STEREOISOMERISM AND DRUG ACTION IN THE NERVOUS SYSTEM

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One of the principle goals of pharmacology is an adequate and acceptable description of molecular dynamics of the interactions of drugs with cells and tissues. There are two essential components to this description, the structure of the drug and the structure of the macromolecule with which the drug interacts. To be adequate, any description must be three-dimensional, and therefore there is no further need for emphasizing the steric aspects of the structure of the drug or the macromolecule. Certain generalizations can provide guidance into the three-dimensional study of drugs and their interactions with biochemical molecules which can be summarized by the following simple ideas (1); the first is that two molecules cannot be in the same place at the same time; the second is that unlike charges between two molecules attract and like charges repel; and the third states that chemical processes depend upon molecular contact ("molecular fit") between substances or functional groups that are interacting.

The stereochemical aspects of optical isomers are denoted by Fisher's nomenclature (D or L) [see Eliel (2)], sequence notation (R or S) of Cahn et al (3), and the sign notation (+ or −) wherever possible. In Fisher's nomenclature the symbols D and L relate to the configuration of a standard substance. When a series of compounds have the same configurational symbol, their projection formulae may be written in a certain specified way. If this series of compounds are interrelated by chemical transformation or common precursor (4), their pharmacological parameters can be compared with the pharmacological parameters of the series of compounds of opposite configuration. The configuration of the asymmetric moiety with the optimal pharmacological activity may be written by Fisher's projection formula. Fisher's nomenclature is useful when it is applied to compounds with one asymmetric carbon; difficulties arise when it is applied to compounds with more than one asymmetric carbon. The sequence notation (3) is based on the actual three-dimensional formula of the compound to be named; and therefore it is self-consistent for the molecule in question and cannot be used to relate a series of compounds. For example, L(−)-alanine and L(−)-cysteine are related configurationally and have the same absolute configuration. According to sequence notation L(−)-alanine has S-configuration while L(−)-cysteine has R-configuration. A series of compounds with the same

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configuration may have different rotations. Therefore, the sign of rotation is not useful to relate the configuration with the pharmacological activity.

Many authors have used (and are using) the term "stereospecificity" where "stereoselectivity" is used in this review. Stereospecificity means that one of the isomers of the drug is active, while the second isomer has negligible similar pharmacological activity. Stereoselectivity indicates semiquantitative and quantitative modulation, such as "highly stereoselective, weakly stereoselective" etc. With improved pharmacological methods using drugs of absolute isomeric purity, some of the highly stereoselective processes may turn out to be stereospecific processes.

STEREOSELECTIVE PROCESSES IN THE CHOLINERGIC NERVOUS SYSTEM

The concept of "molecular fit" indicates that there are many processes in the nervous system that may be stereoselective. A number of processes of the cholinergic nervous system are known, in which the interactions between a

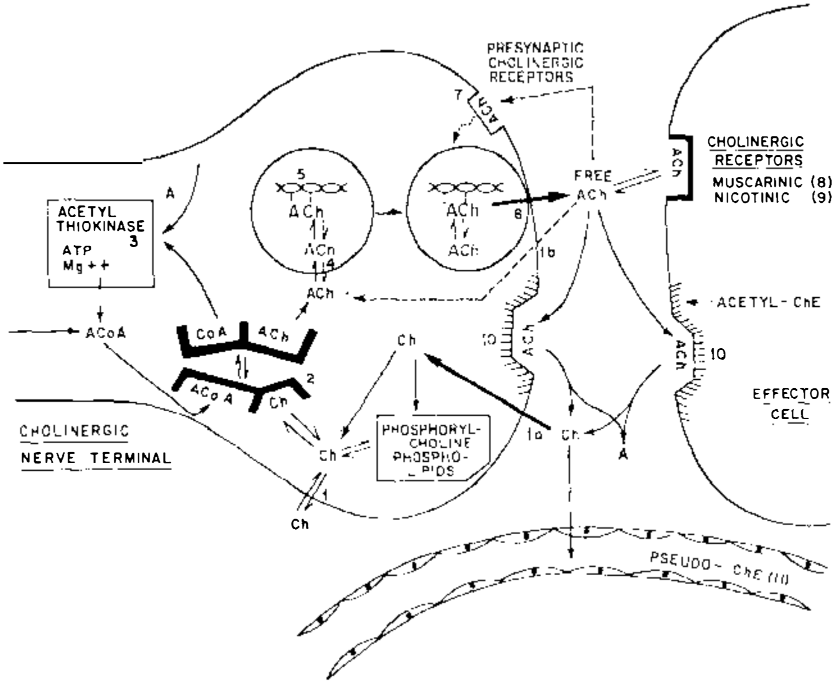

FIG. 1. Schematic drawing showing possible stereoselective sites in a typical cholinergic nerve terminal and the effector cell. Ch: Choline; ACoA: acetyl-coenzyme A; CoA = coenzyme A; ACh: acetylcholine; A: acetate; ChE: cholinesterase. For identification of sites 1–11, see text.

macromolecule (a receptor, a carrier, an enzyme) and acetylcholine (ACh) or choline are known to occur, indicating the importance of molecular fit in these situations. The above processes are related to (*a*) the synthesis, storage, release of the neurotransmitter, ACh, (*b*) interaction of ACh with cholinergic receptors, and (*c*) the termination of the action of ACh. The possible stereoselective sites in the various stages of cholinergic transmission are schematically represented in Fig. 1. The data, on which the above scheme is based, were obtained by a number of investigators using in vitro and in vivo experimental models under a variety of conditions. Not all of these processes are based on firm evidence and some are only tentative. However, this schematic representation provides an outline for the discussion of stereoselective sites in the cholinergic nervous system, and future investigations on the same subject.

STEREOSELECTIVE PROCESSES AT THE PRESYNAPTIC CELL OF THE CHOLINERGIC NERVOUS SYSTEM

There is less published information about the stereoselectivity of the processes in the presynaptic cell (or synaptosome; Fig. 1, sites 1–7) of the cholinergic nervous system than the stereoselectivity of the processes at the effector cell (Fig. 1, sites 8–11). Choline, a precursor for ACh synthesis, is taken up by synaptosomes by a saturable carrier system (Fig. 1; sites 1, 1a, and 1b). ACh competes with choline for this carrier system but has a lower affinity for it (5, 6). The stereoselectivity of this carrier system with respect to the analogs of choline or ACh has yet to be investigated.

ACh is synthesized from acetyl coenzyme-A (ACoA) and choline in the presence of choline acetyltransferase (ChA) (Fig. 1, site 2) possibly through a Theorell–Chance mechanism (7–9). ChA exhibits stereoselectivity towards the optical isomers of α-methylcholine and β-methylcholine (10) D(+)-α-methylchloline is a better substrate for ChA than L(−)-α-methylcholine. L(+)-β-methylcholine is not a substrate for ChA. D(+)-α-methylcholine is a better substrate than D(+)-β-methylcholine. The above observations indicate that the steric hindrance of the methyl group in the β-substituted compounds is probably greater than in the α-substituted compounds. It is of interest as to whether ChA exhibits stereoselectivity towards optical isomers of acyl-CoA with an asymmetric carbon in the acyl radical. Lactoyl-CoA is known to occur in mammalian tissues (11). In one study, impure acetylthiokinase (Fig. 1, site 3) was used to prepare CoA derivatives of D(−)- and L(+)-lactic acids which were directly coupled with choline in presence of ChA (12). In this study, formation of L(−)-lactoylcholine was significantly higher than D(+)-lactoylcholine. However, it is not known whether the lactoylation of CoA or choline or both will contribute for the above stereoselectivity.

There is less information on certain aspects of the organization of the cholinergic nerve terminal and certain processes in the cholinergic nervous system (Fig. 1, sites 4–7). The main site of ACh synthesis in synaptosomes is probably in the cytosol (6); it is probably not synthesized in vesicles but conveyed there by an uptake mechanism (Fig. 1, site 4) which has yet to be demonstrated in vitro. The vesicular ACh is in a bound form (Fig. 1, site 5) and does not detectably exchange, in vitro, with radioactive ACh under a variety of conditions (13). Stimulation increases the release of ACh (Fig. 1, site 6). It has been proposed that a fraction of the released-ACh stimulates the release of further quantities of ACh or acts as ACh-release amplication mechanism (Fig. 1, site 7) at certain cholinergic terminals (14, 15). Studies on the uptake, intravascular binding, and release of the asymmetric analogs of ACh by vesicles; and stimulation of the release of ACh by asymmetric analogs of ACh, may elucidate ACh-macromolecular interactions involved in the above presynaptic processes.

STEREOSELECTIVE PROCESSES AT THE POSTSYNAPTIC EFFECTOR CELL OF THE CHOLINERGIC NERVOUS SYSTEM

ACh that is released from the presynaptic nerve terminal stimulates muscarinic or nicotinic types of cholinergic receptors (Fig. 1, sites 8 and 9). Although ACh is optically inactive, it is possible that reactions of cholinergic receptors with either asymmetric agonists or antagonists are sensitive to differences in the respective configurations of such substances (16, 17). A number of investigators have studied the optical isomers of ACh analogs, in which one of the two carbon atoms of ethanolamine moiety or the carbon atom in the acetyl group was made asymmetric by proper chemical manipulation (18–22). Due to these studies the stereoselectivity exhibited by cholinergic receptors is a well recognized phenomenon. Previous surveys on the relationship between chemical structure and biological activity in these *Annual Reviews* (23) and a number of recent monographs (24–27) have treated this aspect of the subject in a comprehensive manner.

In the above studies with agonists, the pharmacological activities were expressed in terms of potencies or relative molar activities which are derivatives of their ED_{50}s. It has been well established in recent years, that ED_{50}s do not give exact measures of affinities (28), which are required to make valid conclusions on the drug-receptor interactions and the nature of receptor surfaces. Further, a question arises as to whether the differences in the potencies of a pair of stereoisomers are due to the differences in their affinities or to intrinsic efficacies. For these reasons, one should have the following information to make definite conclusions for delineating receptor surfaces using drug-receptor interactions: (*a*) the dissociation constant of agonists (K_A) and antagonists (K_B) that act at the same receptors, (*b*) the absolute configurations of the compounds, and (*c*) interrelationships between the configurations of agonists and antagonists acting at the same receptors.

Muscarinic receptors.—Very few studies have been reported about dissociation constants of optical isomers of agonists and antagonists at cholinergic receptors (Fig. 1, site 8). Available information on K_As of agonists and K_Bs of antagonists at cholinergic receptors and the configurational aspects of these agents are summarized in Table 1. D(+)- and L(−)-lactoylcholines are agonists at muscarinic receptors and there is no significant difference in their intrinsic efficacies (ε). The K_A of D(+)-lactoylcholine is lower than the K_A of the L(−)-isomer at

ABLE 1. Dissociation Constants and Intrinsic Efficacies of Cholinergic and Anticholinergic Agents[1]

Compound and Configuration	Biological Activity		
	Type of receptor (Test system)	Dissociation Constant (K_A or K_B)	Relative Intrinsic efficacy
Acetylcholine	Muscarinic (l.i.m.)	1.08×10^{-6}	1.00
	Nicotinic (or a.m.)	2.17×10^{-6}	1.00
D(+)R-Lactoylcholine	Muscarinic	7.3×10^{-5}	0.52
	Nicotinic	1.85×10^{-5}	1.07
L(−)S-Lactoylcholine	Muscarinic	3.02×10^{-4}	0.30
	Nicotinic	8.08×10^{-5}	1.15
D(−)R-Acetyl-β-methylcholine	Muscarinic	Inactive	—
L(+)S-Acetyl-β-methylcholine	Muscarinic (Active isomer)	1.24×10^{-6}	—
D(−)R-Mandeloylcholine	Muscarinic	3.00×10^{-6}	Not significant
L(+)S-Mandeloylcholine	Muscarinic	5.22×10^{-6}	Not significant
D(−)S-Tropinoylcholine	Muscarinic	2.15×10^{-8}	Not significant
L(+)R-Tropinoylcholine	Muscarinic	3.26×10^{-7}	Not significant
D(−)S-Hyoscyamine	Muscarinic	4.47×10^{-10}	Not significant
L(+)R-Hyoscyamine	Muscarinic	1.41×10^{-8}	Not significant

[1] Muscarinic activities are tested on the guinea pig longitudinal ileal muscle (l.i.m.) n all cases except acetyl-β-methylcholine, which is tested on the circular muscle from ndus of rabbit stomach. Nicotinic activities are tested on the frog rectus abdominis muscle (a.m.). The above data are quoted from references 29–35 and 41.

the muscarinic receptor; therefore D(+)-isomer has higher affinity to the muscarinic receptor than the L(−)-isomer (29, 30). Mandeloylcholines and tropinoylcholines are competitive antagonists of ACh and lactoylcholines at the muscarinic receptors (31–34). Among these antagonists, the D-isomer has higher affinity ($1/K_B$) than the corresponding L-isomer. The above antagonists exhibited insignificant intrinsic efficacies at the muscarinic receptors. The alpha carbon to the carbonyl-carbon of the ester group is asymmetric in agonists (lactoylcholines) and their competitive antagonists (mandeloylcholines and tropinoylcholines). These observations indicate that the D-isomers have the preferred configuration to bring it into definite spacial position with the muscarinic receptor. This conclusion is supported by the fact that D(−)-hyoscyamine has higher affinity to the muscarinic receptor than L(+)-hyoscyamine (35). Among the optical isomers of dimethylamino-2-cyclohexyl-2-hydroxy-2-phenylacetate, one of the isomers is about 100 times more active as an anticholinergic agent at the muscarinic receptor than the second isomer (36); and the configuration of the isomer with higher activity is related to the configuration of D(−)-hyoscyamine (37).

The muscarinic receptor contains at least two sites, an anionic site (site 1) and a site 2 separated by a distance of 3.2 ±0.2 Å (38, 39). The quaternary ammonium head and the negative charge of the ether oxygen atom of the ester bond in ACh interact with the anionic site and site 2 respectively. A third site (site 3) has been postulated for the interaction of the carbonyl-oxygen atom of ACh at the muscarinic receptor. However, interaction at two sites (the anionic site and site 2) is sufficient for a molecule of a quaternary ammonium compound, which binds strongly for proper alignment with the receptor. The acetoxy methyl group may also contribute for properalignment of the molecule with the receptor.

Among choline esters whose K_As at the muscarinic receptors are determined, ACh exhibits highest affinity and does seem to fit the muscarinic receptor optimally. The presence of other groups in ACh analogs does seem to interfere with the proper agonist-receptor interaction. The four mono-halogeno-acetylcholines (fluoro-, cholro-, bromo- and iodo-acetylcholines) have larger acyl groups than the acetyl group of ACh and exhibited lower affinities to the muscarinic receptor than ACh (39, 40). Similarly, propionylcholine, acryloylcholine, and both enantiomers of lactoylcholine have larger acyl groups than ACh, and lower affinities than ACh. All of these observations indicate the following: (*a*) the size of the acetyl group of ACh is optimum for proper fit at the muscarinic receptor and the acyl groups larger than the acetyl group induce steric hindrance for proper alignment of the agonist with the receptor; (*b*) there is an asymmetric site adjacent to site 2, which is complementary to the D-configuration. This asymmetric site is not essential for stimulation of the muscarinic receptor because both isomers of lactoylcholine have the same intrinsic efficacy which is lower than that of ACh.

The dissociation constants of the optical isomers of acetyl-β-methylcholine at the muscarinic receptors are not known. The affinity and intrinsic efficacy of the DL-isomer are about 70% of the corresponding parameters of ACh (41). Obviously, the differences between the DL-isomer and ACh are too close to make definite conclusions between agonist and receptor interaction. Therefore, it is necessary to determine K_A and ε values for each isomer separately in order to clarify the situation.

The introduction of a cyclic radical into the acyl group of ACh or a choline ester with cholinomimetic properties leads to a change in the pharmacological properties (17). Without lowering and even strengthening the affinity for the muscarinic receptor this change abolishes or blocks the action of the chemical transmitter, ACh. These anticholinergics exhibit competitive properties with

ACh at the muscarinic receptor. The cationic head and the cyclic radical interact with the anionic site and with a site adjacent to the site 2 of the muscarinic receptor. The cyclic radical interacts with the receptor by hydrophobic or van der Waals forces. This area adjacent to site 2 is stereoselective for the D-configuration of mandeloylcholine, tropinoylcholine, and hyoscyamine (31–34).

Preliminary investigations on *cis-trans* isomers of rigid and semirigid analogs of ACh and atropine, with or without asymmetric centers in their molecules, have been reported by a number of investigators (42–46). When K_A s (or K_Bs) and εs of these compounds at the muscarinic receptor become available, they will be useful tools for delineation of muscarinic receptors and for predicting the proper conformation of ACh to provide optimal fit to the muscarinic receptor.

Nicotinic receptors.—K_As and εs of only a limited number of choline esters at nicotinic receptors on the skeletal muscle (Fig. 1, site 9) have been determined (30). These studies have indicated some steric requirements for the interaction of agonists at the nicotinic receptors on the skeletal muscle. This type of nicotinic receptor contains at least two active sites, an anionic site and a site 2 separated by a distance of 4.85 ± 0.1 Å (47). The quaternary ammonium head and the negative charge of the carbonyl-oxygen of choline esters interact with the anionic site and the site 2 of nicotinic receptors. If no changes are made in the choline moiety, the binding of choline esters to the nicotinic receptors is related to the electron density of the carbonyl-oxygen (30, 40). The area adjacent to the site 2 of the nicotinic receptor can accommodate larger groups than the methyl of the acetoxy group of ACh. Iodoacetylcholine exhibited higher affinity than ACh to the nicotinic receptor (40). Among lactoylcholines, D(+)-lactoylcholine has about 4 times higher affinity at nicotinic receptors than the L(−)-isomer. As there is no difference in their relative intrinsic efficacies, the difference in their nicotinic potencies must be due to the difference in their affinities. Besides the carbonyl-oxygen atom, two other groups on the asymmetric carbon of lactoylcholines interact with an asymmetric site in the vicinity of the site 2 of nicotinic receptors (30). However, this asymmetric carbon is not essential for a nicotinic agent to exhibit high affinity. ACh exhibits high affinity to the nicotinic receptor but does not contain an asymmetric carbon.

A number of reviews have been published on the structure-activity relationships of ganglionic stimulants and blocking agents (48, 49) however, there is little information on the stereoselectivity of nicotinic receptors on ganglia. The ganglionic receptor exhibits stereo selectivity for the D-configuration of lactoylcholine (50). There is only a small dependence of gangliolytic activity upon stereochemical variation among some diastereoisometric dimethylaminobornyl acetates and their methiodides (51).

Stereoselectivity of cholinesterases.—The stereoselectivity exhibited by cholinesterases (Fig. 1, sites 10, 11) from different sources in their interactions with substrates and inhibitors is a well established phenomenon (52–54).

It is interesting to compare the stereochemical requirements of cholinergic receptors and cholinesterases (ChE). The asymmetric site adjacent to the esteratic site of acetyl-ChE (electric eel, bovine erythrocytes) has been shown to be stereoselective for the L-configuration of tropinoylcholine, while the muscarinic receptors are stereoselective for D-configuration of tropinoylcholine and mandeloylcholine (33, 34, 52, 53). Some investigators have considered pseudo-ChE as a model for nicotinic receptors (55). Therefore, it is interesting to compare the stereoselectivities of nicotinic receptors and ChE. Whereas pseudo-ChE is stereoselective for L-configuration, the nicotinic receptors are stereoselective for the D-configuration of lactoylcholine, tropinoylcholine, and mandeloylcholine (33, 34, 52, 53).

Conformations of ACh and related compounds.—The conformational analysis of ACh and related agonists has been discussed in a number of reviews (27, 56–58).

In the following discussion, the various atoms in the ACh molecule are indicated by the following nomenclature: ether-oxygen 01, carbonyl-oxygen 02, three carbon atoms in methyl groups attached to the nitrogen atom C1 C2 C3, α- and β- carbons in choline moiety C4 C5, carbonyl-carbon C6, carbon-atom in the methyl group of acetoxy radical C7, and quaternary nitrogen-atom N. The molecules of ACh and related compounds that are potent muscarinic type agonists have the following torsion angles (58): C5-C4-N-C3 ($\tau 1) = 180°$; 01-C5-C4N ($\tau 2) = +73°$ to $+137°$; C6-01-C5-C4 ($\tau 3) = 180 \pm 35°$; and C7-C6-01-C5 ($\tau 4$) =either 180° or $-137°$. They have the following interatomic distances: N^+-01 = 320; N^+-C6 = 450; and N^+-01 = 320; N^+-C6 = 450; and N^+-C7 = 540 pm. All known agonists stereospecific for the muscarinic receptor have $\tau 2$ positive in the range $+73°$ to $+137°$.

The crystal structures of potent nicotinic agonists, ACh, acetyl-α-methylcholine, lactoylcholine, 1, 1-dimethyl-4-phenylpiperazine (DMPP), and nicotine have been analyzed to determine the conformation of cholinergic agonists relevant to the nicotinic receptor (59). The torsion angles equivalent to the conformational parameters of ACh, 01-C5-C4-N, and C6-01-C5-C4 are fixed in DMPP and nicotine which give values approximately equal to those found in acetyl-α-methylcholine and lactoylcholine. The only conformation of ACh consistent with the observed structures of rigid molecules, DMPP, and nicotine is that shown by acetyl-α-methylcholine and lactoylcholine; and it has torsion angles 01 C5-C4-N = approximately 75° and C6-01-C5-C4 = approximately 180°.

The affinities ($1/K_A$) and εs at muscarinic and nicotinic receptors of the number of agonists used in the conformational analysis are not known. The correlation of potency with structure alone, neglecting affinity and ε may give misleading results. A molecule may have low affinity for a receptor site but a high ε [D(+) lactoylcholine at the nicotinic receptor] or the affinity may be high for a particular receptor but the measured ε may be negligible [D(−) tropinoylcholine and other competitive antagonists]. A low potency does not necessarily imply that it is not in a conformation for interaction with the receptor that will produce the desired response.

STEREOSELECTIVE PROCESSES IN THE ADRENERGIC NERVOUS SYSTEM

Adrenergic agents can serve as a prototype for studies on the relationships between configuration and pharmacological activity because the lead compound norepinephrine, is optically active. It is synthesized from another optically active compound, tyrosine. A number of intermediate steps are asymmetric, and are controlled by stereoselective processes. Several recent reviews contain discussions on the relationships between stereoselectivity and the pharmacological activity of catecholamines and related compounds (24, 60–63). This review is focussed on the stereoselective sites for the synthesis storage and release of norepinephrine (Fig. 2, sites 1–8); the stimulation of adrenergic receptors (Fig. 2, sites 10–11) and termination of the action of norepinephrine (Fig. 2, sites 8, 9, 10, 12).

The configuration of two natural catecholamines, norepinephrine and epinephrine, and a number of related compounds, has been established by chemical

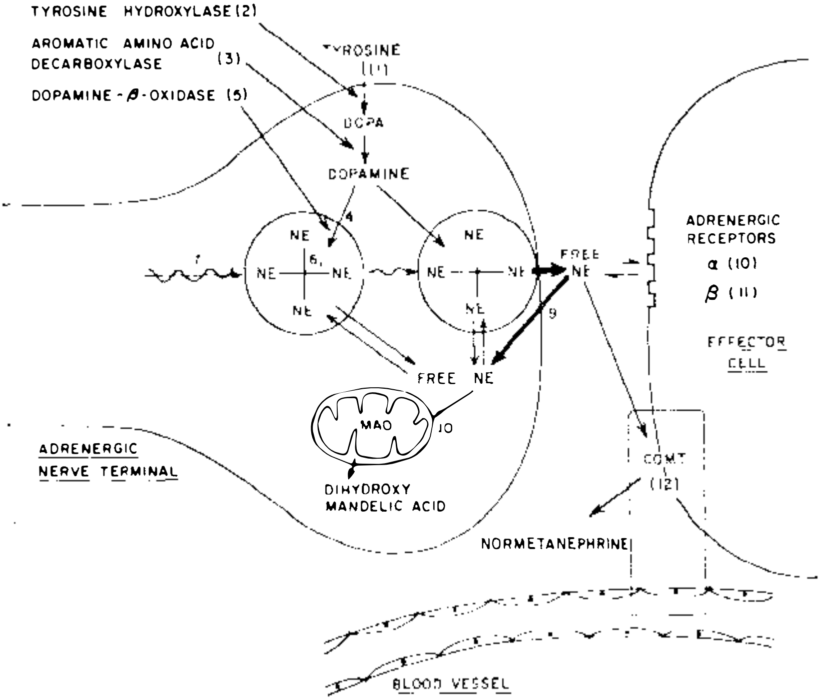

FIG. 2. Schematic drawing showing possible stereoselective sites in a typical adrenergic nerve terminal and the effector cell. NE: norepinephrine, MAO: Monoamine oxidase, COMT: Catechol O-methyltransferase. For identification of sites 1–12, see text.

interconversion not affecting bonds to the asymmetric carbon atom (64). According to these interconversions, the configurations of (−)-norepinephrine and (−)-synephrine are correlated via relays with D(−)-mandelic acid. On the basis of sequence rule (3) the above laevorotatory forms are R forms.

STEREOSELECTIVE PROCESSES AT THE PRESYNAPTIC CELL OF THE ADRENERGIC NERVOUS SYSTEM

At the adrenergic synapse, stereoselectivity has been reported for (*a*) various steps in the biosynthetic pathway of norepinephrine and epinephrine, (*b*) transport of norepinephrine and its analogs in the adrenergic neurone, (*c*) blockade of the uptake of norepinephrine and related compounds by the adrenergic neurone, (*d*) binding and retention of norepinephrine analogs by the granules and (*e*) monoamine oxidase. The stereochemical features necessary for the release of norepinephrine or false transmitters from the granules have yet to be investigated. For a complete survey on the stereoselectivity of the above processes, the review by Patil et al (63) should be consulted.

The biosynthetic pathway by which norepinephrine and epinephrine are formed has been studied extensively and a number of steps in this pathway are stereoselective (63). L(−)-Tyrosine is taken up by the nerve terminal (Fig. 2, site 1) from which D(−)-norepinephrine is synthesized. The conversion of L(−)-tyrosine to L(−)-dihydroxyphenylalanine (dopa) by tyrosine hydroxylase (Fig. 2, site 2) is highly stereospecific (65). D(+)-Tyrosine is a poor substrate of tyrosine hydroxylase. The conversion of L(−)-dopa to dopamine is brought about by aromatic L-amino acid decarboxylase (Fig. 2, site 3), which is stereospecific for the L-configuration of dopa (66). Aromatic L-amino acid decarboxylase does not decarboxylate D(+)-dopa. The conversion of D(+)-dopa to L(−)-dopa (and then to dopamine) takes place in vivo through the keto acid followed by transamination (67). Aromatic L-amino acid decarboxylase converts L(−)-α-methyl-dopa into L(+)-α-methyldopamine (68).

Dopamine does not contain an asymmetric carbon. It is converted into (−)-norepinephrine that has D-configuration by dopamine β-oxadase (69) (Fig. 2, site 5). Although its natural substrate is not asymmetric, dopamine β-hydroxylase exhibits stereoselectivity towards asymmetric substrates. Several studies have demonstrated that among substrates with α-methyl group, only one enantiomer is β-hydroxylated (63). The introduction of the hydroxyl group at the β-carbon is stereospecific, yielding compounds whose absolute configurations at the β-carbon are the same as D(−)-norepinephrine.

The uptake of norepinephrine (Fig. 2, site 9) and its analogs is a two-stage process: (*a*) uptake by neuronal membrane into the cytoplasm and (*b*) uptake by granules from the cytoplasm. A number of studies have been reviewed that suggest that both of these processes are stereoselective (63, 70–72). In most of these studies, it is difficult to dissociate the contribution of each one of the above processes to the final stereoselectivity exhibited by the optical isomers of norepinephrine and related compounds. In a number of these studies, it is difficult to distinguish between accumulation by adrenergic nerve endings and extraneuronal uptake. The uptake by adrenergic nerve granules has been shown to be stereoselective for the D-configuration of norepinephrine. The uptake system has about 6 to 9 times greater affinity for D(−)-norepinephrine than for L(+)-norepinephrine. D(−)isomers of norepinephrine and epinephrine exhibit stereoselectivity for the release of ^{3}H-norepinephrine (63). (−)-Isomers of metraminol, ephedrine, and norephedrine exhibit stereoselectivity for the uptake site of norepinephrine. The storage site (Fig. 2, site 6) shows stereoselectivity for D-configuration at the β-carbon of norepinephrine or false transmitters (63). Similarly, the release process is stereoselective for D(−)-configuration of the β-carbon of norepinephrine and related compounds.

STEREOSELECTIVE PROCESSES AT THE POSTSYNAPTIC EFFECTOR CELL OF THE ADRENERGIC NERVOUS SYSTEM

It is well established that α- and β-adrenergic receptors are stereoselective for the D-configuration of norepinephrine, and this information has been reviewed by a number of investigators. The dissociation constants and εs of D(−)-isomers of norepinephrine, epinephrine, and phenylephrine at α-adrenergic receptors have been reported (Table 2). All three compounds have the same intrinsic efficacy (73). Therefore differences in affinity for receptors are accounted for by their differences in potency.

The dissociation constants of L(+)-isomers of norepinephrine, epinephrine, and phenylphrine are not available in the literature. The potencies (pD_2) of L(+)-isomers are considerably lower than those of D(−)-isomers. The maximal effects (E_m) of L(+)-isomers are lower than those of D(−)-isomers on the

TABLE 2. Dissociation Constants, Intrinsic Efficacies and Potencies of α-adrenergic agents[1]

Agonists	K_A Moles/liter	ε	Normal		After reserpine	
			pD_2	Em	pD_2	Em
D(−)R-norepinephrine	1.8×10^{-7}	1.0	5.23	99	4.80	100
L(+)S-norepinephrine	—		4.51	107	4.08	78
D(−)R-epinephrine	1.7×10^{-7}	1.0	5.78	84	5.39	91
L(+)S-epinephrine	—		4.51	106	3.96	70
D(−)R-phenylephrine	7.9×10^{-7}	1.0	5.05	109	5.19	91
L(+)S-phenylephrine	—		4.16	84		7

[1] Dissociation constant (K_A) and intrinsic efficacy (ε) are measured on the isolated strips of rabbit aorta (73). Potencies ($pD_2 = -\log ED_{50}$, ED_{50} in moles/liter) and maximal effects (Em) with and without reserpine pretreatment are measured in the rat vas diferens (74).

reserpinized tissues. These observations suggest that L(+)-isomers have considerably lower affinities than those of D(−)-isomers. Therefore, α-adrenergic receptors are stereoselective for the D(−)-configuration of norepinephrine.

The dissociation constants of isopropylnorepinephrine and related compounds at β-adrenergic receptors are not available in the literature. For further information on the stereoselectivity exhibited by β-adrenergic agonists, and α and β adrenergic antagonists, the recent reviews should be consulted (24, 60–63).

Conformations of sympathomimetics and their antagonists.—Conformational factors of norepinephrine, epinephrine, and their antagonists have not been studied extensively. Gill (75) and Kier (76) have discussed probable conformations of epinephrine and ephedrine respectively. The problems of relating a specific conformation with its agonist-activity at the receptor were discussed in a previous section. Belleau's proposal that Dibenamine and related antagonists of norepinephrine adopt a phenylethylamine-like conformation at the receptor site has made possible a satisfactory analysis of structure activity relationships of α-adrenergic blocking agents (77).

STEREOCHEMICAL MODELS OF CHOLINERGIC AND ADRENERGIC RECEPTORS

A number of specific three-dimensional visualizations have been offered for cholinergic and adrenergic receptors. In the light of the established ACh-atropine antagonism, the lipoprotein nature of cell membranes, and the modern views on structural proteins, Kuznetsov & Golikov (78) have suggested that the active part of the muscarinic receptor in the cell membrane consists of two parallel protein chains linked by ionic and hydrogen bonds, and possibly Van der Waals' forces. The receptor proteins may undergo molecular perturbation during the interaction of ACh with the cholinergic receptor, and this change in the receptor protein may be prevented by a suitable blocking agent (79). Smythies (80, 81) sketched drug-receptor complexes based upon stereo-chemical relationships between ribonucleic acid and various agonists. Bloom (82) and Belleau (83) have discussed models of adrenergic receptors. There is yet no complete experimental data to support or refute the above models. Both quantitative measurements of structure and function requiring the use of the most incisive, modern physical techniques, determination of relevant pharmacological parameters, and creative model building will play a critical role in elucidating the molecular nature of drug-receptor complexes.

STEREOISOMERISM AND DRUGS ACTING IN THE CENTRAL NERVOUS SYSTEM

It is well known that drugs acting in the central nervous system are stereoselective for one of the enantiomers; this aspect of the subject has been discussed in a number of reviews (23–25). The recent publications with stereoisomers of analgetics (84–86), barbiturates (87, 88) and hallucinogens (89–91) support the earlier observations. However, definite conclusions are not possible until pharmacological techniques are developed to study the receptors in the central nervous system. Structure-activity relationships of centrally acting drugs and their analogs at receptors will become a fruitful area for investigation in the next decade.

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