Topographical Model of the Renal Vascular Dopamine Receptor

PAUL W. ERHARDT

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Abstract □ Based on review and examination of recent additions to dopaminergic structure–activity relationships, a topographical model of the renal vascular dopamine receptor is presented. The implications of this model for the design of new dopaminergic drug candidates are discussed briefly.

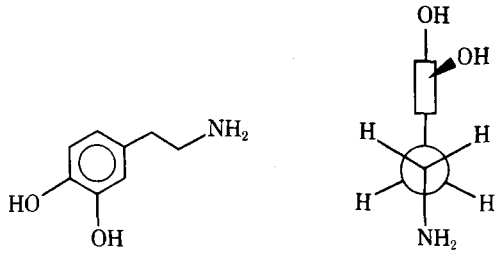
Keyphrases □ Dopamine—topographical model of renal vascular receptor □ Drug–receptor interactions—topographical model of renal vascular dopamine receptor □ Structure–activity relationships—dopaminergic drugs

Several reports (1–4) suggested that the preferred conformation for dopamine, when it is interacting with its biological receptor sites, resembles the fully extended *trans*-form (I). In this conformation, the catechol ring and amine function are in an antiperiplanar arrangement. Cannon and coworkers (5–7) suggested that a biologically significant conformer has the *m*-hydroxy group rotated toward the amine, as depicted in I. This arrangement has been designated as the α-rotamer, and the antiperiplanar conformation having the *m*-hydroxy group rotated away from the amine function has been designated as the β-rotamer (5). Both a dihedral angle approximating 180° (8, 9) and near coplanarity (5, 7) of the catechol ring and ethylamine system have been implicated as important structural features for dopaminergic activity.

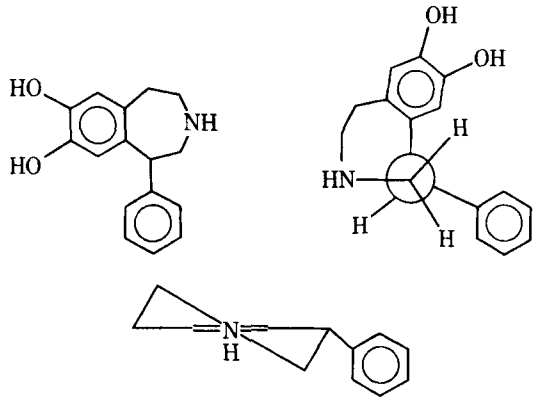
BACKGROUND

The benzazepine derivative II recently was reported to possess significant renal dopaminergic-mediated vasodilator properties[1] (10). In this molecule, the catechol and amine functions can exist only in *gauche* and eclipsed conformations, while the phenyl ring and amine system can assume a nearly antiperiplanar arrangement. Although there are examples of nonoxygenated 2-aminotetralins that show central dopaminergic activity (11, 12), there is no precedent for such systems having renal dopaminergic activity where an intact catechol function appears to be a requisite structural feature for agonist action. Therefore, the pharmacological profile for II seems to contradict the hypothesis that an antiperiplanar arrangement of the key pharmacophoric groups is important in determining dopaminergic activity. Alternatively, as shown in its side view, there is a partially eclipsed conformation for II in which the amine function lies within the plane established by the catechol ring.

Examination of various dopamine agonists reveals that aryl–amine coplanarity or very near coplanarity is a feature common to all of the agents, whereas the dihedral angle varies considerably. Even certain 2-



I



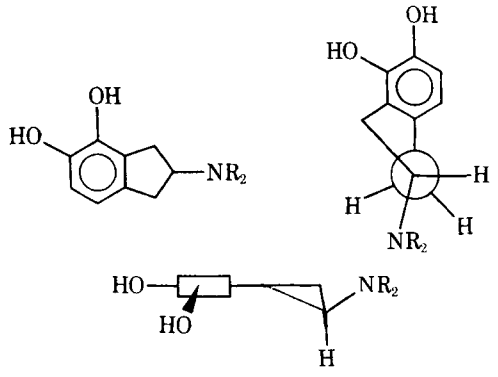
II

indanamine derivatives (III), previously regarded as an enigma (3, 5), possess aryl ring–amine coplanarity when assuming an envelope conformation (13).

In addition to coplanarity, structure–activity relationships indicate that specific nitrogen to hydroxyl group distances are optimal for interaction with certain dopaminergic receptor populations (5, 9, 14). Because of the noted differences in dopamine receptors (15–19), it is important to specify which receptor population is under consideration when addressing this structural parameter. Table I indicates the nitrogen to *p*-hydroxy and nitrogen to *m*-hydroxy distances and the renal dopaminergic activity for several dopamine analogs. In active compounds, the *m*- and *p*-hydroxy groups reside ~7–8 Å away from the amine function. Apomorphine, which has a somewhat shorter nitrogen to *m*-hydroxy group distance, is an exception. However, its pharmacological profile also is somewhat different; apomorphine is best classified as a weak, partial agonist in the renal dopaminergic system (16). Furthermore, its activity may be partially derived from additional binding contributions from its molecular portions outside of its apparent dopaminergic pharmacophore (17).

More interesting is the inactivity observed for isoapomorphine, which satisfies both coplanarity and amine–hydroxy group distance criteria. Two receptor models were proposed to account for this finding. Grol and Rollema (21) suggested that a receptor boundary is present which hampers interaction with molecules bearing bulky groups on the side of the molecule opposite the *m*-hydroxy group. Goldberg *et al.* (16, 17) also attributed isoapomorphine inactivity to a steric parameter and further emphasized an improper orientation of its amine free electron pair for preferred interaction with a stereospecific amine recognition site on the receptor.

Recent experiments in these laboratories provided additional insight into dopaminergic structure–activity relationships. The synthesis (24,



III

[1] Comparison between intravenous injection of II and injection of II directly into the renal artery (10) indicates that II itself is an active drug and not dependent on aromatic hydroxylation or any other metabolic process for its activation.

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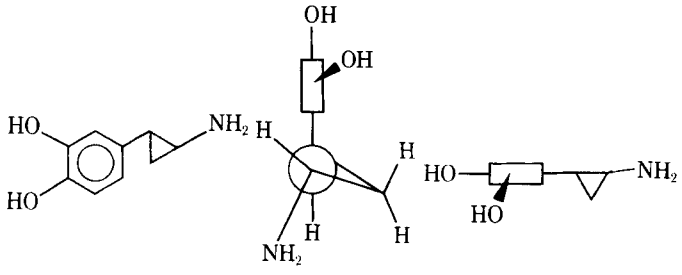
Table I—Amine-to-Hydroxy Group Distances [a] for Selected Dopamine Analogs [b]

Compound	Distance, Å		Renal Dopaminergic Activity
	Nitrogen to *p*-Hydroxy	Nitrogen to *m*-Hydroxy[c]	
Apomorphine	7.8	6.5	Partial agonist (16)
Isoapomorphine	7.8	7.3	Inactive (16, 17)
Tetrahydroisoquinolines[d]	6.0	6.4	Inactive (14)
II	7.0	7.0	Active (10)
Dopamine, antiperiplanar, β-rotamer	7.8	7.3	Active[e]
Dopamine, partially eclipsed[f]	7.0	7.0	Active [g]
2-Amino-6,7-dihydroxytetralin[h]	7.8	7.3	Active (14)
2-Amino-5,6-dihydroxytetralin[h]	7.8	6.5	Inactive (14)
IV	7.7	7.4	Inactive (23)

[a] Determinations agree with various literature values within ±0.1 Å (3–5, 20, 21). [b] All compounds can possess aryl ring–amine coplanarity or near coplanarity. [c] Analogous to the *meta*- and *para*-positions of dopamine. [d] 6,7-Dihydroxytetrahydroisoquinoline and *N*-methyl-6,7-dihydroxytetrahydroisoquinoline. Although the preferred conformations for these systems are such that the amine function resides above or below the plane of the aromatic ring (22), coplanarity of these groups is not thermodynamically precluded, especially when considering that drug–receptor associations may produce a net energetically favored situation. [e] The β-rotamer is thought (14) to be optimal for interaction with renal dopaminergic receptors. [f] Conformation superimposed on that depicted for II. [g] By analogy to II. [h] Determined with the nitrogen in a pseudo-equatorial orientation, as is thought to be the active conformer (6, 9).



IV

25) and pharmacological activity (23, 25, 26) of *E*- and *Z*-2-(3,4-dihydroxyphenyl)cyclopropylamines, two semirigid analogs of dopamine, were reported. Since the *E*-isomer (IV) is similar to conformer I in terms of aryl–amine coplanarity, its inactivity as a renal dopaminergic agonist or antagonist was surprising. However, the additional steric bulk resulting from incorporation of the methylene unit forming the cyclopropyl system resembles that present in α-methyldopamine, which also is inactive as a renal dopaminergic agonist (27). In α-methyldopamine and in IV, the bond between the β-carbon and the aryl ring is free to rotate such that both the α- and β-rotameric conformers are accessible. Furthermore, this rotation should proceed with minimal thermodynamic constraint; conformational considerations, therefore, seem an unlikely explanation for the inactivity of these compounds.

Alternatively, if one observes IV from the side as shown, it is apparent that the methylene unit protrudes perpendicularly out from the plane established by the aryl ring and amine function. This protrusion results in a molecular thickness of ~2 Å midway between the aromatic ring and the amine moiety. If a steric boundary were localized in a corresponding location above the receptor, then this protrusion would be expected to preclude effective receptor binding. The fact that this boundary must be localized specifically in this region is apparent from the activity observed for compounds such as apomorphine, 2-amino-6,7-dihydroxytetralin, and II, whose somewhat smaller but similar bulk in this region is directed toward the α- and β-carbons. Interestingly, Sheppard and Burghardt (28), employing Newman projections, also referred to a steric parameter localized specifically in the "9 o'clock position" to explain certain structure–activity relationships observed for aryl-substituted analogs derivatized in the 2-position.

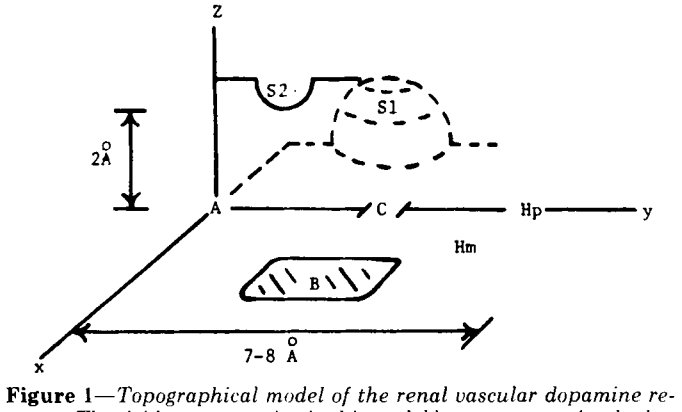


Figure 1—*Topographical model of the renal vascular dopamine receptor. The rigid representation in this model is not meant to imply that a more dynamic relationship, such as mutual molding, is not operative during drug–receptor interaction.*

THEORETICAL

Combining the structural parameters discussed affords a three-dimensional map (29) of the renal dopamine receptor that contains the following topographical features (Fig. 1):

1. A single plane containing amine (A) and catechol (Hm, Hp, and C) recognition sites.
2. A distance between the amine recognition site and *p*- (Hp) and *m*- (Hm) hydroxy group recognition sites of ~7–8 Å.
3. A steric parameter (S1) located to one side of the principal pharmacophoric recognition site. Depending on the α- or β-rotameric relationship, this parameter could limit the bulk on the side opposite to the *m*-hydroxy group of molecules attempting to align with the receptor properly (21). An additional hydrophobic binding region (B) located on the same side as the analogous *m*-hydroxy group also may be present in the plane established by A, C, Hp, and Hm (17).
4. A second steric parameter (S2) located ~2 Å above the plane of the receptor and localized specifically along the analogous α- and β-carbon chain region.

DISCUSSION

Although conceptual in nature, topographical mapping of receptors can be useful in the design of new drug entities. In this regard, the receptor model described here implies that new renal dopaminergic structural candidates should possess overall planarity and a somewhat narrow molecular thickness, especially in the analogous α- and β-carbon region. Concern about an appropriate dihedral angle or even about a classical two-carbon bridge between the amine and aromatic functions is not necessary as long as key nitrogen-to-catechol hydroxyl group distances are maintained. Furthermore, significant steric bulk opposite the position analogous to the dopamine *m*-hydroxy group should be avoided, while incorporation of hydrophobic character on the same side as the analogous *m*-hydroxy group could be beneficial for receptor binding.

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Thalifaurine and Dehydrodiscretine, New Quaternary Protoberberines from *Thalictrum fauriei*

CHUNG-HSIUNG CHEN ˣ, TZER-MING CHEN, and CHRISTINE LEE

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Abstract □ Two new quaternary protoberberines, thalifaurine and dehydrodiscretine, were isolated from the ethanolic extract of *Thalictrum fauriei* Hayata. Based on spectral analysis and correlation with compounds of known structure, thalifaurine was shown to be 3-hydroxy-2-methoxy-10,11-methylenedioxyberbinium chloride and dehydrodiscretine was established as 3-hydroxy-2,10,11-trimethoxyberbinium chloride. The structural assignment was confirmed by synthesis of both compounds. Magnoflorine also was isolated and identified.

Keyphrases □ Thalifaurine—new quaternary protoberberine isolated from *Thalictrum fauriei*, structural determination □ Dehydrodiscretine—new quaternary protoberberine isolated from *Thalictrum fauriei*, structural determination □ Protoberberines, quaternary—thalifaurine and dehydrodiscretine, isolation from *Thalictrum fauriei*, structural determination □ *Thalictrum fauriei*—isolation of thalifaurine and dehydrodiscretine and their structural determination

Thalictrum fauriei Hayata (Ranunculaceae) is a perennial herb that is distributed widely over the mountainous area of Taiwan, especially in wet places (1). In view of an increasing interest in the biological activity of some Thalictrum alkaloids (2), a study was initiated on the alkaloidal constituents of *T. fauriei*.

Previous reports from this laboratory described the isolation and characterization of three known aporphines, (+)-oconovine (Ia) (3), (+)-isocorydine (Ib) (3), and (+)-corydine[1] (Ic), from the tertiary base fraction. Continuing investigation of the quaternary base fraction has provided two new protoberberinium salts, thalifaurine (IIa) and dehydrodiscretine (IIb), in addition to the known aporphine magnoflorine (III). The isolation and structural characterization of these quaternary salts are described in this report.

[1] C.-H. Chen, T.-M. Chen, and C. Lee, unpublished data.

RESULTS AND DISCUSSION

The ethanolic extract of the whole plant material of *T. fauriei* was processed by the usual acid–base treatment and solvent partitioning to separate the quaternary alkaloid fraction from the tertiary base fraction. The quaternary salt was precipitated with Mayer reagent and then was exchanged by an anionic resin into the chloride form. Extensive fractionation of this chloride salt on silica gel columns yielded three crystalline compounds, designated as alkaloids Q-3, Q-4, and Q-6 according to their increasing polarity on TLC plates.

Alkaloid Q-4—Alkaloid Q-4 was isolated as the chloride salt, mp 258–260°, and was optically inactive. The UV spectrum appeared as a complicated pattern with absorption maxima at 241, 263, 291, and 341 nm and shoulders at 310 and 380 nm. This pattern was characteristic of quaternary protoberberine salts, and the shoulder at 310 nm suggested a 2,3,10,11-substituted pseudoprotoberberinium pattern (4). Bathochromic shifts in the presence of bases and the broad IR absorption bands at 3510 and 3326 cm^{-1} indicated the phenolic nature of Q-4. The NMR spectrum of Q-4 revealed one methoxy group at δ 4.02, one methylenedioxy group at δ 6.33, two triplets of two protons each at δ 3.17 and 4.74 (J = 6 Hz), and six aromatic protons at δ 6.87 (s, 1H), 7.51 (s, 2H), 7.64 (s, 1H), 8.59 (s, 1H), and 9.25 (s, 1H) ppm.

Simanek *et al.* (5) made a detailed analysis of the chemical shifts for each aromatic proton on various protoberberinium and pseudoprotoberberinium salts. The data for pseudopalmatinium (IIe) and pseudoepiberberinium (IIf) salts were taken from their report and compared with those of Q-4 (Table I); the data for Q-4 were consistent with the 2,3,10,11-substitution pattern. In the chemical-ionization mass spectrum of Q-4 with isobutane as the reagent gas, the molecular ion M^+ appeared at m/e 322 and base ion c appeared at m/e 320; both were highly abundant, which reflected the unusual stability of the parent ion under the chemical-ionization mode. Ion a at m/e 323 and ion b at m/e 337 represented the result from thermal disproportionation of the parent ion (M^+), a fact proven for berberine derivatives by Habermehl *et al.* (6). Ions d (m/e 177), e (m/e 178), and f (m/e 176) suggested the presence of hydroxy and methoxy groups on ring A. Ion g (m/e 148) served to locate the methylenedioxy group on ring D.

Two structures were compatible with the evidence: 3-hydroxy-2-methoxy-10,11-methylenedioxyberbinium chloride (IIa) and 2-hydroxy-3-methoxy-10,11-methylenedioxyberbinium chloride (IIc).

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