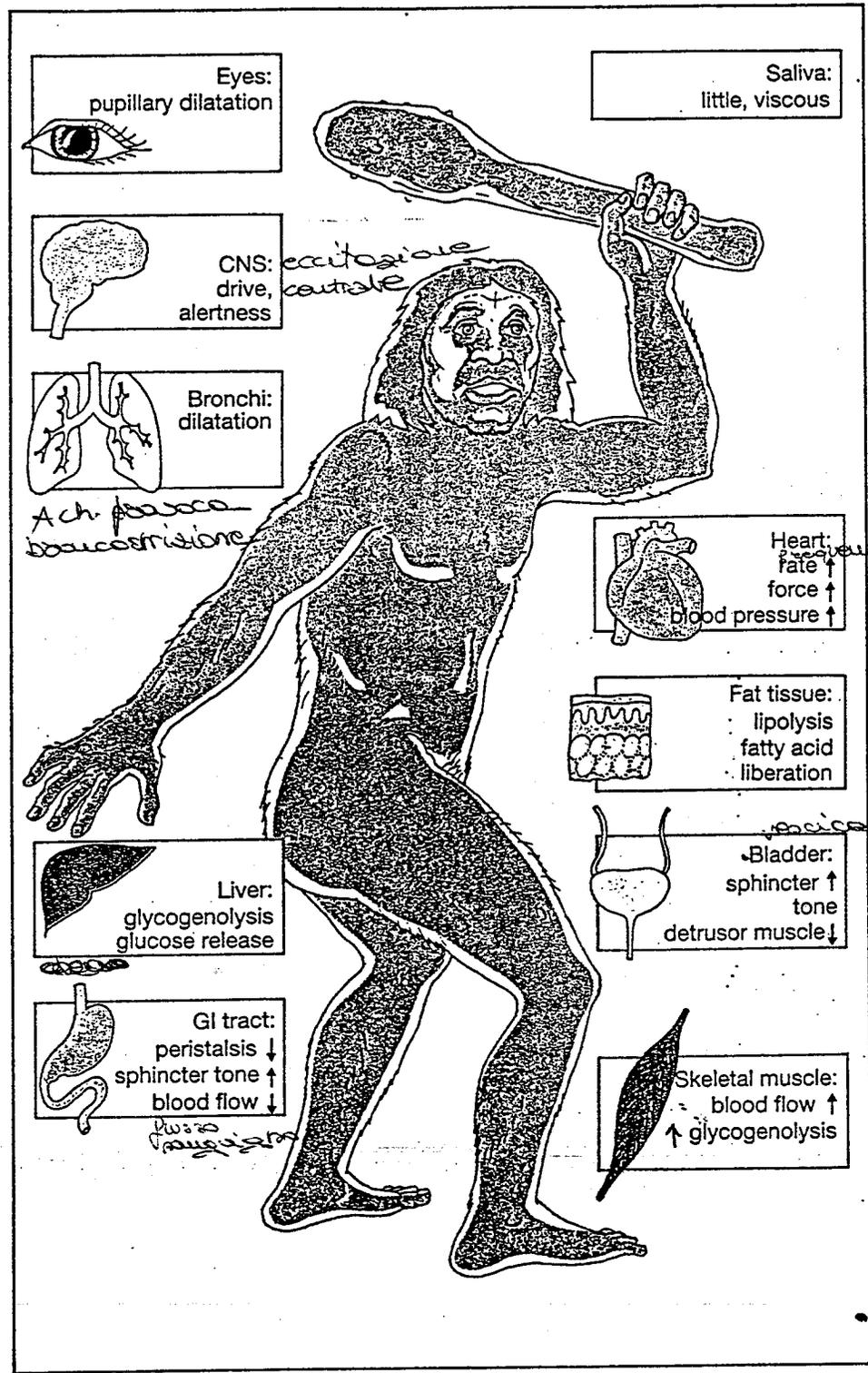
Drugs Acting on the Sympathetic Nervous System

mpathetic
visage the
re sympa-
divisions
hetic acti-
is, activat-
ion can be
which the
te of max-
quired in

a need for
l muscula-
supply of
d flow in
d; cardiac
anced, re-
me being
on. Nar-
d vessels,
vascular

ood in the
e and only
ulsion of
to the ex-
ishes and
wever, in
supply to
ose from
; from ad-
into the
lated, en-
alveolar
ed.

anervated
alms due
e are ex-
urotrans-



A. Responses to sympathetic activation

79

c) Farmaci che inibiscono l'immezzamento ed il rilascio dei neurotransmettitori

1) Farmaci che svuotano le terminazioni nervose di NE

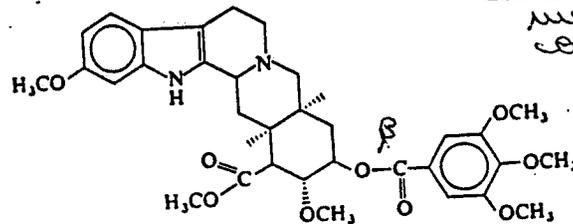
caratteristici:

14, 15, 16, 17, 18, 20

H 3 a B

15, 20 H 2

16 B

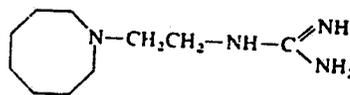


Reserpine

(alcaloide della Rauwolfia) e in apocynaceae

successo ridotto + antidepressivo

2) Farmaci che prevengono il rilascio delle vescicole di accumulo



Guanethidine

[2-(esaidio 1(2H)-azocini-etil)] guanidina

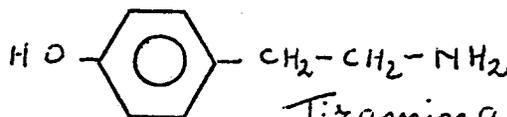


2H-1H-azocina

d) Farmaci che impediscono il reuptake delle catecolamine

1) Falsi neurotransmettitori

antidepressivi

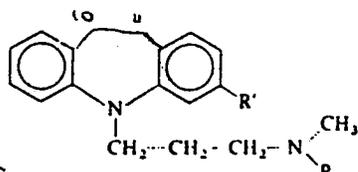


Tiramine e octopamina

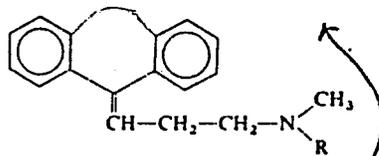
2) Blocco del reuptake

SB dimetiletilamminopropililidene/dibenzos

triamine cicliche

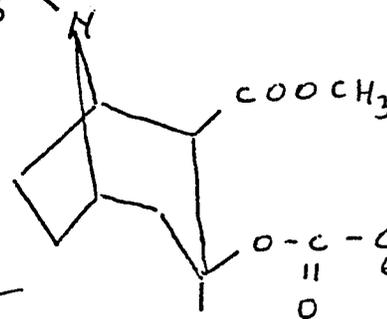


R = CH ₃	R' = H	imipramine	4-54
CH ₃	Cl	chlorimipramine	4-55
H	H	desipramine	4-56



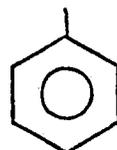
R = CH ₃	amitriptyline	4-57
H	nortriptyline	4-58

H₃C, CO, d]C[4.4]



Cocaine 241

10, 11 diidro N,N dimetil 1H diidro 1b, f) 2-terpila CH₂-CH-NH₂ 15 - pefaramina



Amfetamine

Prof. Gasco "Chem. Farm. I"

(14)

15.02.99

f. 100

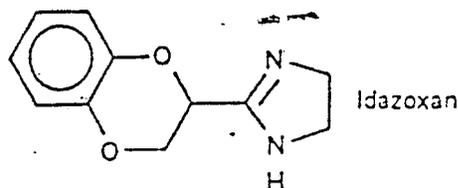
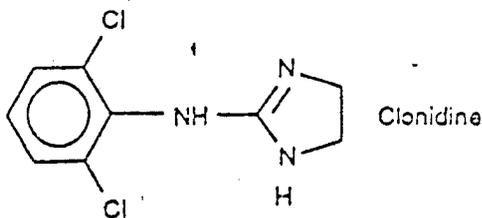
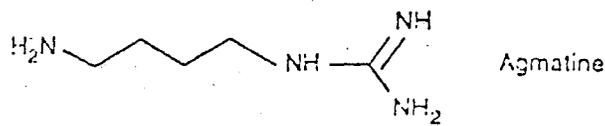


Fig. 3. Structures of agmatine, clonidine, and idazoxan.

11.26 PERIPHERAL ADRENERGIC MECHANISMS

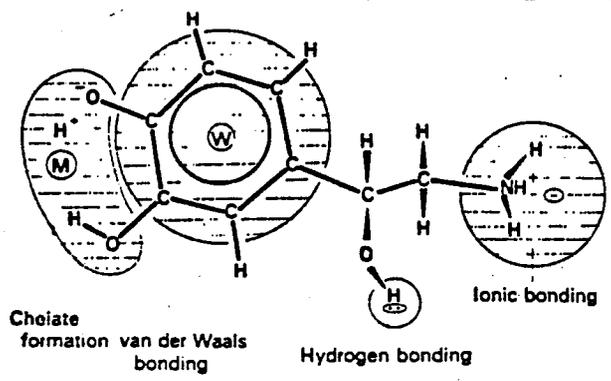


FIG. 11.20. Schematic diagram of the attachment of (-)-D-noradrenaline to an adrenoceptor. The anionic group is denoted by \ominus , the lone pair of electrons by \odot , the metal atom engaging in chelate formation by \textcircled{M} and the van der Waals' binding site by \textcircled{W} .

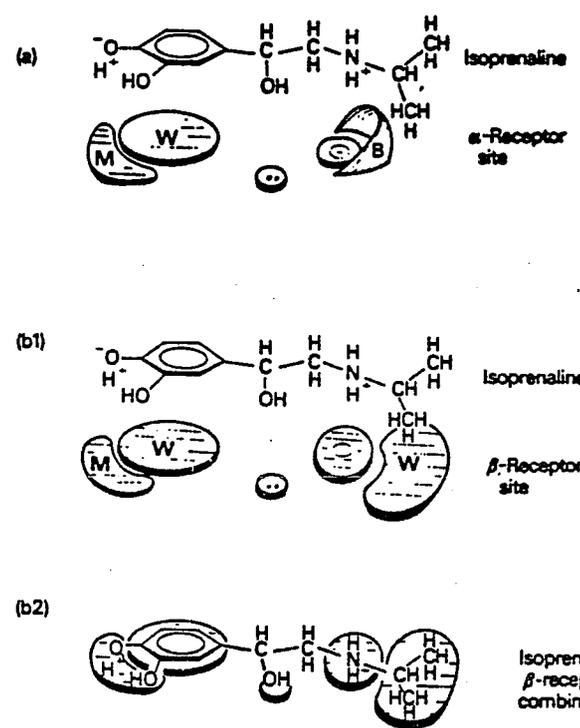
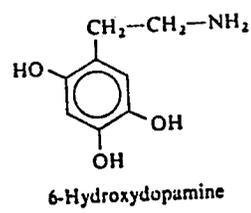
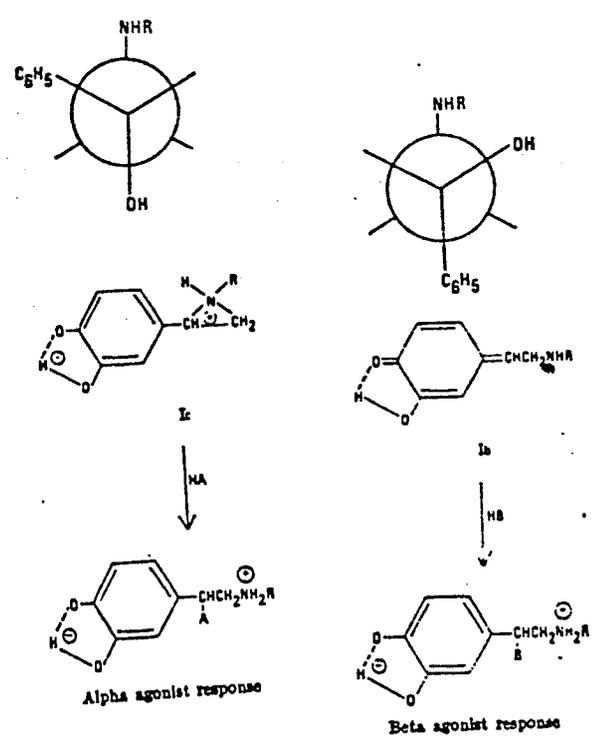
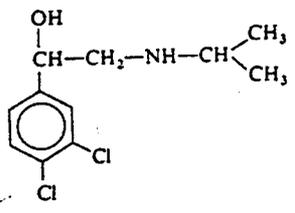


FIG. 11.21. Isoprenaline and adrenoceptors. (a) An isoprenaline molecule is depicted in close proximity to an α -receptor site, with binding sites as shown in Fig. 11.20, but in addition, a barrier, B, which hinders the attachment of the isopropyl-amine group to the anionic binding site is shown. (b1) An isoprenaline molecule is depicted in close proximity to a β -receptor site which has an additional binding site to that shown for the adrenoceptor in Fig. 11.20. (b2) The attachment of isoprenaline to the β -receptor site, including the bond formed by the substituent isopropyl group with a van der Waals' binding site.

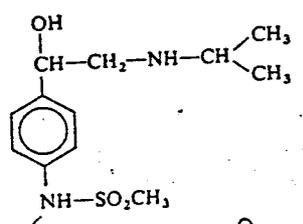


75

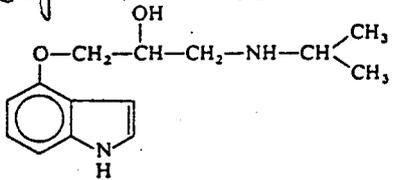
Beta-adrenergic antagonists.



DCI
4-80

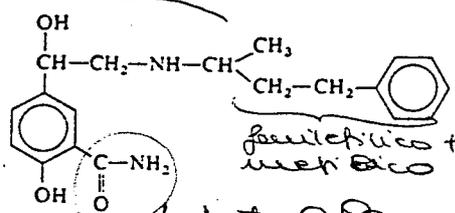


metassulfamidico $\beta_1 \sim \beta_2$



pindolol
4-84

catena di isopropamide

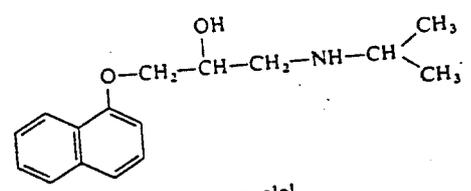


farmaceutico + met. dico

labetalolo
labetalol (also z,)

4-83

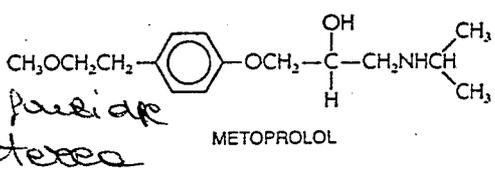
amidico \Rightarrow β antagonista



propranolol
4-86

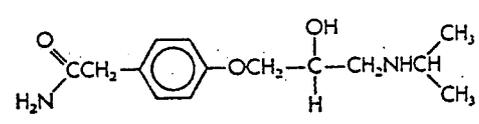
potente β -antagonista
non selettiva

β_1 -selective antagonists



farm. di etere

METOPROLOL



farm. amidico

ATENOLOL

Agonisti ai β recettori

74

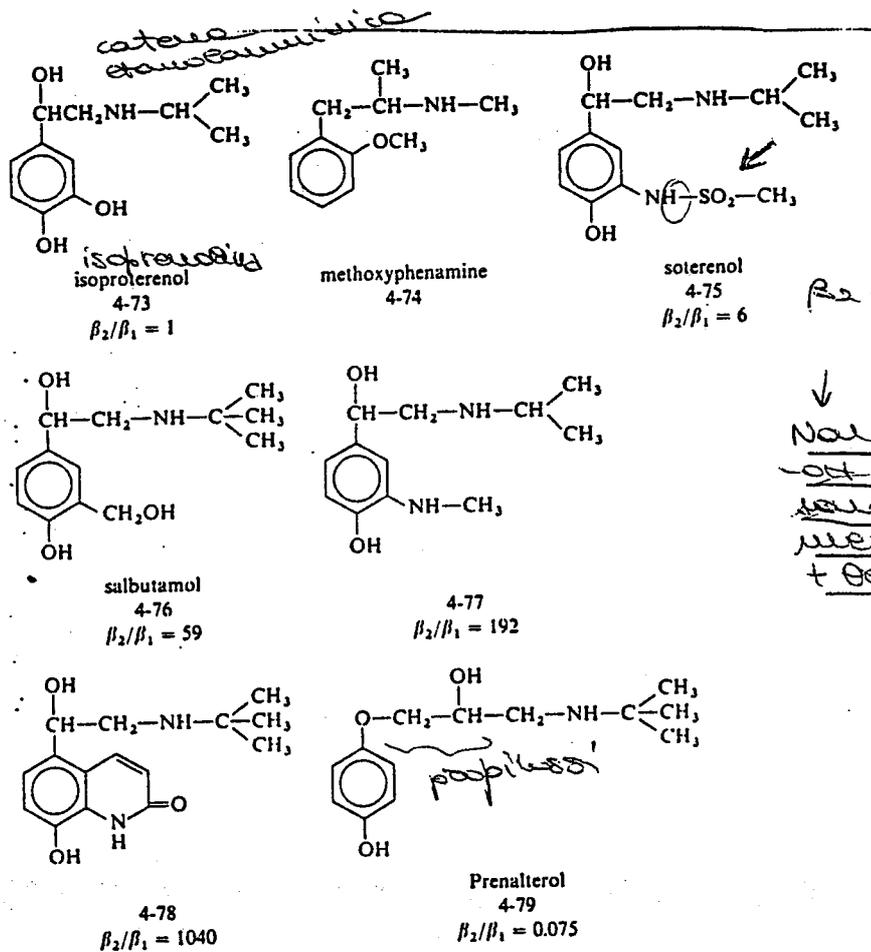
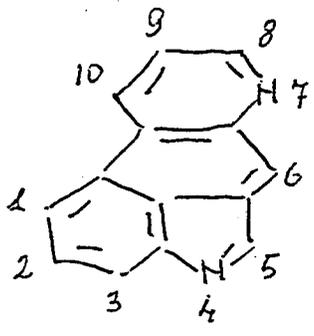


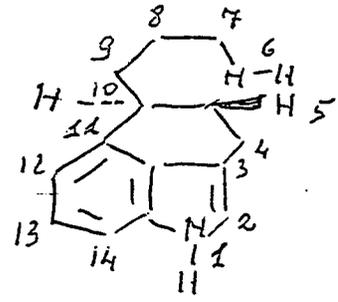
Fig. 4.28. Beta-adrenergic agonists.

238

Alcaloidi della regale, comune



Indolo [4,3-f,9]chinoline



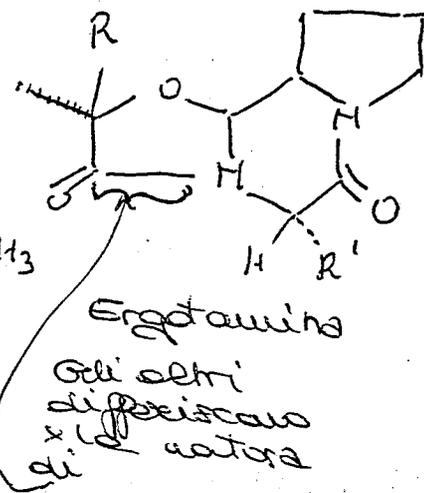
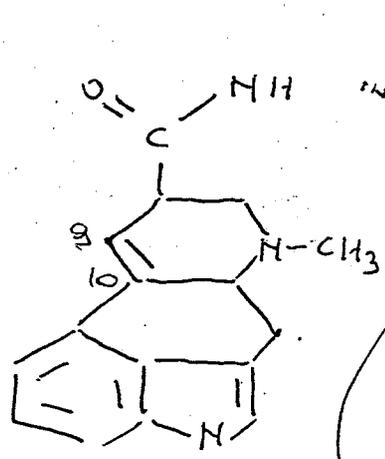
Ha sei O
sono in
TRANS

Ergoline

(6a R-trans)-4,6,6a,7,8,9,10,10a-ottaidolo indolo [4,3-f,9] chinoline

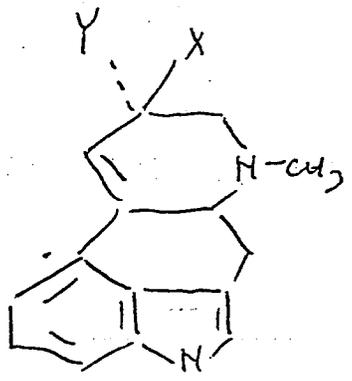
È presente in:

① Alcaloidi ammino acidi: (derivati di forme acido eterico che è ergoline con un metil; un doppio O; + PtO, + NH₃ + acido picrico (o un suo derivato) + un altro acido (o acido picrico))



Ergotamina
Gli altri differiscono x la natura di

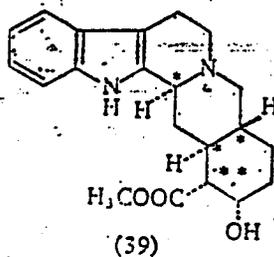
Acido || Liserico
Ergotamina
Ergosina
Ergostina
Famiglie dell'ergotossina



Acido liserico COOH H
Ergosina
Metilergosina
Lisuride

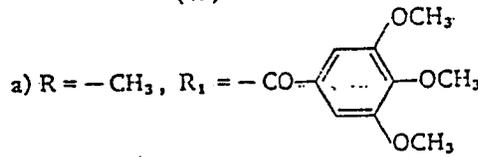
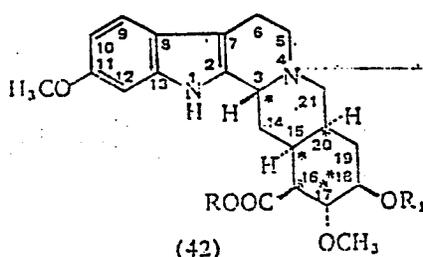
Yohimbina

È il principale alcaloide estratto dalla corteccia di *Corynanthe yohimbe* (rubiacea); ma è presente anche in diverse apocinacee, fra le quali la *Rauwolfia serpentina*. Ad essa compete la struttura e configurazione (39).



Estere metilico dell'acido 17- α -idrossioimban-16 α -carbonilico

Alcaloidi delle Rauwolfie (apocinacee)

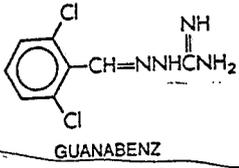
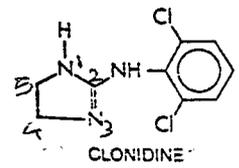


Estere metilico dell'acido 14,17 α -dimetossi-18 β (3,4,5-trimetossibenzoilossi)-3 β -20 α -ioimban-16 β -carbonilico

237

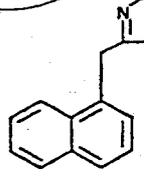
α - Agonisti

o-o' di cloro bore aldeide
candurata e formate un guanidina
etero con
siale centrale

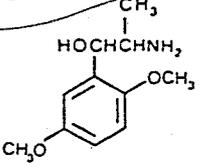


prevalentemente α_2

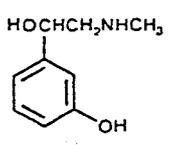
a livello centrale
antipertensivo
2^a per un altro: inibisce il
rilascio di NA



$\alpha_1 \approx \alpha_2$



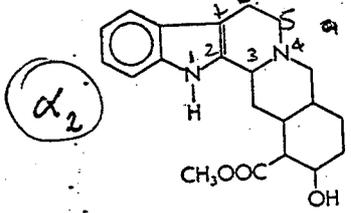
α_1



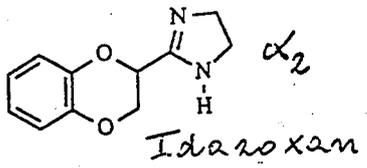
prevalentemente

α - Antagonisti

Indoles

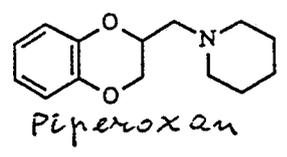


α_2



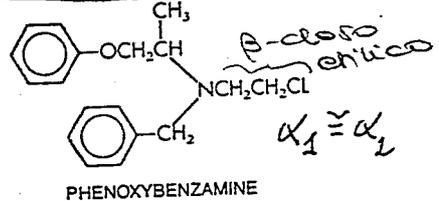
α_2

Benzodiazepinici



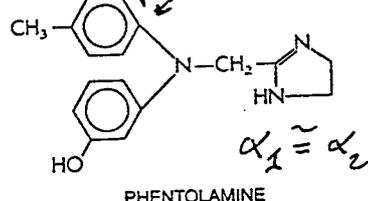
$\alpha_1 = \alpha_2$

Alkylating agent



$\alpha_1 \approx \alpha_2$

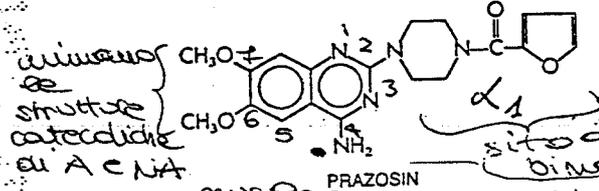
Imidazolines



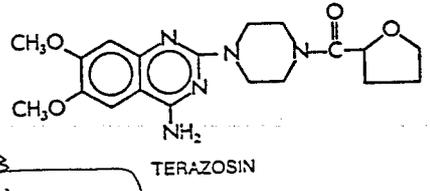
$\alpha_1 \approx \alpha_2$

Bloccanti selettivi degli α_1

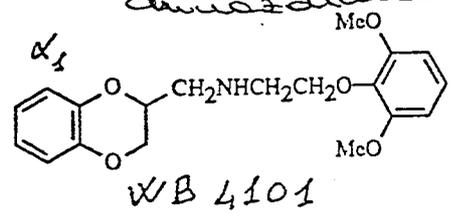
Piperaziny quinazolines



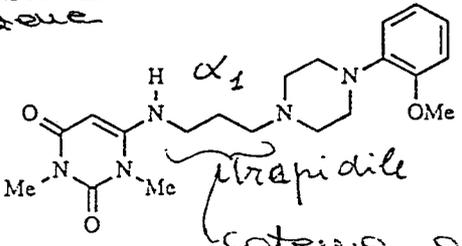
sito di binding



prodotto
ideggiato
sol forato



α_1



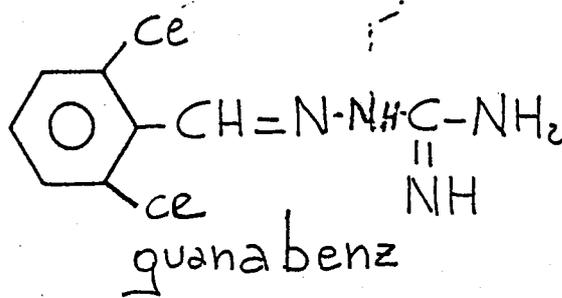
prapridile

catena associata

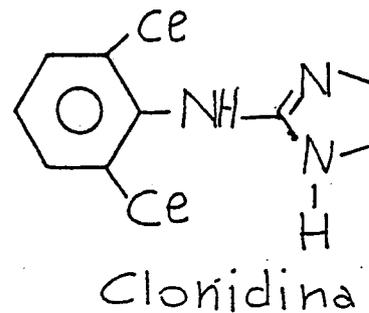
Agonisti ed antagonisti

α Agonisti

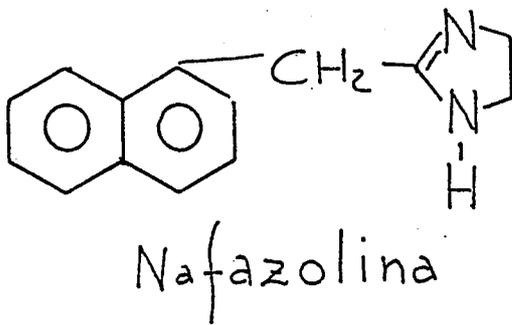
Prevalentemente α₂



>



α₁ ≅ α₂



Prevalentemente α₁

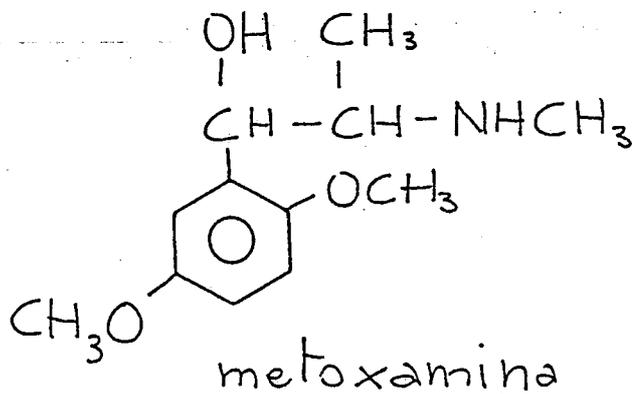
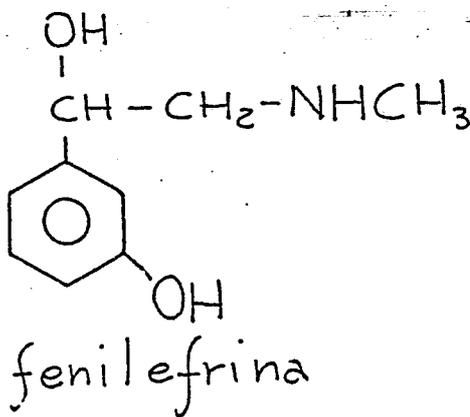
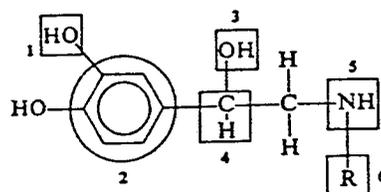
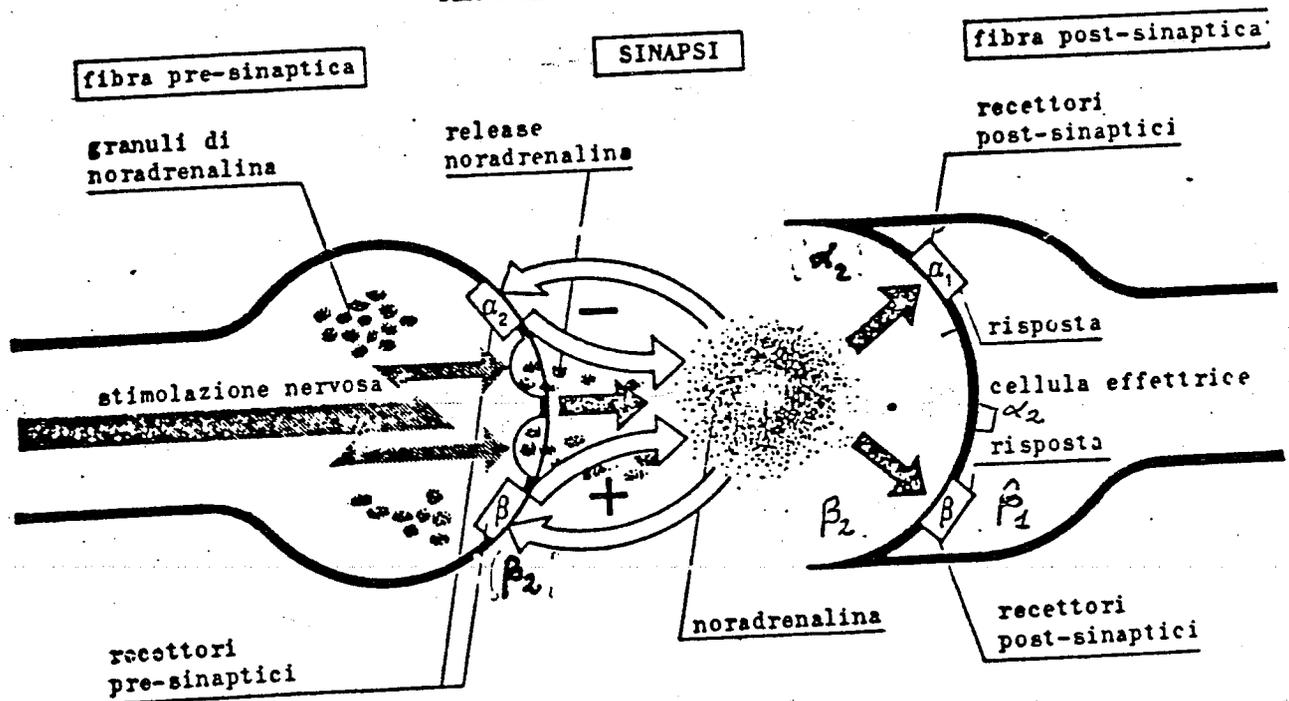


Table 4.4. Adrenergic Receptor Differentiation

Effector organ	Receptor response		
	α	β_1	β_2
Vascular system	Constriction	—	Dilation
Uterus	Constriction	Dilation	Dilation
Intestine	Decreased motility	Decreased motility	Decreased motility
Heartbeat	—	Increase	—
Bronchial muscle	Constriction	—	Relaxation (prevalente)
Relative Agonist Sensitivity			
NE	100	25	1-2
Isoproterenol	5	100	100
Biochemical effect			
cAMP production	—	+	+
Lipolysis	—	Increase	—
Glycogenolysis	—	—	Increase

adrenaline

TERMINAZIONE NERVOSA ADRENERGICA



Metabolismo

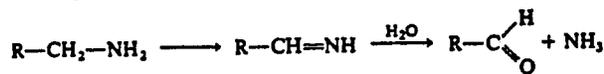
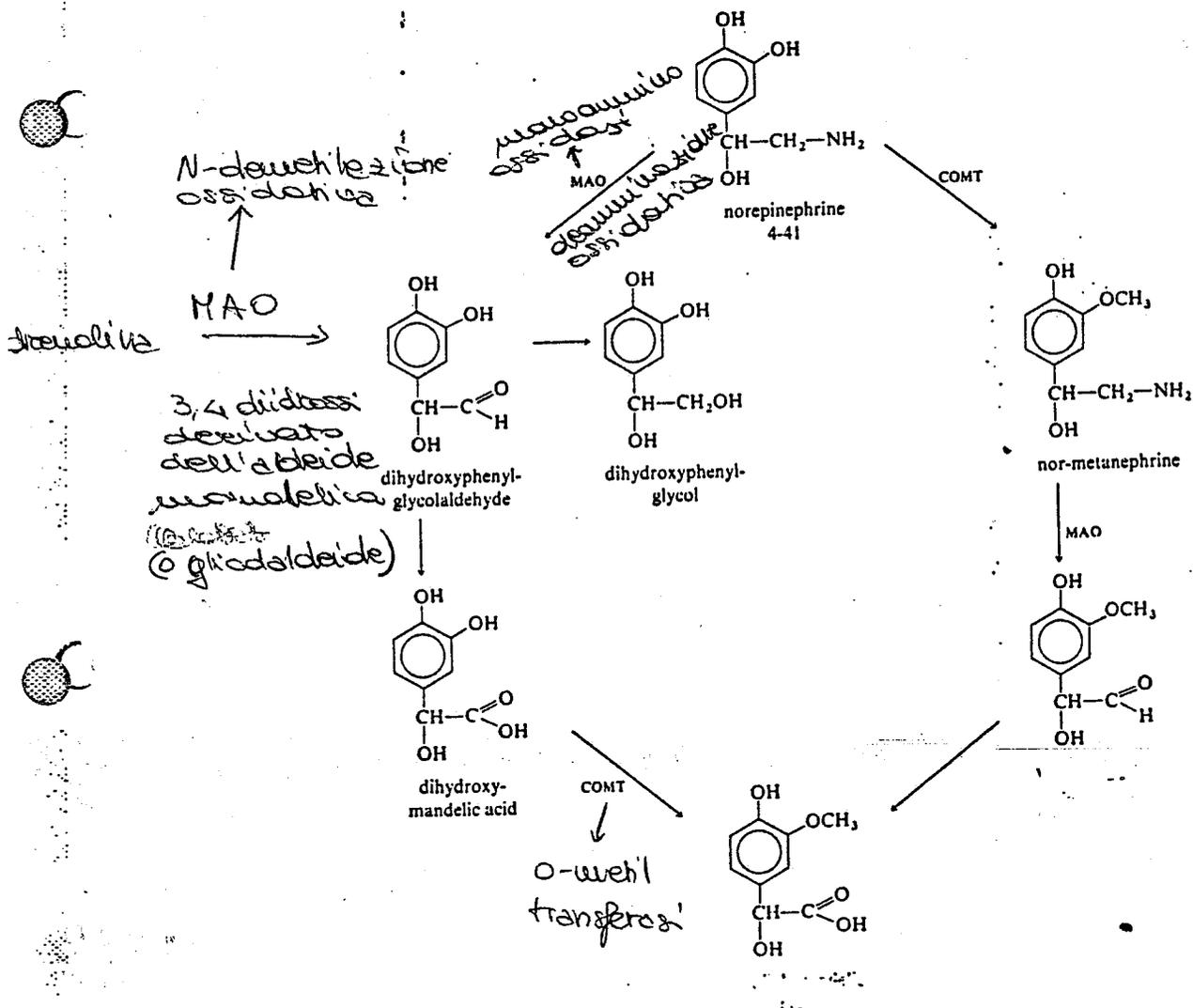
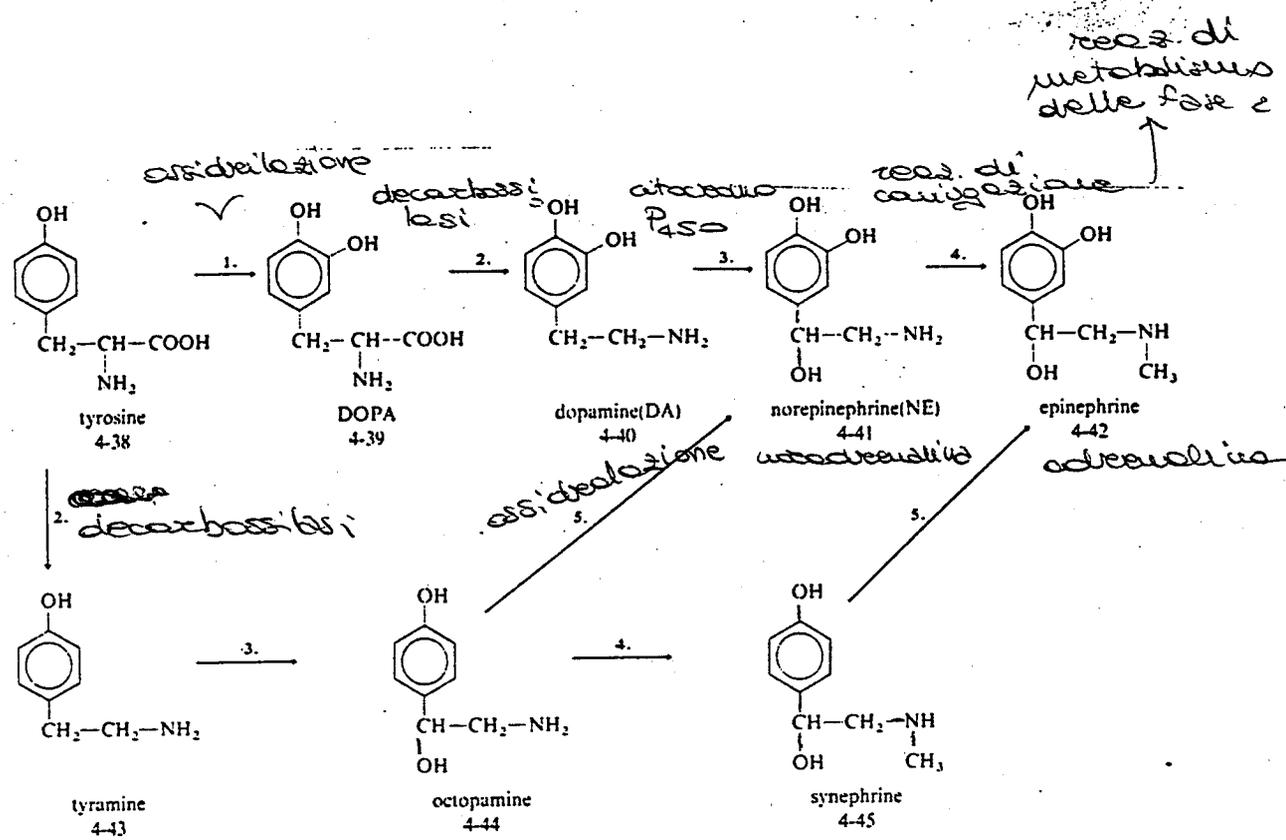


Fig. 4.22. Degradative metabolism of norepinephrine.



Ci sono 2 schemi ≠ che portano allo stesso risultato

Biosintesi delle catecolamine



- Enzymes involved:**
1. Tyrosine hydroxylase
 2. aromatic amino acid decarboxylase
 3. dopamine-β-oxidase
 4. phenylethanolamine-N-methyl transferase
 5. catechol forming enzyme

Fig. 4.20. Biosynthesis of catecholamines.

DOPA = didrossi fenilalanina

Prof. GASCO H 02-PP
 "Chimica Tossic. II" 200 (12)

NERVOUS CONTROL OF BLOOD PRESSURE 23.15

cardiovascular homeostasis. The level towards which the baroreceptor reflexes tend to return the blood pressure is termed the *set-point*.

The cardiovascular changes elicited by baroreceptor reflexes are mostly mediated through cardiac sympathetic and para-sympathetic nerves (accelerans and vagus), the splanchnic nerve to the adrenal medulla and sympathetic vasomotor nerves to the splanchnic region. There are usually only minor contributions from vasomotor nerve activity to the skin, kidney or muscle. However, if there is a marked and persistent fall in blood pressure, vasoconstriction in these tissues contributes significantly to the rise in peripheral resistance. The control circuit of baroreceptor reflexes is shown diagrammatically in Fig. 23.13.

Carotid sinus baroreceptors

The carotid sinus is an enlarged portion of the internal carotid artery at its origin from the common carotid artery. The sensory nerve running from these receptors is called the nerve of Hering or simply the carotid sinus nerve. It enters the skull with the glossopharyngeal (IXth cranial) nerve and runs to the medulla oblongata.

Occlusion of the common carotid arteries results in a fall of pressure in the sinus and elicits a rise in blood pressure; this is known as the carotid sinus pressor reflex. Conversely, application of pressure to the carotid sinus elicits a reflex fall in blood pressure. The mechanism by which pressures in the carotid sinus reflexly alter the blood pressure was elucidated by the Belgian physiologist, Heymans. He supplied the carotid sinus of one dog, the recipient, with blood from another dog, the donor. When the nervous connections between the carotid sinus and brain of the recipient were left intact, and the blood pressure of the donor dog was increased, that of the recipient decreased; conversely, when the donor's blood pressure was decreased, that of the recipient increased.

A rise in pressure in the carotid sinus increases the rate at which impulses are discharged along the carotid sinus nerve, and this results in a reciprocal decrease in output from vasoconstrictor nerves and an increase in cardiac vagal activity. Conversely, a fall in the carotid sinus pressure leads to increased activity in vasomotor and cardiac sympathetic nerves and to inhibition of vagal tone.

The change in the rate of discharge of impulses in the carotid sinus nerve per unit change in pressure is greatest in the pressure

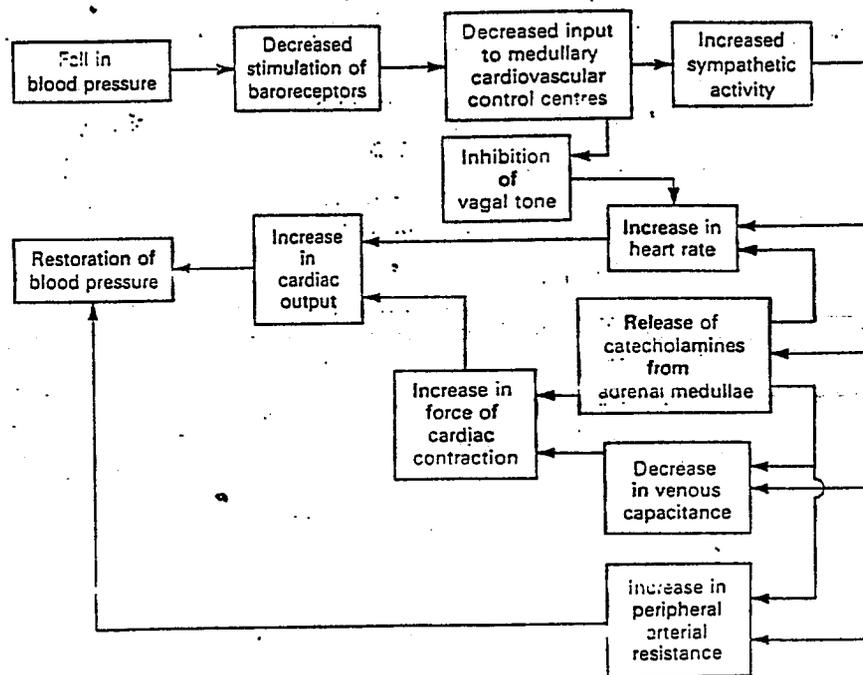


FIG. 23.13. The baroreceptor reflex loops for homeostatic control of blood pressure, showing the peripheral receptors responding to a fall in blood pressure. Opposite effects are elicited by a rise in blood pressure.

234

1
20
67

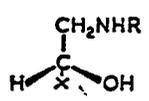


FIG. IX.5. Absolute configuration of noradrenaline and adrenaline.

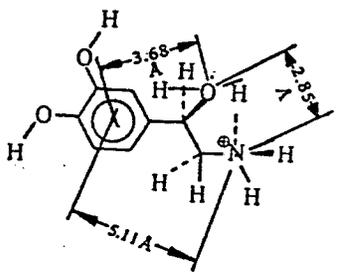
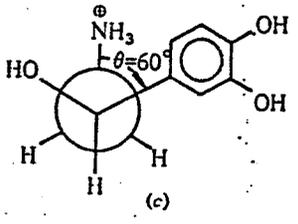
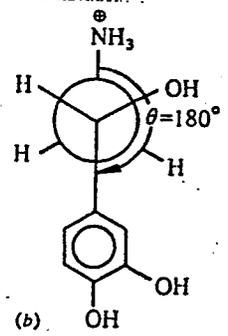
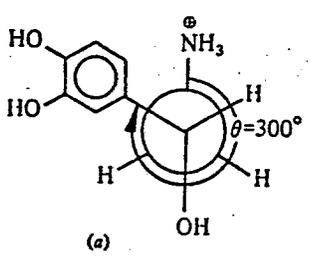


(nor epinefrine)
(epinefrine)

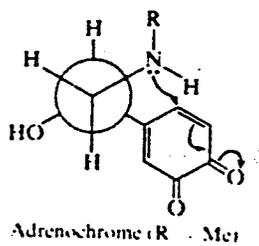
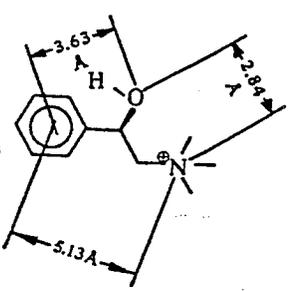
R = CH(CH₃)₂; R-isoprenaline (-)
(isoproterenolo)

NON
teammale
c'è gruppo
isopropilico

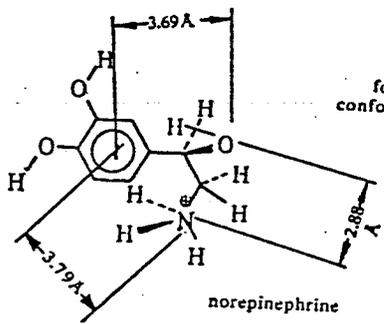
⊖ + p-pibato + che + stabile
↑
Trans +
equiche



extended conformations



H₂O₂, Fe(NO₃)₃
reagente di Fenton
Adr > Isop > Nor
Ciclizzazione



folded conformations

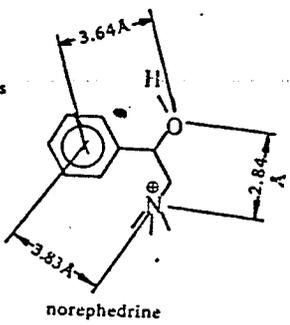


Figure 14.2 Interatomic distances in two sympathomimetic amines (norepinephrine and norephedrine) in their extended and folded forms. [As calculated by Pullman et al., Mol. Pharmacol., 7, 397 (1971).]

3) decolorati a struttura proprieta' amminica

4) vescicole degli ammassi
pietolo [3,4, b] indole sostituito con
-CH₃ e -OCH₃

le MAO distinguono NA e A

Luc 79

Rosapina parente della yimbina (presente in
Rubiaceae)

Le piante che in queste vescicole di accumulo
c'è equilibrio di NA e di A che entra ed
esce. NA viene metabolizzata da MAO (perato,
reversibile, ~~cooper~~ dove c'è R di NA
autocatalitico -), COMT (nessa atofrasumatica
dove c'è R)

Essa impedisce ~~allo~~ NA di rientrare nelle
vescicole

1) blocca del recettore;

ne impediscono il ricambiamento,
effetto opposto a C) 1-2.

→ potenzia la trasmissione adrenergica

cocaina - eccitante centrale

inibisce il recettore di NA

amfetamina

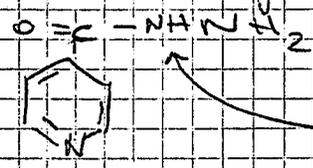
→ bisogna fare arrivare dop. al cervello e ricopilibrare il rapporto, xò questa non sovera la barriera ematoencefalica. Allora mi dà il dopa che lo produce, xò questo prima di arrivare (dopa → dopamina) fa decarbossilazione periferica ed immagazzina in dopamina. Allora lo abbiamo ed inibitori di dopa-decarbossilasi

→ può operare la barriera e-e (come con un altro inibitore) e di arrivare dopamina

b) Inibitori di distro di NA e A che fanno effetti esaltanti centrali
 → inibitori della MAO (anti-depressivi)

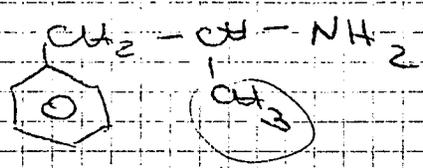
4 categorie

1) derivati della iprazamide correlata
 con isoniazide (p. nel trattamento della TBC)



se si sostituisce un acetile qui → scarsa attività ed effetto cronante
 se si introduce un acetile CC(=O)N1=CC=CC=C1 ⇒ effetto collaterale = anti-depressivo

2) residui con trauipicopropano
 = blocca il metabolismo di NA e A
 → correlato con amfetamina
 (adrenergico indotto)



questo è il residuo di trauipicopropano

me → Effetti autotropi e inotropi (riflessi del baro-
cettori) ⊕

↓
tendenza a riportare l'alta usabilità, non
hanno effetto su di autogonizzati ma su

β_1 (effetto inotropo ⊕)

↓
deveo devo contemporaneamente o vice
su β -bloccante.

Questo molecola è fatto che blocca di
 β → è una molecola IBRIDA

S, S
 R, S } non servono

S, R → α_1 bloccante

R, R → β_1 -bloccante

Come x Ach esistono composti che interferiscono
indirettamente con la media-
di Ach, anche qui esistono:
meccanismi con cui del f. impediscono
la mediazione adrenergica
Lc #7

b) Non distrugge il messaggero

Lc #8

Composti che bloccano la mitica del DOPA
avendo una struttura molto simile a quella
del DOPA stesso (x-metil dopa, ...)

→ bloccano l'enzima che decarbossila il
dopa e lo trasforma in dopamina che
viene poi ossidata → noradrenalina
→ metilata → adrenalina

Inibitori degli aa-decarbossilasi

Usati nel trattamento del morbo di
Parkinson (alterato geneticamente il
rapporto di Dopamina / Ach Ach cresce,
Dop. diminuisce).

A livello del β_2 il potenziale effetto
inotropo e cronotropo (+) e inibitorio per β_2
 di vasodilatazione e bradicardia
 Prevalente il cuore o l'altre delle arterie
 e secondo deve selettività ai β_1 o ai
 β_2

ICI: autog. parziale

una cosa che induce autogonismo al
 β_2 receptor è introdurre nuova catena
laterale e struttura di peptidasi
 (peptidasi / indole)
 ↓
sottosistema
indole

Autipotesi: alta selettività x i β_1
 oppure dovrebbe presentare un trofismo
 x il cuore (dove ci sono solo β_1) anche
 può essere selettivo ai β_1 e β_2

Effetti add. per β_1

po' di struttura base: benzene + catena
peptidica

+ potenziali segg. in fase con
fase acida o fase eterea

debetas: elevata affinità x i β_1

Ra 2 centri chirali

- stereoisomeri: R, R
- S, S
- R, S
- S, R

Block i β non possiede il non invece di
ott. È anche di autogonista

231

Autogonista gli β_2 produce vasodilazione

- WB 4101 : derivato del benzodiazepino
 occupare affinità $\times \alpha_2$

- Ureaprodile : derivato degli urea

15/02/2023

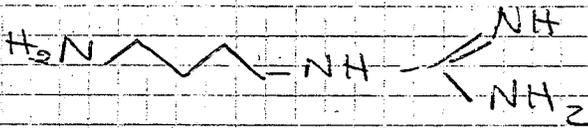
Sottostuttura α_2 radiativa

Struttura di quantina, radiativa
questo che non può recettori α_1 o α_2
è un buon base \times tutte e 2
 Ramo altri R

Aguanine : α_2
 prodotto ^{de} carbossilato delle
 arginina

Causa il rilascio di catecolamine
nelle cosp. periferici

(Trova nel cervello di be)



Idazoxan

Interagisce anche con recettori propri
 collegati al rilascio di catecolamine

Doc #3

Acetabidi della peptida corrente
 presentano un parziale agonismo e
 un parziale antagonismo agli α_1 e α_2
 ma selettivo

Sottostuttura : inibito [4,3, f g] di indina

è il dist. stereoisomero particolarmente idrofilo
 (arginine)

230

Alcoloidi amilici

xi derivati di glicerolo acido erogaico + amilici

Proprietà farmacologiche:
stabilizzano il calcio del vas;

attività ositotica; inibiscono contrazioni dell'utero

Reggono anche R di alpraxina e perstaxina

Struttura che si legano ai β recettori:

Luc 74

Isoproterenolo è presente nei raggi infrarossi
impedisce l'attività x il β_1

Agonisti al β_2 = inotropi positivi
(cronotropi)

Agonisti recettori al β_2 = broncodilatatori o tocolitici
(rilassano il muscolo utero, usati x intorcano per il parto)

Isoproterenolo: viene metabolizzato molto velocemente
(grazie a CMT = metilazione dell'OH in 3; o N-decarbossilazione ossidativa)

Se OH in 3 si sostituisce con metil, con H acido

Appiuntà x il β_1

sostituisce la catena stamobanilica con una catena propilica + catena stamobanilica (permettendo)

Luc 75

Autopossibile

autiperlesioni, autovetturici, autolitici

Sono presenti 4 centri chiralici
in 3, 16, 15, 20, 17

Idoxaxam: R₂ sul nucleo del benzodiazepina
(si ritrova in altri prodotti)
e secando di cuore è positivamente
si può modulare l'attività
ha effetti selettivi
ma (\rightarrow piperoxam) o selettivo α_2
(WB 4101)
c'è 2-imidazidina

Se portasse un piperidino-metile: $\alpha_1 \approx \alpha_2$
(piperoxam)

Furoxibenzammina: a N c'è funz. alchilante
bloccante reversibile di
 α_1 e α_2
Integratore con Na⁺ presente
può R \rightarrow leg. covalente:
blocca irreversibilmente

Fentolamina

Pirazosina: antagonista di α_1
(xipertensivum)
in 2. R₂ pirazosina idrogenata
piperazina a cui è legato il
gruppo dell'ac. 2-formilcarbossilico

Occupa siti addizionali di binding

NT₂ in 4 = sito di posturo, e pot. psicologico
Cavica + delocalizzata \rightarrow
muove la cavica @ della
catenella laterale di A e NA



usati x i poteri e decougestivanti
nasale

Fenilefrina = α a cui è stato eliminato
ott in favore

metossammina parte il gruppo lipidico su C
e 2-OH₂

α₂ = α₂

Alfa 2 olina: derivato dell'2- isopropilammina
in α c'è il gruppo metilico
(decongestionante nasale)

α- autogonisti:

α₂:

Yohimbina: alcaloide (da esoporo)
della corteccia di ma

rubiacae

estere metilico dell'acido idrossimbinico
16α-carbossilico

↓
caratterizzato da
sist. imidico + sist.
quindizionale
parzialmente idrogenato

17α: -ott è α orientato
rispetto all'anello
(verso il basso)

16α: carbossilico è
verso il basso

229

Barorecettori: R reversibili a ΔP del'oss. \rightarrow
 comunicano un messaggio centrale \rightarrow attiva
 sist. adrenergico pe. c'è caduta del P
 (adrenostimolazione)

Il sist. adrenergico è controllato attraverso una
 fibra parasimpatica.)

Classi di f. legati al controllo del sist. adrenergico:
 α -agonisti (x il trattamento dell'ipotesione)
 (decaressivi muscoli e
 congiuntivali)

α -antagonisti (x ipertensione)

β_1 -agonisti (brucodilatatori \rightarrow antagonisti di Ach)
 (tocolitici)

β_1 -antagonisti (effetti cronotropi e inotropi \oplus)

β -bloccanti (antiaritmici; x ipertensione;
 x aterosclerosi)

Strutture capaci di bloccare o attivare
 selettivamente gli α e β R.

loc. #2

Clonidine: c'è fibra efferente ^{centrale} che va in
 periferia: \downarrow NA \rightarrow disattiva fibra efferente
 \rightarrow vasodilatazione (Azione antipertensiva
 e centrale)

Derivato della α -imidazolina

de R₂ in 2 mu 2000. α -D-dicloroamilina
 Sottostuttura guanidinica: a pht
 #4 è protostato (base forte).

Componente non protostato è molto
 bifilica: passa R₂ barriera ematoencef.
 facile e controlla questa fibra
 efferente