ANNUAL REVIEWS Further
Quick links to online content

Ann. Rev. Pharmacol. Toxicol. 1983. 23:103–30
Copyright © 1983 by Annual Reviews Inc. All rights reserved

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org
by Central College on 12/12/11. For personal use only.

STRUCTURE-ACTIVITY RELATIONSHIPS OF DOPAMINE AGONISTS

Joseph G. Cannon

Division of Medicinal Chemistry and Natural Products, College of Pharmacy, University of Iowa, Iowa City, Iowa 52242

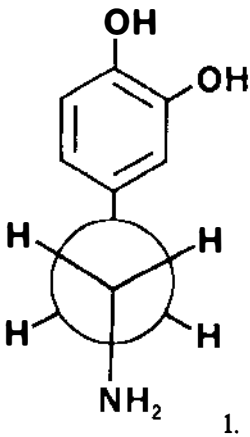
INTRODUCTION

In the several years since Blaschko (1) suggested neurohormonal activity for dopamine, several types of chemical compounds have been found to possess dopamine-like actions. This review surveys classes of structures in which putative dopamine agonism has been reported, and cites structure-activity correlations. Detailed stereochemical aspects of dopamine agonists have been addressed elsewhere (2).

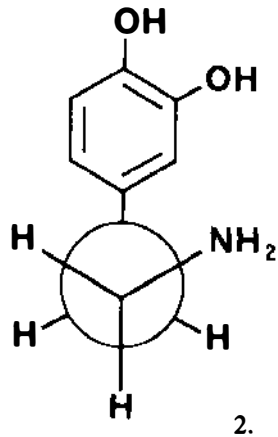
A serious problem in dopamine structure-activity studies arises from the large variety of animal models and in vivo and in vitro pharmacological assays utilized to assess dopaminergic effects. Comparable test data in the same animal species using the same biological endpoint and the same criteria for assessment of activity/potency are not available for many agents. Thus, it is frequently not possible to make valid comparisons of actions and potencies among compounds described in the literature, and a caveat must be expressed with respect to the validity of many attempted structure-activity correlations.

β-PHENETHYLAMINES

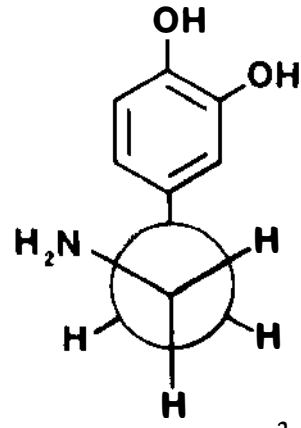
Quantum mechanical calculations led to the conclusion (3, 4) that there are three favored conformations for the dopamine molecule: *trans-* (*antiperiplanar*), illustrated by the Newman projection 1, with the plane of the ring perpendicular to the plane of the side chain; and two folded (*gauche*) forms, Newman projections 2 and 3.



1.



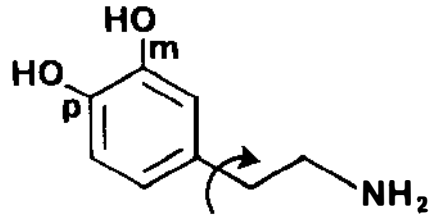
2.



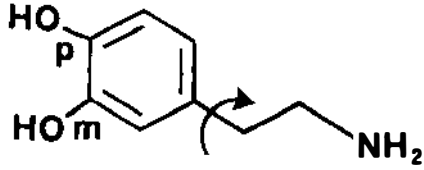
3.

Rotman et al (5) proposed that a *gauche* form of dopamine is permitted, if not preferred, in the reuptake process in nervous tissue. However, Granot (6) concluded that when dopamine interacts with ATP (a component of some dopamine receptors) in aqueous solution, there is a significant preference for a *trans*- conformation of the dopamine molecule. The dopamine-ATP complex is stabilized, *inter alia,* by hydrogen bonding between catechol hydroxyls and purine nitrogens, and by electrostatic interaction between the protonated ammonium group of dopamine and a negative phosphate group.

Cannon (7, 8) defined α- and β-conformers of dopamine (structures 4 and 5), in which the catechol ring is coplanar with the plane of the ethylamine side chain, and proposed that these are significant in agonist-receptor interactions.

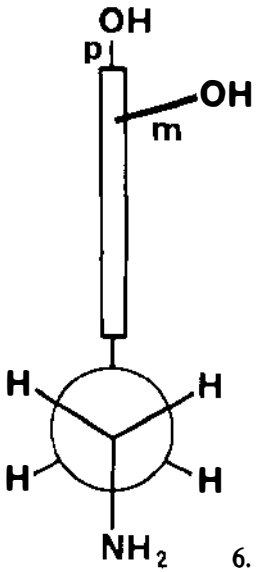


4. α-conformer

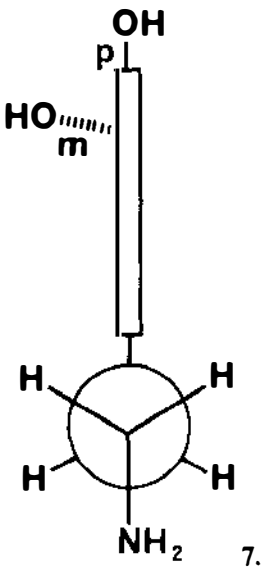


5. β-conformer

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org
by Central College on 12/12/11. For personal use only.



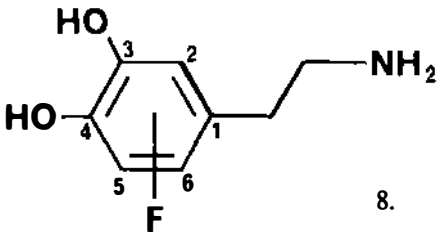
6.



7.

In the α-conformer (Newman projection 6), the *m*-OH is projected over the ethylamine side chain, whereas in the β-conformer (Newman projection 7), the *m*-OH is directed away from the side chain. Other structural features of a dopaminergic agonist may modify the ability of the molecule to interact with dopamine receptors or with specific populations of dopamine receptors, or these structural features may destroy agonist effects. However, the achievement of a conformation that corresponds to or approximates the α- or the β-conformation of dopamine seems to be a sine qua non for dopamine agonist activity in many types of chemical structures.

Katz et al (4) concluded that the *m*-phenolic monoanion of dopamine free base is more stable than the *p*-anion. 2- and 5-Fluorodopamines (structure 8) are equipotent to dopamine in a dog renal vascular assay, whereas the 6-fluoro isomer is four times less potent than dopamine (9).



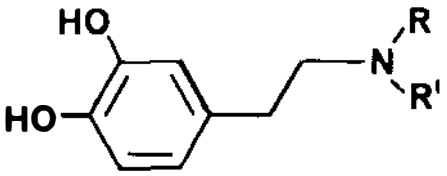
8.

In binding studies on rat striatal tissue, the three monofluoro-dopamines are equipotent to dopamine in displacement of ^{3}H-spiroperidol, but the 2- and

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

6-fluoro systems are less potent than the 5-fluoro or dopamine in displacement of ^{3}H-apomorphine (10). Kirk (11) suggested that a role of fluorine in these molecules is to change the acidity of the phenolic groups, which may modify the character and/or strength of the agonist-receptor interaction. Fluorination of the ring of dopa influences the site of methylation by catechol-O-methyltransferase, due to alteration of the acid strength of the phenolic OH (12).

Studies (13–18) of N,N-disubstituted dopamines reveal that the combinations of alkyl groups in 9*a-d* impart unusually high central and peripheral dopamine agonist effects.



9*a*. R = R' = CH_3

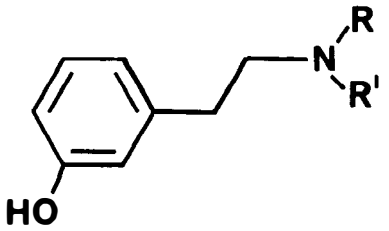
9*b*. R = R' = C_2H_5

9*c*. R = R' = *n*-C_3H_7

9*d*. R = *n*-C_3H_7; R' = *n*-C_4H_9

Remarkably, whereas N,N-di-*n*-propyldopamine (structure 9*c*) and N-*n*-propyl,N'-*n*-butyldopamine (structure 9*d*) are potent dopamine agonists, N,N-di-*n*-butyldopamine is inert (14). It has been suggested (8, 19) that enhanced dopaminergic effects frequently conferred by *N*-*n*-propyl groups are not related merely to the effect of the alkyl chain on solubility or partition phenomena, but rather that certain dopamine receptors have a positive affinity for the N-*n*-propyl group. Longer chains (e.g. *n*-butyl) do not fit the receptor subsite; shorter chains fit, but not optimally.

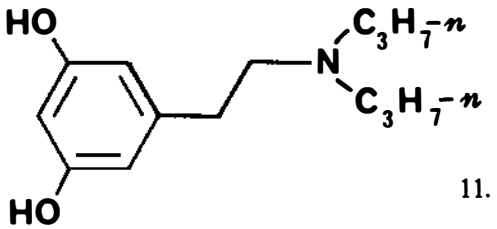
Geissler (20) cited literature evidence that *m*-tyramine (structure 10*a*) is a dopaminergic agonist. However, both *m*-tyramine and *p*-tyramine are inert in hyperactivity/stereotypy assays in rodents (21) and in stimulation of cyclic AMP production (22).



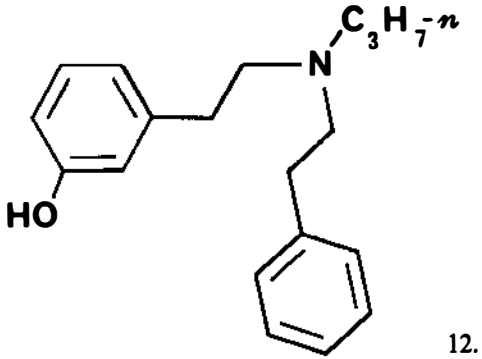
10*a*. R = R' = H

10*b*. R = R' = *n*-C_3H_7

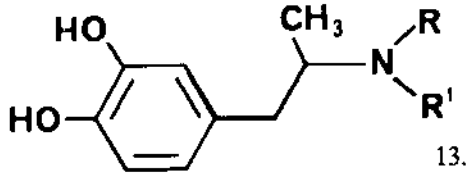
Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.



11.



12.



13.

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

N,N-Di-*n*-propyl *m*-tyramine (structure 10*b*) is a relatively potent selective central and peripheral dopaminergic agonist (20, 23). N,N-Di-*n*-propyl *p*-tyramine apparently has not been evaluated for dopamine-like effects. A unique role has been suggested (7, 8) for the "meta-OH" of dopamine in agonist-receptor interactions, and it is unexpected that the "di-meta-OH" system (structure 11) is inert in a variety of assays for central dopaminergic effects (23).

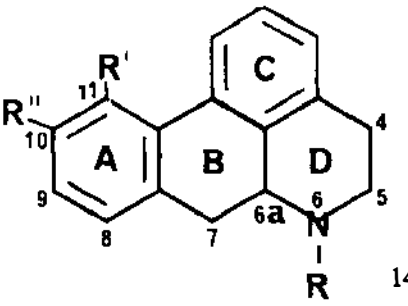
A variation (structure 12) of the *m*-tyramine structure exhibits a variety of dopamine agonist effects (23–26). The added β-phenethylamine moiety does not bestow unique potency, activity, nor spectrum of actions, but the compound has a longer duration of action in a rodent stereotypy assay (23) and in affecting prolactin release from the anterior pituitary (26).

Introduction of a methyl group into the α-position of the dopamine side chain (structure 13) greatly decreases agonist effects in some assays (22, 27) and abolishes effects in others (28). This loss of activity was explained (28)

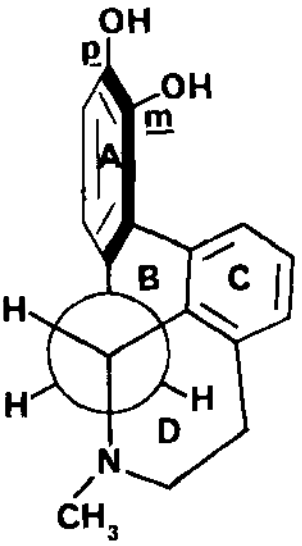
by the effect of the α-methyl group in forcing the catechol ring to lie perpendicular to the plane of the ethylamine side chain, a deviation of the dopamine moiety from either the α- or the β-conformation.

APORPHINES

The prototypical dopaminergic agonist aporphine is apomorphine (structure 14: R = CH_3; R' = R'' = OH).

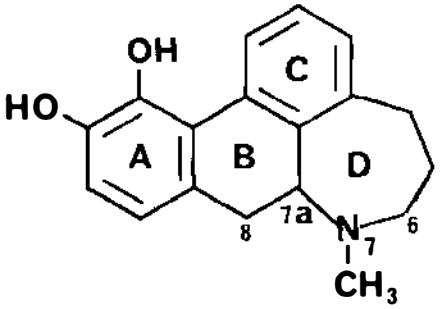


14.

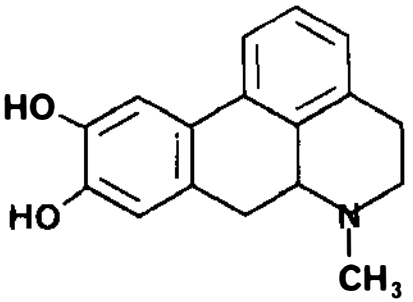


24

15.



16.



17.

Dopaminergic potency and activity in N-substituted homologs of apomorphine (structure 14) vary with the substituent, the highest in most assays residing in *n*-propyl (29–32).

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

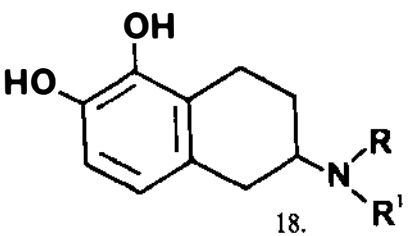
Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

Molecular models reveal that the dopamine moiety within the apomorphine molecule (structure 14: R = R' = OH; N-C_{6a}-C_7-ring A) is held rigidly in the α-conformation, with the catechol ring deviating from coplanarity with the ethylamine side chain by approximately 30°, as illustrated in Newman projection 15. C-8, 9–, 10–, and 11-Monohydroxyaporphines (structure 14) have been investigated (33, 34) and of these the 11-hydroxy isomer (structure 14: R' = OH; R'' = H), a "meta-OH" system, is most potent and active, although less so than apomorphine (33, 35). Expansion of the D ring of apomorphine into a seven-membered ring (structure 16) destroys all dopamine-like effects (36). An x-ray crystallographic study (36) revealed that the seven-membered ring distorts the dopamine moiety in structure 16 (N-C_{7a}-C_8-ring A) away from the α-conformation.

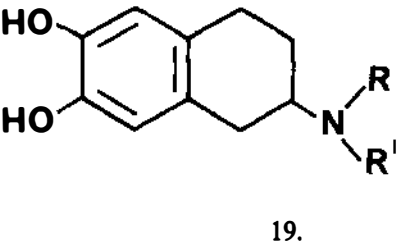
"Isoapomorphine" (structure 17), which bears the dopamine moiety in a β-conformation, is inert as a central (33, 37) and peripheral (38) dopaminergic agonist. On the basis of the prominent agonist effects of dopamine β-conformers derived from 2-aminotetralin (structure 19) (*vide infra*), some activity would be predicted for 17. A rationalization (38) for peripheral agonist inactivity of isoapomorphine invoked its inability to accomodate to the proposed topography of the renal vascular receptor. However, some exceptions to the agonist structural parameters implicit for this hypothetical receptor topography have been cited (39), and no adequate explanation for the inactivity of isoapomorphine has been advanced.

AMINOTETRALINS AND AMINOINDANS

5,6-Dihydroxy-2-aminotetralin derivatives (structure 18) ("A-5,6-DTN") represent a fragment of the apomorphine molecule.



18.



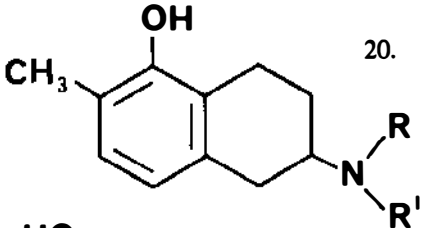
19.

The geometry of 2-aminotetralin ring systems was established by x-ray crystallographic studies (40). The α-conformation of dopamine within 18 bears the catechol ring very nearly coplanar with the plane of the ethylamine side chain. 6,7-Dihydroxy-2-aminotetralin (structure 19) ("A-6,7-DTN") represents a fragment of isoapomorphine 17, and contains a dopamine β-conformer. Derivatives of both 18 and 19 (where R and R' are combinations of hydrogen, methyl, ethyl, *n*-propyl, and 2-propyl) display

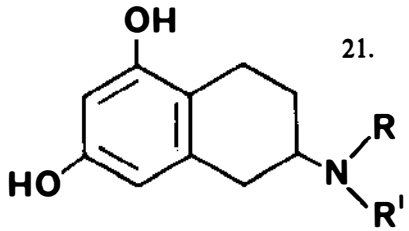
prominent central and peripheral dopaminergic agonist effects (41–43), but the two isomeric systems show different spectra of activities. Attempts to establish general correlations between the pattern of dihydroxylation (5,6- or 6,7-) or the nature of the N-alkyl substituent(s) of dihydroxy-2-aminotetralins and the spectrum of dopaminergic agonist effects, or to predict the type(s) and/or biological sites of activity of the isomeric dihydroxy 2-aminotetralins have not been successful.

In monophenolic 2-aminotetralins, the most prominent central dopaminergic agonist effects and highest potency reside in the 5-hydroxy isomer, a "meta-OH" system (44–47). This reflects a structural consistency with the relatively high potency/activity of 11-hydroxyaporphine and certain *m*-tyramine derivatives. Those 5-hydroxy-2-aminotetralins bearing at least one *n*-propyl group on the nitrogen have the highest activity and potency, and the di-*n*-propyl homolog is the most potent and active (19, 46).

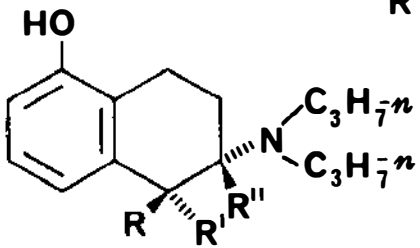
N,N-Diethyl- and di-*n*-propyl-5-hydroxy-6-methyl-2-aminotetralin (structure 20) display a variety of central and peripheral dopaminergic effects, qualitatively different from those reported for 5-hydroxy-2-aminotetralins (48, 49).



20.



21.



	R	R'	R''
22*a*.	CH_3	H	H (*trans*)
22*b*.	H	CH_3	H (*cis*)
22*c*.	CH_3	CH_3	H

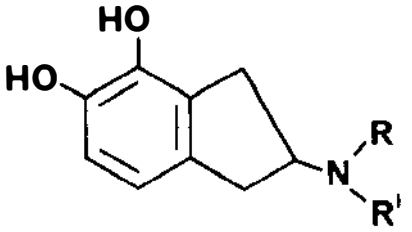
The primary amine and the N,N-dimethyl homolog of 20 demonstrate no receptor agonist activities. It is likely that the active members of the series 20 undergo metabolic activation (49), perhaps by hydroxylation of the 6-methyl group. This series may represent a novel type of dopaminergic prodrug.

Resorcinol-derived 2-aminotetralins (structure 21), which have the "meta-OH" pattern of both the α- and the β- dopamine conformations, are less potent and less active than their catechol-derived isomers 18 and 19 (101) but, unlike the β-phenethylamine resorcinol derivative 11, they are not dopaminergically inert.

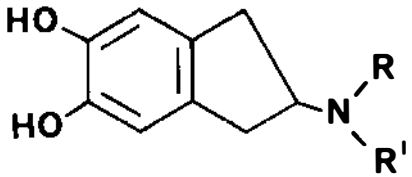
Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

The two stereoisomeric 1-methyl-2-aminotetralin derivatives 22*a*(*trans*) and 22*b* (*cis*) are equipotent at central dopamine receptors, and both compounds are less potent than the non-C-methylated system (structure 22: R = R' = R" = H) (50). The equipotency of the *cis*- and *trans*- isomers 22 *a*, 22*b* is surprising, in view of the inactivity of the 1,1-dimethyl derivative 22*c* and the marked difference in potency between *cis*- and *trans*- isomers in the octahydrobenzo(f)quinoline series 42 (*vide infra*).

4,5-Dimethoxy-2-dimethylaminoindan 23*b* is approximately four times as potent an emetic as apomorphine in the pigeon, but in the dog emesis model it is 0.008 times as potent as apomorphine (41).



23*a*. R = R' = H
23*b*. R = R' = CH_3
23*c*. R = R' = C_2H_5
23*d*. R = R' = n-C_3H_7



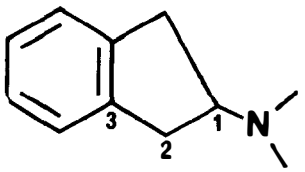
24. R, R' = combinations of H, CH_3, C_2H_5, n-C_3H_7

Compound 23*b* resembles apomorphine and the analogous 2-aminotetralin 18 (R = R' = CH_3) in a rat circling assay, although the indan derivative is less potent (51). The primary amine 23*a* is inert in these assays. Homologs 23*c* and 23*d* (N,N-diethyl- and di-*n*-propyl) are approximately equipotent to apomorphine in blocking response to stimulation of the cat cardioaccelerator nerve, an index of peripheral presynaptic dopaminergic effect (52), but the other members of series 23 are inert. Compounds 23*c* and 23*d* are potent emetics in the dog. None of the compounds of series 23 are effective in binding studies on calf caudate homogenates (52). No members of a series of indan hydroxyl group positional isomers (structure 24) show any dopamine-like activity in the dog emesis assay or in the cat cardioaccelerator nerve, nor are they effective in binding studies (52). The inactivity of the indan series 24 contrasts with the high potency/activity described for the structurally analogous 6,7-dihydroxy-2-aminotetralins (structure 19), but is consistent with the inactivity of isoapomorphine (structure 17).

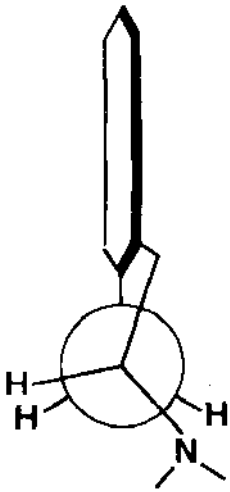
4,5-Dihydroxy- and 5,6-dihydroxy-2-aminoindan molecules hold the dopamine moiety rigidly in a steric disposition *approaching* the *trans*-conformation, and the benzene ring approaches coplanarity with the ethylamine side chain. However, in the indan system, the torsion angle τ_2 (struc-

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

ture 25: N-C_1-C_2-C_3) is 140–150° (illustrated in Newman projection 26), rather than 180° as in apomorphine 15 and the 2-aminotetralins.



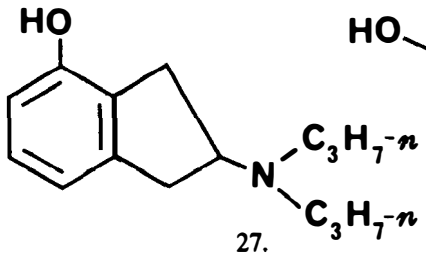
25.



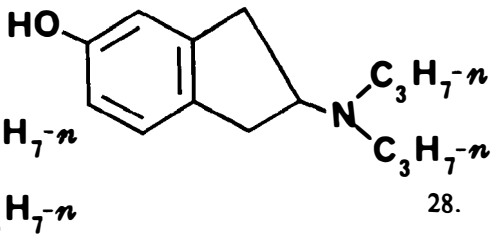
26.

Thus, the isomeric 2-aminoindans 23 and 24 approximate, respectively, the α- and β-conformations of dopamine. These analogies may be invoked to explain the prominent dopamine-like effects of derivatives of 23, but they do not explain the inactivity of the series 24.

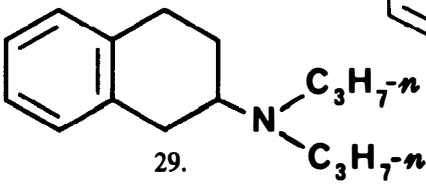
2-Di-*n*-propyl-4-hydroxyindan (structure 27) is much more potent and active in a series of CNS dopamine assays than the isomeric 5-hydroxyindan (structure 28) (53), which further illustrates the pharmacological importance of the "meta-OH" in the α-conformer of dopamine.



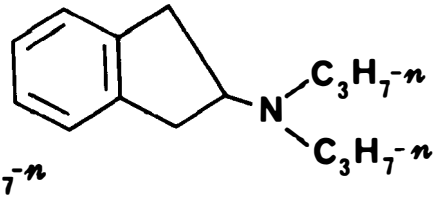
27.



28.



29.



30.

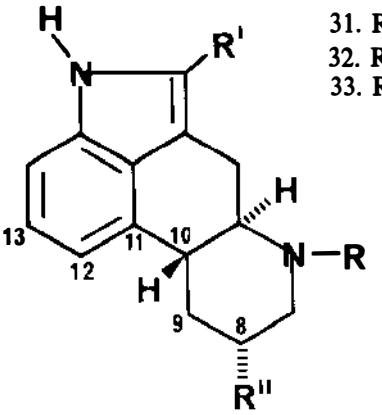
Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org
by Central College on 12/12/11. For personal use only.

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

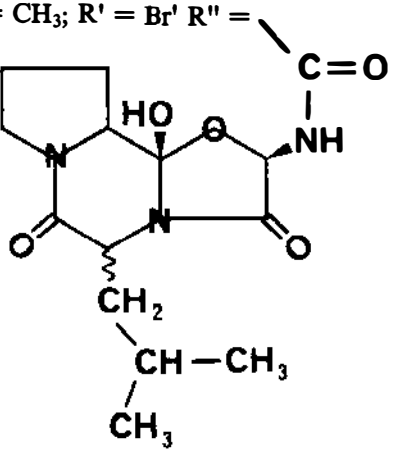
Some non-hydroxylated 2-aminotetralin and 2-aminoindan systems, especially those bearing the N,N-di-*n*-propyl group (structures 29 and 30), exhibit prominent dopamine-like effects (47, 54). It is uncertain whether these compounds are themselves direct agonists, or whether they are metabolically activated (by benzene ring hydroxylation?). The positive effect of *n*-propyl groups on dopamine-like activity is again noted: the primary amino- and N,N-dimethyl homologs of 29 are inert (54). While the inclusion of a catechol group in an appropriate steric disposition generally provides maximal dopaminergic effect, it is possible to design nonphenolic dopamine-active molecules. It is not possible, however, to correlate sites or spectrum of dopaminergic effects with presence or absence of phenolic OH groups. β-Phenethylamine, the non-oxygenated congener of dopamine, does not seem to possess any dopamine-like activity (55).

ERGOT ALKALOID DERIVATIVES AND FRAGMENTS

Central dopaminergic agonist properties of semisynthetic ergoline derivatives lergotrile (structure 31), pergolide (structure 32), bromocriptine (structure 33), and lisuride (structure 34) are established (56–60), and CNS

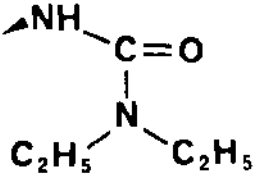


31. R = CH_3; R' = Cl; R'' = CH_2CN
32. R = n-C_3H_7; R' = H; R'' = CH_2-S-CH_3
33. R = CH_3; R' = Br' R'' =

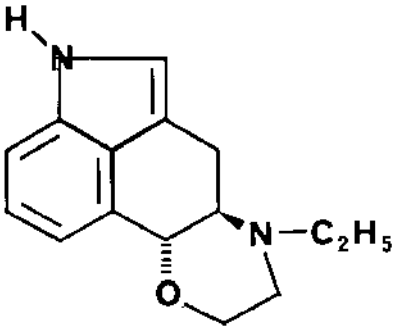


34. R = CH_3; R' = H; R'' = H;

C-8 =

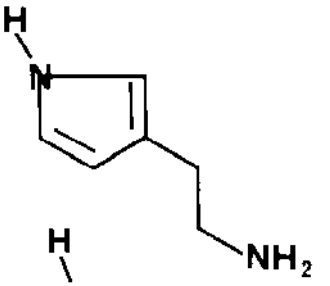


dopaminergic activity in man has been described for some of these (61–63). Some studies suggest that ergot alkaloids have the properties of mixed "agonist-antagonist" with respect to certain presynaptic and postsynaptic dopamine receptors (64). A new chemical class, *cis*- and *trans*-D-heteroergolines, was designed, in which the π-electron center present in the Δ^9-ergolines (such as bromocriptine, structure 33) has been replaced by the unoccupied p orbitals of oxygen. (–)-*trans*-6-Ethyl-9-oxaergoline (structure 34*a*), which has the same absolute configuration as the natural ergolines, is said to possess potent dopamine agonist properties (103), whereas the (+)-enantiomer shows greatly diminished activity.

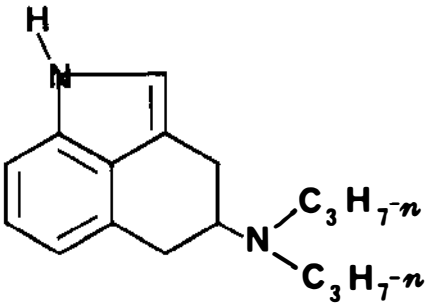


34*a*.

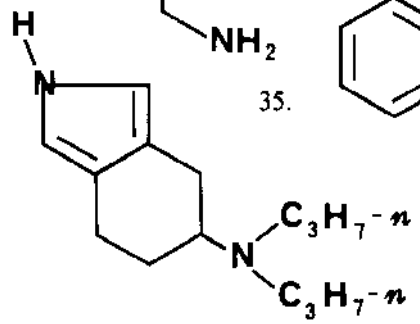
N-*n*-Propyl groups frequently enhance dopamine agonist effects in the ergoline derivatives. Bach et al (65) studied fragments and congeners of fragments (structures 35–41) of potent ergoline-derived dopaminergic agonists.



35.

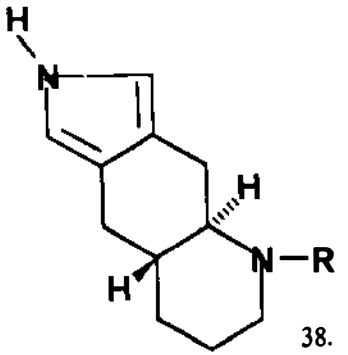


36.

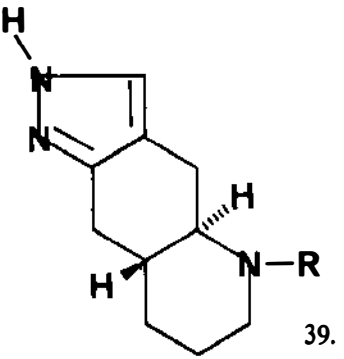


37.

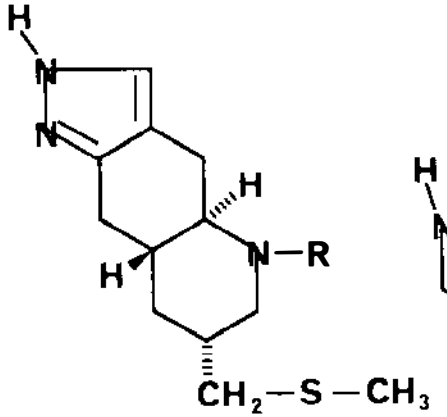
Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.



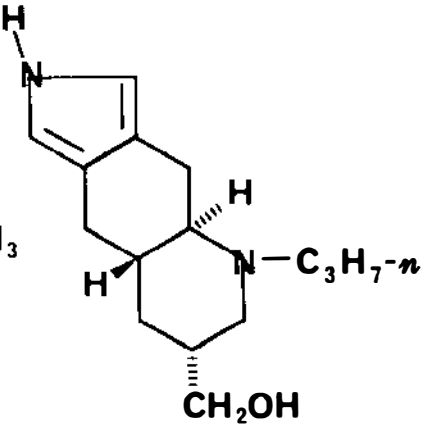
38.



39.



40.

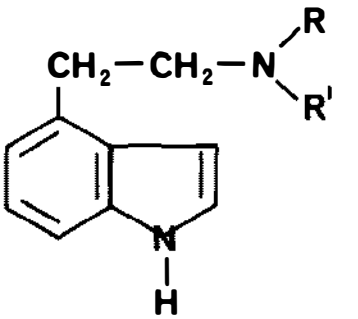


41.

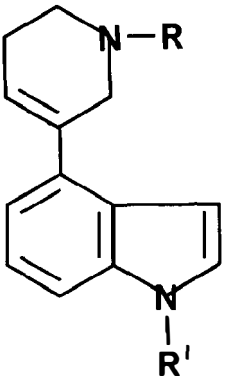
The simple pyrrole-3-ethylamine (structure 35) is inert because, it was suggested (65), of its rapid inactivation by monoamine oxidase. Of the other compounds, 36–41, only the linear tricyclic pyrazoles, 39 and 40, (R = *n*-propyl) are comparable in potency to pergolide 32. It was concluded (65) that the benzene ring of ergoline is not essential for dopaminergic activity, and that the 3-pyrrole ethylamine moiety of the ergolines is the dopamine-active portion of the class, despite the inactivity of 35.

Based on the premise that the pharmacophore of the ergolines is a 4-(2-aminoethyl) indole system, Cannon et al (66, 67) investigated a series 42*a–c*.

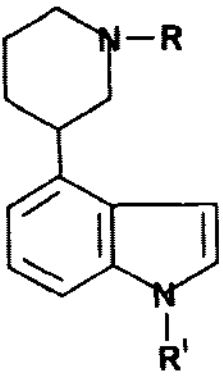
Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.



42*a*. R = R' = CH_3
42*b*. R = R' = C_2H_5
42*c*. R = R' = *n*-C_3H_7



44.



43.

The N,N-dimethyl homolog 42*a* is inert in the cat cardioaccelerator nerve assay, but the diethyl- and di-*n*-propyl systems 42*b* and 42*c* are active, the potency of the latter homolog approaching that of lergotrile 31. Both 42*b* and 42*c* exhibit a lag period of 25–30 minutes after intravenous administration before maximal pharmacological response is noted, and this suggests metabolic activation of the molecules. In an in vitro assessment of the response of the isolated right atrium of the cat to electrical stimulation, compounds 42*a–c* were inactive. Binding studies (calf caudate tissue) showed only very weak binding abilities for 42*b* and *c*, and almost none for 42*a*. A portion of the dopaminergic effect of lergotrile 31 is produced by a C-13 hydroxy metabolite (68), and it is possible that an analogous metabolic hydroxylation occurs to 42*b* and 42*c*. However, metabolic activation is not a prerequisite for agonist activity in all of the ergoline derivatives and fragments.

Nedelec et al (69) prepared 43 and 44 as simple 3–5 *seco* ergoline derivatives. Significant dopaminergic effect in 43 and 44 occurs only in compounds in which R' = H. When R is methyl, ethyl, or *n*-propyl in 43 and 44, potent in vivo dopaminergic agonist effects are observed. There is no clear phar-

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

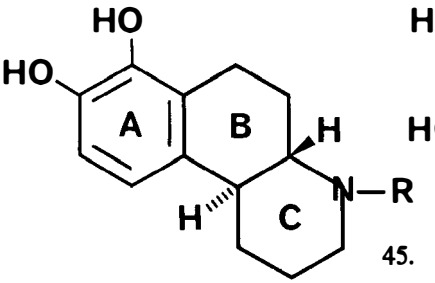
Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

macological difference between the saturated series 43 and the unsaturated series 44. None of the active compounds of either series has more than a weak affinity for dopamine receptors in binding studies, and all are inactive in inhibition of prolactin secretion in vitro. The activities observed for both the saturated and the unsaturated compounds were ascribed to formation of active metabolites.

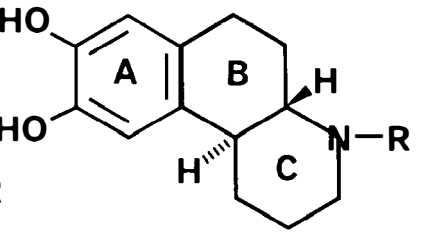
Molecular models reveal that the pyrrole nitrogen of the ergoline derivatives 31–43 and of the 4-substituted indoles 42–44 is at the same position on the benzene ring with respect to the ethylamine side chain of the β-phenethylamine moiety as is the "meta-OH" in the α-conformer of dopamine. Although the ring nitrogen of indole is a much weaker acid than a phenolic group, it has been proposed (67) that a receptor subunit might not discriminate between a phenolic OH and an indole ring N-H, and that the indole N-H and the "meta"-OH of dopamine are bioisosteric. Reasonable conformations can be shown for the ergolines 31–34*a*, for the partial ergoline structures 35–41, and for the 4-substituted indoles 42–44 in which the compounds coincide with a hypothetical template for the α-conformer of dopamine, such that the basic (amino) nitrogen interacts with a complimentary anionic receptor subsite coincident with interaction of the indole N-H with the receptor subsite that is complimentary to the "meta"-OH of dopamine. The distance between the amino nitrogen and the indole ring nitrogen in reasonable conformations of each compound is approximately 6.5 Å, which closely approximates the *m*-OH-to-amino nitrogen distance in the α-conformer of dopamine.

BENZOQUINOLINE DERIVATIVES

The octahydrobenzo(f)quinolines 45 and 46 represent a structural bridge between the 2-aminotetralins and the ergolines.



45.



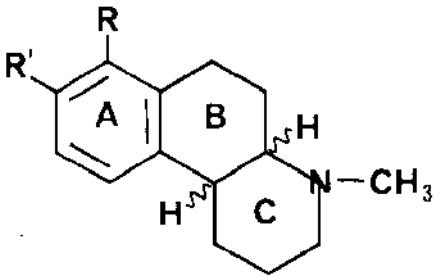
46.

a. R = H

b. R = CH_3

c. R = C_2H_5

d. R = *n*-C_3H_7



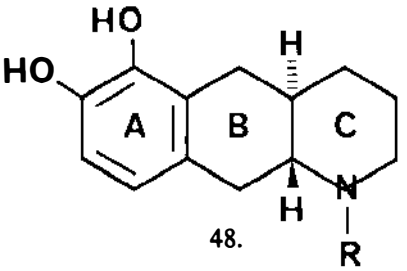
47*a*. R = OH; R' = H
47*b*. R = H; R' = OH
47*c*. R = R' = H

The ring systems 45 and 46 can exist as *trans*- (illustrated) or *cis*- fused B/C ring isomers. Activity in the series 45 resides almost exclusively in the *trans*- (70, 71), in which the dopamine moiety is held rigidly in the α-conformation. Derivatives of *trans*- 45 where R = ethyl or *n*-propyl are more potent than apomorphine in a variety of central and peripheral dopaminergic assays in several animal species (71, 72). In most tests, the N-*n*-propyl homolog exhibits higher potency than the N-ethyl. The *cis*- 45 system is flexible, and the *cis*- molecules lack the ability to maintain the dopamine moiety in a conformation conducive to dopaminergic agonist effects (71).

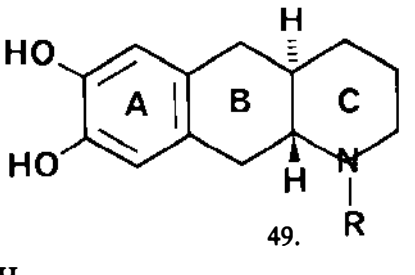
The B/C *trans*- system 46 represents a rigidly held β-conformer, and the flexible *cis*- 46 molecule lacks the ability to maintain the dopamine moiety in a β-conformation. In *trans*- 46 (illustrated) where R = methyl, ethyl, or *n*-propyl, extremely potent effects on the cat cardioaccelerator nerve are noted (39), and these compounds have moderate ability to inhibit striatal dopa accumulation (D. B. Rusterholz, J. P. Long, unpublished data). All of the *cis*- and *trans*- B/C ring fused derivatives of 46 are inert in the dog renal vascular assay, and all are inert in modification of cerebral mechanisms involved in motor control (39). This is a different spectrum of effects from that described for the analogous 2-aminotetralin derivatives 19. Of the *cis*- and *trans*- noncatechol systems (structure 47), only the *trans*-fused B/C ring molecule bearing the "meta-OH", 47*a*, an α-conformation, showed dopamine-like effects, albeit of low potency (70).

The linear octahydrobenzo(g)quinoline 48 is an apomorphine molecule lacking the nonoxygenated benzene ring and, like apomorphine, it bears the dopamine moiety in an α-conformation when (as illustrated) the stereochemistry of B/C ring fusion is *trans*.

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.



48.



49.

a. R = H

b. R = CH_3

c. R = C_2H_5

d. R = *n*-C_3H_7

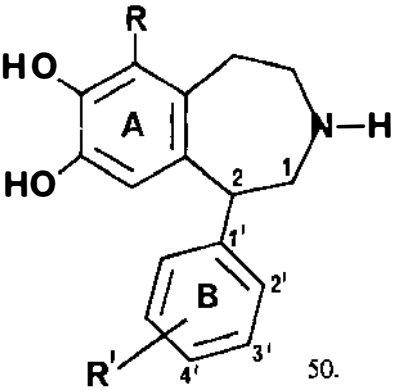
The secondary amine 48*a* exhibits low potency and activity. However, the tertiary amines 48b–d are somewhat more potent than apomorphine in inhibition of striatal dopa accumulation in the rat (74), and they also produce stereotypy in mice; the N-ethyl- and *n*-propyl homologs 48*c* and 48*d* are at least equipotent to apomorphine, and the N-methyl 48*b* is less potent. The N-methyl- and *n*-propyl homologs 48*b* and 48*d* induce a circling response in unilaterally lesioned rats, but the N-ethyl homolog 48*c* produces no rotational response at doses ten times those required for good response to 48*d* or to apomorphine. Costall et al (75, 76) have suggested that gross, centrally mediated rotational effects produced by dopaminergic drugs may result from more than one physiological mechanism, involving more than one population of dopamine receptors, having different agonist structural requirements. The rotational inactivity of the N-ethyl homolog 48*c* is difficult to rationalize on chemical structural bases. Only the *n*-propyl derivative 48*d* exhibits a marked dopamine-like effect in the dog renal blood flow assay (74), having a potency ratio to dopamine of 0.2. This value is a tenfold increase in potency over that reported (16) for N,N-di-*n*-propyldopamine 9*c*.

All of the β-conformer homologs, *trans*- 49*a–d,* like isoapomorphine, are inert in central and peripheral assays in which A-6,7-DTN 19 is active (39).

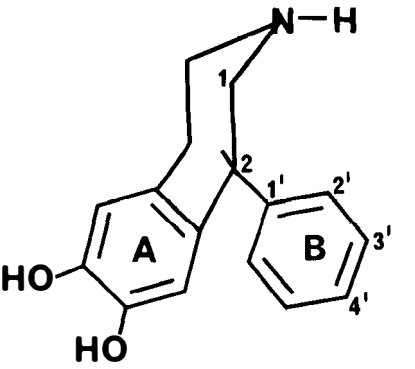
BENZAZEPINES

The benzazepine derivative 50 (R = R' = H) dilates the renal vascular bed of the dog. It is a partial agonist in the striatal adenylate cyclase assay, and it is an agonist in the rat rotation model (77, 78).

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.



50.



51.

Compound 50 does not affect prolactin levels nor dopamine turnover, nor is it an emetic in the dog. It does not induce stereotypy in normal rats (78). The unusual dopaminergic profile for 50 may reflect its agonist specificity for D-1 receptors (56). Analysis of molecular models indicates that the dopamine moiety of 50 (N-C_1-C_2-ring A) deviates significantly from either an α- or a β-conformation. However, in the chair form of the azepine ring with benzene ring B attached by an equatorial bond, the β-phenethylamine system (structure 51: N-C_1-C_2-ring B) can assume the *antiperiplanar* disposition (τ_2, N-C_1-C_2-$C_{1'}$ = 180°) with the plane of ring B coplanar with the plane of the ethylamine side chain, N-C_1-C_2. Whether ring B in 50 is indeed a portion of the dopamine-active portion of the molecule has not been established. Kaiser et al (102) found that dopaminergic activity in 50 (R = R' = H) resides almost exclusively in the *R* enantiomer (C_2 is asymmetric). These workers suggested that the 1-phenyl substituent interacts with a chirally defined accessory site on the receptor. Erhardt (79) noted that, while there are examples of nonoxygenated 2-aminotetralins that show some central dopaminergic activity, literature precedent mandates an intact catechol group as a requisite for renal vascular dopamine agonist activity. It is possible that the benzazepines represent an exception to the proposed requirement of an α- or a β-conformation for dopamine agonism.

When the benzazepine bears a chlorine at position 6 (50: R = Cl), the effect in the dog renal vascular assay is increased; potency/activity in the rat rotational model is retained; and the stimulation of rat adenylate cyclase is greatly increased (80). The 4'-hydroxy-6-chloro analog (50: R = Cl; R' = 4'-OH) has greatly increased renal vasodilator activity and a powerful effect as a stimulant of adenylate cyclase. However, this compound does not penetrate the blood-brain barrier. When the chlorine atom is removed (50: R = H; R' = 4'-OH), the renal vasodilator activity is lost (80). It was speculated (80) that the chlorine atom "enhances binding at the receptor

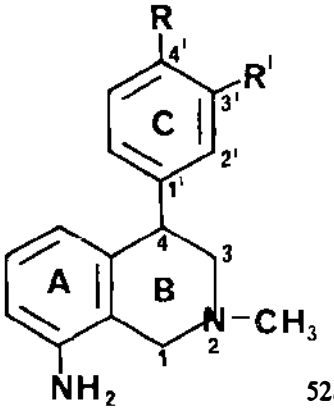
Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

in a conformation which induces maximum activation of the renal receptor." Moreover, the 4'-OH enhances the polarity of the molecule, which decreases entry into lipophilic compartments, and thus produces higher concentrations in the kidney. This rationalization does not explain the lack of renal vascular effect of the 4'-OH deschloro derivative (50: R = H; R' = 4'-OH).

In an extended series of 6-chloro-l-phenylazepines (50: R = Cl) (81), the most potent compounds in the dog renal vascular assay contain a hydroxyl group in the 3' or 4' positions, or are substituted at the 3' position with chlorine, methyl, or trifluoromethyl. The compounds with the most prominent central effects are the most lipophilic ones; are substituted in the 3'-position; and bear an N-methyl or allyl group. The high potency of N-allyl derivatives is noteworthy in that N-allylnorapomorphine is comparable to apomorphine in emetic potency in the dog, but is less potent than apomorphine in production of stereotypy in mice and pecking in pigeons (82). The literature does not reveal sufficient examples of N-allyl dopaminergic agonists to permit conclusions about consistent effects (if any) of allyl groups on dopamine-like activity.

MISCELLANEOUS STRUCTURES

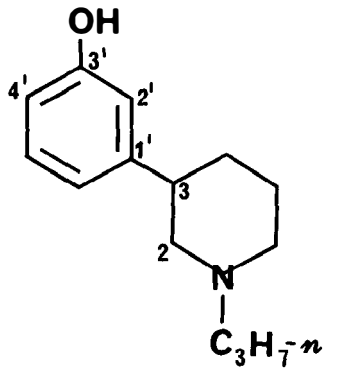
Nomifensine 52*a* produces dopamine-like stereotypy in the rat, which was stated to be related to dopamine-releasing properties of the drug (83). More recent studies (84) suggest that nomifensine blocks dopamine uptake into striatal synaptosomes, and that it also inhibits release of dopamine, due to agonist (*sic*) effect on presynaptic dopamine receptors.



52*a*. R = R' = H

52*b*. R = OH; R' = H

52*c*. R = R' = OH



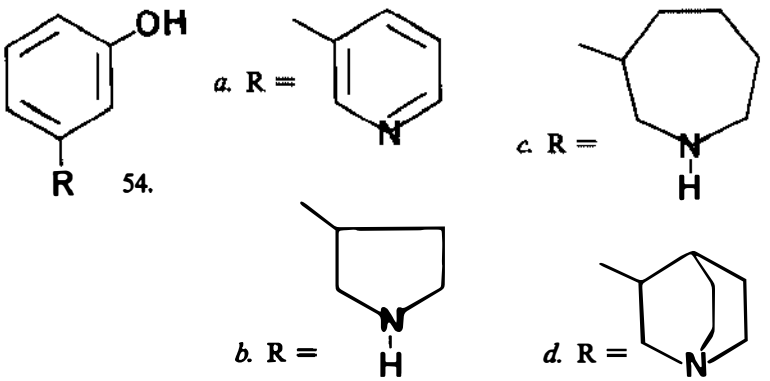
53.

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

Nomifensine 52*a* and the 4'-hydroxy congener 52*b* have no effect on rat striatal dopamine-sensitive adenylate cyclase (85, 86). However, the catechol system 52*c* (which has been proposed but not established to be a metabolite of nomifensine) is described as a potent agonist in stimulation of adenylate cyclase of rat striatum (86). The catechol derivative produces powerful dopamine-like effects upon injection into the nucleus accumbens of the mouse (87). Analysis of molecular models shows that the dopamine moiety in 52*c* (N_2-C_3-C_4-ring C) can assume the α- or β-conformation.

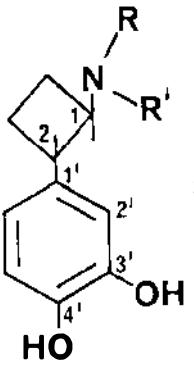
3-PPP 53 was compared with apomorphine and with *TL-99* (structure 19: R = R' = CH_3) for dopaminergic actions (88–90). *3-PPP* is a more selective dopaminergic autoreceptor agonist than TL-99 (89). Molecular models reveal that in a stable conformation for 53 (piperidine ring in a chair form; benzene ring attached to C_3 by an equatorial bond), the β-phenethylamine system (N-C_2-C_3-benzene ring) assumes a *trans-* (*antiperiplanar*) conformation, and there seems to be no steric impediment to the 3'-OH to assume either the α- or the β-conformation. However, no proposal has been advanced to designate the preferred conformer in interaction of *3-PPP* with receptor(s). Movement of the 3'-hydroxy group of *3-PPP* to the 2'- or the 4'-position results in loss of dopaminergic activity (91). Remarkably, the 3',4'-dihydroxy derivative is *less* potent than the 3'-monohydroxy. Replacement of the piperidine ring in 53 by pyridine 54*a,* pyrrolidine 54*b,* azepine 54*c,* or quinuclidine 54*d* results in loss of biological activity.



The inactivity of the saturated ring analogs 54*b–d* is explained by the inability of the ring system (b–d) to attain or to maintain the β-phenethylamine moiety in the *antiperiplanar* conformation. In the case of the pyridine ring 54*a,* it may be that the lowering of the base strength of the ring nitrogen (in pyridine, as compared with piperidine) is detrimental to interaction with receptor subsite(s). The completely aromatic congeners of the highly potent and active 2-amino-5,6-dihydroxytetralins (structure 18)

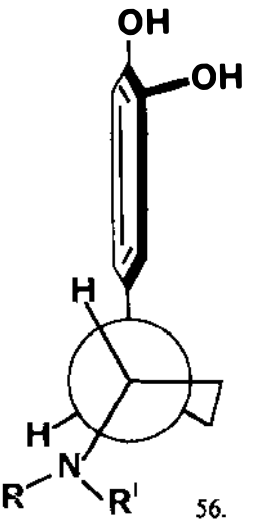
are inert in production of stereotypy in mice, pecking in pigeons, and emesis in dogs, and they exhibit only very low potency in the pigeon emesis model (92). An obvious difference between 2-aminonaphthalene and 2-aminotetralin is the decidedly lower base strength of the aromatic amine.

The *trans*- cyclobutane derivatives 55*a–b* are more potent than their *cis*- isomers in binding studies on rat corpus striatum membrane tissue (93), but the potency is much lower than that of dopamine.

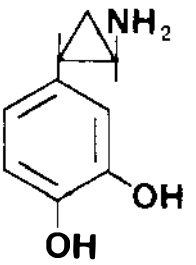


55*a*. R = R' = H

55*b*. R = R' = CH_3



56.



57.

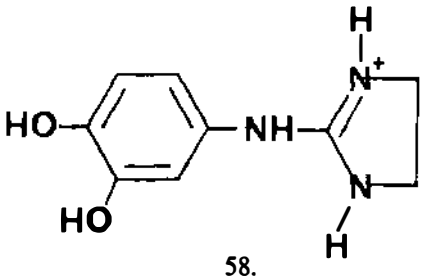
The cyclobutane ring is not planar, but rather it exists in a puckered conformation. Conformational analysis of 55 reveals that the torsion angle τ_2, N-C_1-C_2-$C_{1'}$, lies within the limits 110–160° (shown in the Newman projection 56 as approximately 160°). Thus, the overall shape of the molecule permits an approximation of either the α- (illustrated in 56) or the β-conformer of dopamine. The low potency of the *trans*- system 55 may be a reflection of less-than-optimal correspondence of the dopamine moiety with the geometry of the dopamine receptors. The *cis*- isomer of 55 presents

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

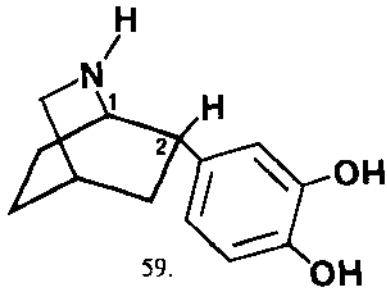
the dopamine moiety in an approximate *gauche* (see structure 2 or 3) arrangement.

The dopaminergic inactivity of a *trans*- cyclopropane derivative (structure 57) (94, 95) is rationalized on stereochemical grounds. As was proposed previously for the α-methyldopamine molecule 13, it has been suggested (95) that the molecular structure of 57 is such that the catechol ring is held perpendicular to the plane of the ethylamine side chain of the dopamine moiety, which is detrimental to receptor interactions.

DPI 58 has been described as a dopaminergic agonist in the brain of the snail, *Helix aspersa* (96) and in the cat caudate nucleus (97).



58.



59.

However, this compound is inactive in an adenylate cyclase assay, in the renal vascular assay in the dog, and in binding studies (98), and its status as an agonist seems unclear. Molecular models suggest that the ring nitrogen-protonated canonical form shown in 58 may fit a dopamine α- or β-conformer template. However, the positive charge of guanidinium cation is highly dispersed over the three nitrogens and the included carbon atom, and if this delocalization occurs in 59, a structural similarity between *DPI* and dopamine becomes less apparent; the catechol ring-to-cation distance in the two molecules will be different.

The *exo*-azabicyclooctane derivative 59 maintains the dopamine moiety ($N\text{-}C_1\text{-}C_2$-catechol ring) in the *trans*- disposition, and the catechol ring seems able to assume either the α- or the β-conformation. This compound is inert in several assays for dopamine-like effect, possibly a result of steric interference to receptor interaction caused by the bulky bicyclic ring (99). The molecule 59 is typical of a number of compounds in which extraneous structural features predominate over the desirable steric disposition of the dopamine portion, and nullify dopaminergic actions. The achievement of conformational integrity of dopamine structure by incorporating it into a complex molecule frequently is at the expense of biological activity.

It has been suggested (100) that attempts to define the preferred rotameric conformation for dopamine agonist action in a single definitive form

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

may be an "illusory quest." Biochemical studies may indicate a preferred α- or β-rotameric conformation, dependent upon the dopamine agonist used and the biochemical index of agonist action, but the preference may change *within* a chemical series, depending upon the degree of N-alkylation.

Thus, while analysis of rotameric variations of dopamine is a useful strategy in drug design, it must be recognized that structure-activity relationships of dopamine agonists are exquisitely subtle, and are not yet understood.

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

ACKNOWLEDGMENTS

This work was supported in part by grant GM-22365, National Institute of General Medical Sciences, and in part by a grant from Eli Lilly and Company.

Literature Cited

1. Blaschko, H. 1957. Metabolism and storage of biogenic amines. *Experientia* 13:9–12
2. Cannon, J. G. 1983. Dopamine analogue stereoisomers. In *Handbook of Stereoisomers: Drugs in Psychopharmacology*, ed. D. F. Smith. Boca Raton, Fla: CRC. In press
3. Pullman, B., Coubeils, J.-L., Courrière, Ph., Gervois, J.-P. 1972. Quantum mechanical study of the conformational properties of phenethylamines of biochemical and medicinal interest. *J. Med. Chem.* 15:17–27
4. Katz, R., Heller, S. R., Jacobson, A. E. 1973. A molecular orbital study of norepinephrine and 3,4-dihydroxyphenethylamine: a reevaluation of structure-activity relationships in norepinephrine. *Mol. Pharmacol.* 9: 486–94
5. Rotman, A., Lundstrom, J., McNeal, E., Daly, J., Creveling, C. R. 1975. Norepinephrine uptake sites in cardiac tissue. Lack of affinity of 6-hydroxynorepinephrine and related compounds. *J. Med. Chem.* 18:138–42
6. Granot, J. 1978. Nuclear magnetic resonance studies of catecholamines. Complex formation with adenosine 5'-triphosphate in aqueous solution. Stoichiometry and molecular conformations. *J. Am. Chem. Soc.* 100:1539–48
7. Cannon, J. G. 1975. Chemistry of dopaminergic agonists. *Adv. Neurol.* 9:177–83
8. Cannon, J. G. 1979. Dopamine congeners derived from the benzo(f)quinoline ring. *Adv. Biosci.* 20:87–94
9. Goldberg, L. I., Kohli, J. D., Cantacuzene, D., Kirk, K. L., Creveling, C. R. 1980. Effects of ring fluorination on the cardiovascular actions of dopamine and norepinephrine in the dog. *J. Pharmacol. Exp. Ther.* 213:509–13
10. Nimit, Y., Cantacuzene, D., Kirk, K. L., Creveling, C. R., Daly, J. W. 1980. The binding of fluorocatecholamines to adrenergic and dopaminergic receptors in rat brain membranes. *Life Sci.* 27:1577–85
11. Kirk, K. L. 1976. Photochemistry of diazonium salts. 4. Synthesis of ring-fluorinated tyramines and dopamines. *J. Org. Chem.* 41:2373–76
12. Firnau, G., Sood, S., Pantel, R., Garnett, S. 1981. Phenol ionization in dopa determines the site of methylation by catechol-O-methyltransferase. *Mol. Pharmacol.* 19:130–33
13. Ginos, J. Z., Cotzias, G. C., Tolosa, E., Tang, L. C., Lo Monte, A. J. 1975. Cholinergic effects of molecular segments of apomorphine and dopaminergic effects of N,N-dialkylated dopamines. *J. Med. Chem.* 18:1194–1200
14. Cannon, J. G., Hsu, F.-L., Long, J. P., Flynn, J. R., Costall, B., Naylor, R. J. 1978. Preparation and biological actions of some symmetrically N,N-disubstituted dopamines. *J. Med. Chem.* 21: 248–53
15. Kohli, J. D., Weder, A. B., Goldberg, L. I., Ginos, J. Z. 1980. Structure-activity relationships of N-substituted dopamine derivatives as agonists of the dopamine vascular and other cardiovas-

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

cular receptors. *J. Pharmacol. Exp. Ther.* 213:370–74
16. Kohli, J. D., Goldberg, L. I., Volkman, P. H., Cannon, J. G. 1978. N,N-di-*n*-propyldopamine: a qualitatively different dopamine vascular agonist. *J. Pharmacol. Exp. Ther.* 207:16–22
17. Ilhan, M., Long, J. P., Cannon, J. G. 1974. Inhibition of responses to stimulation of the cardioaccelerator nerves of the cat by N,N-dimethyldopamine and apomorphine. *Arch. Int. Pharmacodyn. Ther.* 212:247–54
18. Massingham, R., Dubocovich, M. L., Langer, S. Z. 1980. The role of presynaptic receptors in the cardiovascular actions of N,N-di-*n*-propyldopamine in the cat and dog. *Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol.* 314: 17–28
19. Hacksell, U., Svensson, U., Nilsson, J. L. G., Hjorth, S., Carlsson, A., Wikström, H., Lindberg, P., Sanchez, D. 1979. N-Alkylated 2-aminotetralins: central dopamine-receptor stimulating activity. *J. Med. Chem.* 22:1469–75
20. Geissler, H. E. 1977. 3-(2-Dipropylamino-äthyl)-phenol, ein neuer, selektiver dopaminerger agonist. *Arch. Pharm.* (Weinheim) 310:749–56
21. Costall, B., Naylor, R. J., Pinder, R. M. 1974. Design of agents for stimulation of neostriatal dopaminergic mechanisms. *J. Pharm. Pharmacol.* 26:753–62
22. Miller, R., Horn, A., Iversen, L. 1974. Effects of dopamine-like drugs on rat striatal adenylate cyclase have implications for CNS dopamine receptor topography. *Nature* 250:238–41
23. Sumners, C., Dijkstra, D., de Vries, J. B., Horn, A. S. 1981. Neurochemical and behavioral profiles of five dopamine analogs. *Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol.* 316:304–10
24. Nedelec, L., Dumont, C., Oberlander, C., Frechet, D., Laurent, J., Boissier, J. R. 1978. Synthèse et étude de l'activité dopaminergique de dérivés de la di (phenylethyl) amine. *Eur. J. Med. Chem.-Chim. Therap.* 13:553–63
25. Boissier, J. R., Dumont, C., Laurent, J., Oberlander, C. 1980. Profil psychopharmacologique d'un nouvel agoniste dopaminergique, le Ru-24213. *Psychopharmacology* 68:15–23
26. Euvrard, C., Ferland, L., DiPolo, T., Beaulieu, M., Labrie, F., Oberlander, C., Raynaud, J. P., Boissier, J. R. 1980. Activity of two new potent dopaminergic agonists at the striatal and anterior pituitary levels. *Neuropharmacology* 19:379–86
27. Borgman, R. J., Baylor, M. R., McPhillips, J. J., Stitzel, R. E. 1974. α-Methyldopamine derivatives. Synthesis and pharmacology. *J. Med. Chem.* 17: 427–30
28. Cannon, J. G., Perez, Z., Long, J. P., Rusterholz, D. B., Flynn, J. R., Costall, B., Fortune, D. H., Naylor, R. J. 1979. N-Alkyl derivatives of (±)-α-methyldopamine. *J. Med. Chem.* 22:901–7
29. Atkinson, E. R., Bullock, F. J., Granchelli, F. E., Archer, S., Rosenberg, F. J., Teiger, D. G., Nachod, F. C. 1975. Emetic activity of N-substituted norapomorphines. *J. Med. Chem.* 18: 1000–3
30. Koch, M. V., Cannon, J. G., Burkman, A. M. 1968. Centrally acting emetics. II. Norapomorphine and derivatives. *J. Med. Chem.* 11:977–81
31. Haubrich, D. R., Pflueger, A. B. 1982. The autoreceptor control of dopamine synthesis: an in vitro and in vivo comparison of dopamine agonists. *Mol. Pharmacol.* 21:114–20
32. Miller, R. J., Kelly, P. H., Neumeyer, J. L. 1976. Aporphines. 15. Action of aporphine alkaloids on dopaminergic mechanisms in rat brain. *Eur. J. Pharmacol.* 35:77–83
33. Saari, W. S., King, S. W., Lotti, V. J., Scriabine, A. 1974. Synthesis and biological activity of some aporphine derivatives related to apomorphine. *J. Med. Chem.* 17:1086–90
34. Neumeyer, J. L., Dafeldecker, W. P., Costall, B., Naylor, R. J. 1977. Aporphines. 21. Dopaminergic activity of aporphine and benzylisoquinoline derivatives. Synthesis of 8-hydroxyaporphines and 1-(hydroxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinolines. *J. Med. Chem.* 20:190–96
35. Neumeyer, J. L., Granchelli, F. E., Fuxe, K., Ungerstedt, U., Corrodi, H. 1974. Aporphines. 11. Synthesis and dopaminergic activity of monohydroxyaporphines. Total synthesis of (±)-11-hydroxyaporphine, (±)-11-hydroxy noraporphine, and (±)-11-hydroxy-N-*n*-propylnoraporphine. *J. Med. Chem.* 17:1090–95
36. Berney, D., Pechter, T. J., Schmutz, J., Weber, H. P., White, T. G. 1975. Conformations and biological properties of apomorphine and its phenanthro(10,1-b,c)azepine homologue. *Experientia* 31:1327–28
37. Neumeyer, J. L., McCarthy, M., Battista, S., Rosenberg, F. J., Teiger, D. G. 1973. Aporphines. 9. Synthesis and pharmacological evaluation of (±)-9,10-

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

dihydroxyaporphine (isoapomorphine), (+)-, (–)-, and (±)-1,2-dihydroxyaporphine, and (+)-1,2,9,10-tetrahydroxya- *J. Med. Chem.* 16:1228–33

38. L. I., Kohli, J. D., Kotake, A. N., Volkman, P. H. 1978. Characteristics of the vascular dopamine receptor: comparison with other receptors. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 37:82–88
39. Cannon, J. G., Lee, T., Goldman, H. D., Long, J. P., Flynn, J. R., Verimer, T., Costall, B., Naylor, R. J. 1980. Congeners of the β-conformer of dopamine derived from cis- and trans-octahydrobenzo(f)quinoline and trans-octahydrobenzo(g)quinoline. *J. Med. Chem.* 23:1–5
40. Giesecke, J. 1980. The crystal structure of (+)-2-di-propylamino-5-hydroxytetralin hydrochloride. *Acta Crystallogr. Sect. B* 36:110–14
41. Cannon, J. G., Kim, J. C., Aleem, M. A., Long, J. P. 1972. Centrally acting emetics. 6. Derivatives of β-naphthylamine and 2-indanamine. *J. Med. Chem.* 15:348–50
42. McDermed, J. D., McKenzie, G. M., Phillips, A. P. 1975. Synthesis and pharmacology of some 2-aminotetralins. Dopamine receptor agonists. *J. Med. Chem.* 18:362–67
43. Cannon, J. G., Lee, T., Goldman, H. D., Costall, B., Naylor, R. J. 1977. Cerebral dopamine agonist properties of some 2-aminotetralin derivatives after peripheral and intracerebral administration. *J. Med. Chem.* 20:1111–16
44. McDermed, J. D., McKenzie, G. M., Freeman, H. S. 1976. Synthesis and dopaminergic activity of (±)-, (+)-, and (–)-2-dipropylamino-5-hydroxy-1,2,3,4-tetrahydronaphthalene. *J. Med. Chem.* 19:547–49
45. Tedesco, J. L., Seeman, P., McDermed, J. D. 1979. The conformation mine at its receptor: binding of droxy-2-aminotetralin enantiomers and positional isomers. *Mol. Pharmacol.* 16:369–81
46. Arvidsson, L.-E., Hacksell, U., Nilsson, J. L. G., Hjorth, S., Carlsson, A., Lindberg, P., Sanchez, D., Wikström, H. 1981. 8-Hydroxy-2-(di-*n*-propylamino)tetralin, a new centrally acting 5-hydroxytryptamine receptor agonist. *J. Med. Chem.* 24:921–23
47. Feenstra, M. G. P., Rollema, H., Dijkstra, D., Grol, C. J., Horn, A. S., Westerink, B. H. C. 1980. Effect of noncatecholic 2-aminotetralin derivatives on dopamine metabolism in the rat striatum. *Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol.* 313:213–19
48. Cannon, J. G., Koble, D. L., Long, J. P., Verimer, T. 1980. Derivatives of 5-hydroxy-6-methyl-2-aminotetralin. *J. Med. Chem.* 23:750–54
49. Verimer, T., Long, J. P., Bhatnagar, R. K., Koble, D. L., Cannon, J. G., Flynn, J. R., Goodale, D. B., Arneric, S. P. 1981. Dopamine receptor stimulating activity of 5-hydroxy-6-methyl-2-aminotetralin derivatives. *Arch. Int. Pharmacodyn. Ther.* 250:221–41
50. Hacksell, U. 1981. Agents stimulating central dopamine receptors. *Synthesis and structure-activity relationships.* PhD thesis. Univ. Uppsala, Uppsala, Sweden. 62 pp.
51. Cheng, H. C., Long, J. P., Van Orden, L. S., Cannon, J. G., O'Donnell, J. P. 1976. Dopaminergic activity of some apomorphine analogs. *Res. Commun. Chem. Pathol. Pharmacol.* 15:89–106
52. Cannon, J. G., Perez, J. A., Bhatnagar, R. K., Long, J. P., Sharabi, F. M. 1982. Conformationally restricted congeners of dopamine derived from 2-aminoindan. *J. Med. Chem.* In press
53. Hacksell, U., Arvidsson, L.-E., Svensson, U., Nilsson, J. L. G., Wikström, H., Lindberg, P., Sanchez, D., Hjorth, S., Carlsson, A., Paalzow, L. 1981. Monophenolic 2-(dipropylamino)indans and related compounds: central dopamine receptor stimulating activity. *J. Med. Chem.* 24:429–34
54. Rusterholz, D. B., Long, J. P., Flynn, J. R., Cannon, J. G., Lee, T., Pease, J. P., Clemens, J. A., Wong, D. T., Bymaster, F. P. 1979. Dopaminergic effects of nonhydroxylated rigid analogs of apomorphine. *Eur. J. Pharmacol.* 55:73–82
55. Sabelli, H. C., Borison, R. L., Diamond, B. I., Havdala, H. S., Narasimhachari, N. 1978. Phenethylamine and brain function. *Biochem. Pharmacol.* 27: 1707–11
56. McDermed, J. D., Miller, R. J. 1979. Antipsychotic agents and dopamine agonists. *Ann. Rep. Med. Chem.* 14: 12–21
57. Fuller, R. H., Clemens, J. A., Kornfeld, E. C., Snoddy, H. R., Smalstig, E. B., Bach, N. J. 1979. Effects of (8-β)-8-methylthiomethyl)-6-propylergoline on dopaminergic function and brain dopamine turnover in rats. *Life Sci.* 24: 375–78
58. Thorner, M. O., Flückiger, E., Calne, D. B. 1980. *Bromocriptine: A Clinical and Pharmacological Review,* pp. 56–123. New York: Raven. 181 pp.

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

59. Clemens, J. A., Smalstig, E. B., Schaar, C. J. 1975. Inhibition of prolactin secretion by lergotrile mesylate: mechanism of action. *Acta Endocrinol.* 79:230–37
60. Horowski, R., Wachtel, H. 1976. Direct dopaminergic action of lisuride hydrogen maleate, an ergot derivative, in mice. *Eur. J. Pharmacol.* 36:373–83
61. Calne, D. B., Leigh, P. N., Teychenne, P. F., Bamji, A. N., Greenacre, J. A. 1974. Treatment of Parkinsonism with bromocriptine. *Lancet* 2:1355–56
62. Lieberman, A. N., Leibowitz, M., Neophytides, A., Kupersmith, M., Mehl, S., Kleinberg, D., Serby, M., Goldstein, M. 1979. Pergolide and lisuride for Parkinson's disease. *Lancet* 2:1129–30
63. Lemberger, L., Crabtree, R. E. 1979. Pharmacological effects in man of a potent, long-acting dopamine receptor agonist. *Science* 205:1151–53
64. Goldstein, M., Lew, J. Y., Nakamura, S., Battista, A. F., Lieberman, A., Fuxe, K. 1978. Dopaminephilic properties of ergot alkaloids. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 37:2202–6
65. Bach, N. J., Kornfeld, E. C., Jones, N. D., Chaney, M. O., Dorman, D. E., Paschal, J. W., Clemens, J. A., Smalstig, E. B. 1980. Bicyclic and tricyclic ergoline partial structures. Rigid 3-(2-aminoethyl)pyrroles and 3- and 4-(2-aminoethyl) pyrazoles as dopamine agonists. *J. Med. Chem.* 23:481–91
66. Cannon, J. G., Demopoulos, B. J., Long, J. P., Flynn, J. R., Sharabi, F. M. 1981. Proposed dopaminergic pharmacophore of lergotrile, pergolide, and related ergot alkaloid derivatives. *J. Med. Chem.* 24:238–40
67. Cannon, J. G., Long, J. P., Demopoulos, B. J. 1982. Indole-derived fragments of ergot alkaloids as dopamine congeners. *Adv. Biosci.* 37:189–99
68. Wong, D. T., Bymaster, F. P. 1978. Interaction of ergot alkaloids with dopamine receptors in vitro. *Abstr. Joint Central-Great Lakes Reg. Meet. Am. Chem. Soc.*, Indianapolis, MEDI-25, p. 111
69. Nedelec, L., Guillaume, J., Oberlander, C., Euvrard, C., Labrie, F., Allais, A., Boissier, J. R. 1980. Synthesis and stimulant dopaminergic activity of 4-(piperidin-3-yl) and 4-(1,2,5,6-tetrahydro-3-pyridinyl)1*H*-indoles. *Abstr. 7th Int. Symp. Med. Chem.*, Torremolinos, Spain, p. P168
70. Cannon, J. G., Hatheway, G. J., Long, J. P., Sharabi, F. M. 1976. Centrally acting emetics. 10. Rigid dopamine congeners derived from octahydrobenzo(f)quinoline. *J. Med. Chem.* 19:987–93
71. Cannon, J. G., Suarez-Gutierrez, C., Lee, T., Long, J. P., Costall, B., Fortune, D. H., Naylor, R. J. 1979. Rigid congeners of dopamine based on octahydrobenzo(f)quinoline: peripheral and central effects. *J. Med. Chem.* 22: 341–47
72. Verimer, T., Long, J. P., Rusterholz, D. R., Flynn, J. R., Cannon, J. G., Lee, T. 1980. Dopaminergic activity of cis-trans isomers of benzhydro(f)quinoline analogs. *Eur. J. Pharmacol.* 64:271–77
73. Deleted in proof
74. Cannon, J. G., Beres, J. A., Lee, T., Long, J. P. 1981. Trans-N-alkyl-6,7-dihydroxyoctahydrobenzo(g)quinolines: apomorphine congeners lacking the nonoxygenated aromatic ring. *Med. Chem. Adv*, pp. 369–81. Oxford: Pergamon
75. Costall, B., Naylor, R. J., Cannon, J. G., Lee, T. 1977. Differential activation by some 2-aminotetralin derivatives of the receptor mechanism in the nucleus accumbens of rat which mediate hyperactivity and stereotyped biting. *Eur. J. Pharmacol.* 41:307–19
76. Costall, B., Naylor, R. J., Cannon, J. G., Lee, T. 1977. Differentiation of the dopamine mechanisms mediating stereotyped behaviour and hyperactivity in the nucleus accumbens and caudate-putamen. *J. Pharm. Pharmacol.* 29:337–42
77. Pendleton, R. G., Samler, L., Kaiser, C., Ridley, P. T. 1978. Studies on renal dopamine receptors with a new agonist. *Eur. J. Pharmacol.* 51:19–28
78. Stetler, P. E., Sarau, H. M., Zirkle, C. L., Saunders, H. L. 1978. The central effects of a novel dopamine agonist. *Eur. J. Pharmacol.* 50:419–30
79. Erhardt, P. W. 1980. Topographical model of the renal vascular dopamine receptor. *J. Pharm. Sci.* 69:1059–61
80. Weinstock, J., Wilson, J. W., Ladd, D. L., Brush, C. K., Pfeiffer, F. R. et al. 1980. Separation of potent central and renal dopamine agonist activity in substituted 6-chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepines. *J. Med. Chem.* 23:973–75
81. Pfeiffer, F. R., Wilson, J. W., Weinstock, J., Kuo, G. Y., Chambers, P. A., et al. 1982. Dopaminergic activity of substituted 6-chloro-l-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines. *J. Med. Chem.* 25:352–58
82. Hensiak, J. F., Cannon, J. G., Burkman, A. M. 1965. N-Allylnorapomorphine. *J. Med. Chem.* 8:557–59

Annu. Rev. Pharmacol. Toxicol. 1983.23:103-129. Downloaded from www.annualreviews.org by Central College on 12/12/11. For personal use only.

83. Braestrup, C., Scheel-Krüger, J. 1978. Methylphenidate-like effects of the new antidepressant drug nomifensine (HOE 984). *Eur. J. Pharmacol.* 38:305–12
84. McKillop, D., Bradford, H. F. 1981. Comparative effects of benztropine and nomifensine on dopamine uptake and release from striatal synaptosomes. *Biochem. Pharmacol.* 30:2753–58
85. Woodruff, G. N., Sumners, C. 1979. Structure-activity and conformat onal requirements for dopaminergic agonists; comparison of central and peripheral dopamine receptors. *Adv. Biosci.* 20:57–70
86. Poat, J. A., Woodruff, G. N., Watling, K. J. 1978. Direct effect of a nomifensine derivative on dopamine receptors. *J. Pharm. Pharmacol.* 30:495–97
87. Costall, B., Naylor, R. J. 1978. Studies on the dopamine agonist properties of 8-amino-2-methyl-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline, a derivative of nomifensine. *J. Pharm. Pharmacol.* 30:514–16
88. Hjorth, S., Carlsson, A., Wikström, H., Lindberg, P., Sanchez, D., et al. 1981. 3-PPP, a new centrally acting DA-receptor agonist with select vity for autoreceptors. *Life Sci.* 28:1225–38
89. Martin, G. E., Haubrich, D. R., Williams, M. 1981. Pharmacological profiles of the putative dopamine autoreceptor agonists 3-PPP and TL-99. *Eur. J. Pharmacol.* 76:15–23
90. Watling, K. J., Williams, M. 1982. Interaction of the putative dopamine autoreceptor agonists, 3-PPP and TL-99, with the dopamine-sensitive adenylate cyclase of carp retina. *Eur. J. Pharmacol.* 77:321–26
91. Hacksell, U., Arvidsson, L.-E., Svensson, U., Nilsson, J. L. G., Sanchez, D., Wikström, H., Lindberg, P., Hjorth, S., Carlsson, A. 1981. 3-Phenylpiperidines. Central dopamine-autoreceptor stimulating activity. *J. Med. Chem.* 24: 1475–82
92. Sprenger, W. K., Cannon, J. G., Barman, B. K., Burkman, A. M. 1969. Centrally acting emetics. III. Derivatives of β-naphthylamine. *J. Med. Chem.* 12:487–490
93. Komiskey, H. L., Bossart, J. F., Miller, D. D., Patil, P. N. 1978. Conformation of dopamine at the dopamine receptor. *Proc. Natl. Acad. Sci. USA* 75:2641–43
94. Borgman, R. J., Erhardt, P. W., Gorczynski, R. J., Anderson, W. G. 1978. (±)-(E)-3-(3,4-dihydroxyphenyl)cyclopropylamine hydrochloride (ASL-7003): a rigid analogue of dopamine. *J. Pharm. Pharmacol.* 30:193–94
95. Erhardt, P. W., Gorczynski, R. J., Anderson, W. G. 1979. Conformational analogues of dopamine. Synthesis and pharmacological act v ty of (E)- and (Z)-2-(3,4-dihydroxyphenyl) cyclopropylamine hydrochloride. *J. Med. Chem.* 22:907–11
96. Struyker-Boudier, H. A. J., Teppema, L., Cools, A. R., Van Rossum, J. M. 1975. (3,4-Dihydroxyphenylamino)-2-imidazoline (DPI): a new potent stimulant at dopamine receptors mediating neuronal inhibition. *J. Pharm. Pharmacol.* 27:882–83
97. Cools, A. R., Struyker-Boud er, H. A. J., Van Rossum, J. M. 1976. Dopamine receptors: selective agonists and antagonists of functionally distinct types within the feline brain. *Eur. J. Pharmacol.* 37:283–93
98. Schmidt, M., Imbs, J.-L., Schwartz, J. 1981. The vascular dopamine receptor. *J. Pharmacol.* 12:355–82
99. Law, S.-J., Morgan, J. M., Masten, L. W., Borne, R. F., Arana, G. W., et al. 1982. Rigid analogues of dopamine: synthesis and interaction of 6-exo- and 6-endo-(3',4'-dihydroxyphenyl)-2-azabicyclo (2.2.2)octanes with dopamine uptake sites and receptors. *J. Med. Chem.* 25:213–16
100. Costall, B., Lim, S. K., Naylor, R. J., Cannon, J. G. 1982. On the preferred rotameric conformation for dopamine agonist action: an illusory quest? *J. Pharm. Pharmacol.* 34:246–54
101. Cannon, J. G., Brubaker, A. N., Long, J. P., Flynn, J. R., Verimer, T., et al. 1981. 5,7-Dihydroxy-2-aminotetralin derivatives: synthesis and assessment of dopaminergic and adrenergic actions. *J. Med. Chem.* 24:149–53
102. Kaiser, C., Dandr dge, P. A., Garvey, E., Hahn, R. A., Sarau, H. M., et al. 1982. Absolute stereochemistry and dopaminergic activity of enantiomers of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine. *J. Med. Chem.* 25:697–703
103. Anderson, P. S., Baldwin, J. J., McClure, D. E., Lundell, G. F., Jones, J. H. 1982. A new class of D-heteroergolines: total synthesis and resolution of a 9-oxaergoline, 4,6,6a,8,9,10a-hexahydro-7-ethyl-7*H*-indolo(3,4-*gh*)(1,4)-benzoxazine. *J. Org. Chem.* 47:2184–87