Anticholinergic Agents Based on Ariens' Dual Receptor Site Theory

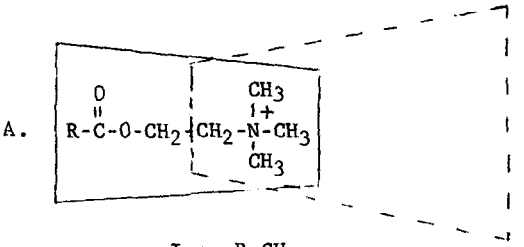
Sir:

Many drugs classed as competitive antagonists seem to bear a close structural resemblance to the corresponding agonist and are presumed to have an affinity for the same receptor. However, it is frequently observed that in many classes of drugs changes in structure of agonists and competitive antagonists do not result in a parallel change in activity. If affinity is the property altered by the structural modification, then classical receptor theory offers no explanation for this. Ariens has suggested that the receptor site for agonists and antagonists in such a case may not be identical (1-3). Thus, competitive antagonists are pictured as occupying a space that overlaps only a portion of the agonist site and gain affinity through attraction to a subsite not utilized by the agonist. This latter portion of the antagonist receptor is referred to as "additional receptor parts."

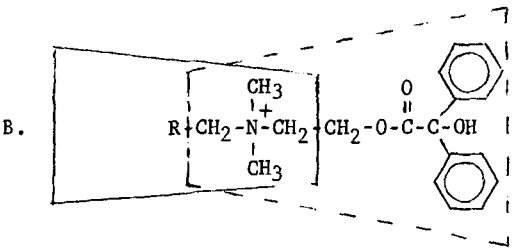
In the case of the cholinergic receptor at postganglionic parasympathetic synapses, an agonist should combine with a certain region of the receptor as shown in Fig. 1A for acetylcholine (Ia) or carbachol (Ib). Classical antagonists such as choline benzilate (IIa) or lachesine (2-dimethylaminoethyl benzilate ethobromide, IIb) are then assumed to combine with a portion of the agonist site and some additional receptor parts (which together make up the antagonist receptor) as shown in Fig. 1B.

The authors became interested in the possibility of preparing compounds such as 2-[(2-acetoxyethyl)methylamino]ethyl benzilate methobromide (IIIa) and 2-[(2-carbamyloxyethyl)-methylamino]ethyl benzilate methochloride (IIIb), which could combine with both the agonist and antagonist receptors as illustrated in Fig. 1C. These two compounds contain a cationic head attached to two chains—one resembling the potent agonists acetylcholine or carbachol and the other resembling the potent antagonist lachesine. If all portions of the molecule can bind to the appropriate portions of the receptor simultaneously, then these compounds should have a greater affinity and, therefore, be more active antagonists than compounds not containing an agonist moiety. The compounds IIIa and IIIb were prepared by alkylation of dimethylaminoethyl benzilate with bromoethyl acetate or chloroethyl carbamate. Compound IIIa has been prepared previously (4).

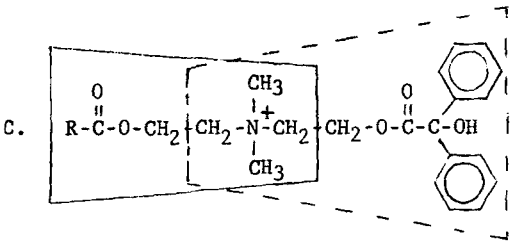
The drugs were evaluated by means of the pA_2 described originally by Schild (5). Segments of isolated ileum from guinea pig were suspended



I a, R=CH_3
b, R=NH_2



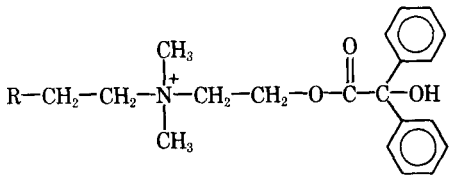
II a, R=H
b, R=CH_3



III a, R=CH_3
b, R=NH_2

Fig. 1—Possible relative position of drugs on the agonist site (solid lines) and antagonist site (dotted lines) of the cholinergic receptor.

TABLE I—AFFINITIES OF LACHESINE AND DERIVATIVES FOR CHOLINERGIC RECEPTORS IN GUINEA PIG ILEUM



Compd.	R	$pA_2 \pm$ S.E.[a] Agonist: Ia	Agonist: Ib
II b	H—	8.71 ± 0.07 (12)[b]	8.70 ± 0.04 (16)
III a	$CH_3-\overset{\overset{O}{\|\|}}{C}-O-$	7.96 ± 0.06 (10)	7.85 ± 0.05 (10)
III b	$H_2N-\overset{\overset{O}{\|\|}}{C}-O-$	7.19 ± 0.07 (8)	6.90 ± 0.10 (7)

[a] S.E. = standard error. [b] Number in parentheses indicates the number of segments of guinea pig ileum used for each determination.

in Tyrode's solution at 25° and aerated with 95% oxygen and 5% carbon dioxide. Tension development was measured by means of FT 0.03 force displacement transducers and recording made on a Grass model 5D polygraph.

Both acetylcholine and carbachol were used as agonists. Four or five dose-response curves were determined on each isolated tissue preparation, and a fresh segment was used for each agonist–antagonist combination. Increasing concentrations of antagonist produced a parallel shift to the right of the dose–response curves of the agonist and did not depress the maximum response. The compounds themselves did not initiate a response in any concentration. Thus, they do behave as true competitive antagonists. The compounds are highly specific for the cholinergic receptors as evidenced by the fact that they do not alter the response of the isolated ileum to potassium.

The compounds IIIa and IIIb were compared with the potent antagonist lachesine which differs only in that it lacks an acetoxy or carbamyloxy group. The pA_2 values were obtained by linear regression analysis according to the method of Steel and Torrie (6). The results are summarized in Table I. There was no significant difference between the pA_2 values obtained with acetylcholine and carbachol. However, differences between antagonists were significant. Lachesine, the model compound for this series, was significantly more effective than either of the derivatives. The addition of an acetoxy group on the ethyl moiety decreased the pA_2 nearly one log unit, and substitution of the carbamyloxy group in the same position further reduced the activity of the derivative.

Clearly the additional acetoxy or carbamyloxy groups attached to lachesine do not lead to the expected increase in affinity for the receptor. A report has appeared recently from Ariens' laboratory involving antihistamine agents based on the same type of agonist–antagonist double molecule (7). These also failed to show any augmented antagonist action.

The present results do not allow any conclusions concerning the general validity of Ariens' dual receptor site theory since several alternative explanations might be advanced for the lack of higher pA_2 values: (*a*) The lower affinity might be only apparent due to a lowered ability of the compounds to reach the site of action. (*b*) The various receptor parts may not be arranged in a linear fashion as depicted in Fig. 1. In such case, the nonbonded interactions within the molecule may hinder the drug from assuming a conformation in which all parts could combine with their respective subsites simultaneously. (*c*) Ariens' dual receptor site theory may not be applicable to the ester-type antagonist used in the present case. Other compounds employing additional cholinergic agonist–antagonist moiety combinations are being studied. Antiadrenergic agents based on a similar approach are also being investigated.

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JAMES F. STUBBINS
PATRICIA M. HUDGINS
JOHN ANDRAKO
ARCHIE J. BEEBE

Department of Chemistry and Pharmaceutical Chemistry
and Department of Pharmacology
Medical College of Virginia
Richmond, VA 23219

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Keyphrases

Anticholinergic agents
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Books

REVIEWS

Matrix Algebra for the Biological Sciences. By S. R. SEARLE. John Wiley & Sons, Inc., 605 Third Ave., New York, NY 10016, 1966. xii + 296 pp. 15 × 23 cm. Price $9.95.

With high school algebra as the only prerequisite, this book shows how to learn matrix algebra, emphasizing its use in biology and statistics. The author points out that his style is informal and that although proofs of the theory are given, they can be omitted if desired in using the text. The mathematical development is illustrated with numerous examples. Matrix algebra up to and including latent roots and vectors and its use in regression analysis are covered. Exercises are included in each chapter.

Staff review

Index Nominum 1966. Swiss Pharmaceutical Society, Zurich, Switzerland 1966. 838 pp. 19 × 25 cm. Price Sw. Fcs. 100.—(about $25.00).

This is the fifth, completely revised edition of the Index, and contains more than 11,000 entries. The Index presents—on an international basis—a completely cross-indexed alphabetical listing of drug entities, their synonyms, trade names (from various countries), and manufacturers. Also given under the main entry for a compound are the chemical and structural formulas and a brief mention of therapeutic use. Nonproprietary names are given and identified as to whether they are the International, British Approved, USAN, *etc.* The compendial status of the drugs in several countries is also given. Supplements keep the index current. Its international basis and comprehensiveness make it a most useful reference.

Staff review

Naming Organic Compounds. A Programmed Introduction to Organic Chemistry. By JAMES E. BANKS. W. B. Saunders Co., W. Washington Sq., Philadelphia, PA 19105, 1967. viii + 276 pp. 18 × 26 cm. Price $4.50. Paperbound.

An interesting approach to the study of organic nomenclature is this programmed instruction manual. It begins with the simplest of hydrocarbons and gradually takes the student through the various functional groups to the more complex organic molecules. The nomenclature information presented is similar to that in any basic organic chemistry text. However, it may be more fun to learn because of the programmed app oach—one reads a section, answers the questions, and proceeds to the next section—or if one answers incorrectly, goes back and reads the section again. The author has designed the book as self-instructional. Little descriptive chemistry is included and no knowledge of organic chemistry is assumed.

Staff review

NOTICES

Pharmaceutical Abstracts. Vol. VII, Issues No. 3 and 4. Edited by HENRY M. BURLAGE, The University of Texas, College of Pharmacy, Austin, TX 78712, 1966. 21 × 28 cm. Price: Issue No. 3, $3.50 No. 4, $4.55. Paperbound.

Pharmaceutical Abstracts. Vol. VIII, Issues No. 1 and 2. Edited by HENRY M. BURLAGE, The University of Texas, College of Pharmacy, Austin, TX 78712, 1967. 21 × 28 cm. Price: Issues No. 1 and 2, $6.00. Paperbound.

Oxidative Coupling of Phenols. Edited by W. I. TAYLOR and A. R. BATTERSBY. Marcel Dekker, Inc., 95 Madison Ave., New York, NY 10016, 1967. xiv + 387 pp. 15.5 × 23 cm. Price $28.50.

Myotatic, Kinesthetic and Vestibular Mechanisms. Ciba Foundation Symposium. Edited by A. V. S. DEREUCK and J. KNIGHT. Little, Brown and Co., 34 Beacon St., Boston, MA 02106, 1967. xi + 331 pp. 15.5 × 23.5 cm. Price $13.50.