Mescaline had no effect on the metabolism of pentobarbitone in mice. Although it also caused increases in accumulation of pentobarbitone in brain, plasma, liver and kidney, the pentobarbitone sleeping time in animals treated with mescaline was shortened. Furthermore, the barbitone sleeping time was unaffected. If the increase of concentration in the tissues of experimental animals was the result of an increase in binding of pentobarbitone by mescaline, a reduction of the "free" pentobarbitone for exerting hypnotic action could account for the resulting decrease of pentobarbitone sleeping time in mice.

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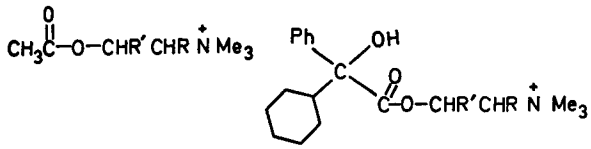
A comparison of the stereochemical requirements of cholinergic and anticholinergic drugs

None of the many theories which have been suggested to explain the observed behaviour of cholinergic and anticholinergic drugs at the muscarinic or postganglionic receptor account satisfactorily for all the experimental data (Goldstein, Aronow & Kalman, 1968). For example, it is difficult to explain why, although the dose-response curves for the antagonism of acetylcholine by atropine on the guinea-pig ileum are indicative of a competitive interaction (with both acetylcholine and atropine having at least one common point of attachment as a receptor site), the well known fact that the rate of washout of atropine from ileum is independent of the concentration of acetylcholine in the rinsing solution is not consistent with such a competitive interaction. There have been many attempts to explain this; for example, it has been suggested recently that the observed apparent competitive antagonism could result if the receptors were quite distinct, but that the presence of an antagonist at a site near to the cholinergic receptor could modify the cholinergic receptor in such a way that the affinity of the agonist for its receptor was reduced (Goldstein & others, 1968). In an attempt to assess whether or not cholinergic and anticholinergic drugs interact with a common receptor we have considered the structure-activity relations of a series of agonists and antagonists which are formally derived from acetylcholine.

Acetylcholine (I) may be converted into an anticholinergic drug by replacement of the acetyl group by a more bulky substituent such as 2-cyclohexyl-2-hydroxy-2-phenylacetyl (II) (Ellenbroek, Nivard & others, 1965). In such anticholinergic drugs the potency is critically dependent on the configuration of the benzylic carbon atom, the *R* enantiomer of II being 100 times as active as the *S* enantiomer (Table 1). Comparison of cholinergic esters of acetic acid and anticholinergic esters of *R*(−)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid may be made in the following manner.

1. Replacement of any of the *N*-methyl substituents in I by other alkyl groups reduces cholinergic activity whereas in II the nature of the *N*-substituents may vary over wide limits without appreciably reducing potency, and in some instances increase potency.



I R=R′=H II R=R′=H
III R=Me, R′=H IV R=Me, R′=H
V R=H, R′=Me VI R=H, R′=Me

Also in anticholinergic drugs the nitrogen may be tertiary or quaternary whereas only quaternary compounds are potent agonists (Abood, 1968).

2. Replacement of one of the α-protons in I with methyl to give acetyl α-methylcholine (III) causes a considerable reduction in muscarinic potency (although the nicotinic potency is little affected.) Also the muscarinic potency is dependent on the absolute configuration of the methyl substituted carbon, the *R* enantiomer of III being 8 times more active than the *S* isomer (Beckett, Harper & Clitherow, 1963). On the other hand, replacement of a α-proton in II with methyl to give IV enhances anticholinergic potency and activity no longer depends on the configuration of the methyl-substituted carbon atom (Table 1).

Table 1. *Affinity of stereoisomeric anticholinergic compounds*

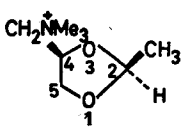
Compound (Configuration)	*log K**
II (*R*)	9·66 (10·4)†
II (*S*)	7·38 (8·4)
IV (*R*-acid, *S*-alcohol)	10·08
IV (*R*-acid, *R*-alcohol)	10·04
VI (*R*-acid, *S*-alcohol)	8·9
VI (*R*-acid, *R*-alcohol)	8·9

* log K values were determined by the method of Barlow, Scott & Stephenson (1963).
† Values in parentheses are pA_2 values recorded by Ellenbroek & others (1965).

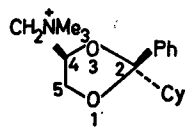
3. The *S* enantiomer of acetyl β-methylcholine (V) is equiactive with acetylcholine whereas the *R* enantiomer is much less active (Beckett & others, 1963). Substitution of the β-carbon of II with methyl to give VI affords a product which is less active than II and in which the absolute configuration of the β-substituted carbon is of little importance (Table 1).

4. Replacement of the alcoholic oxygen in acetylcholine with sulphur considerably reduces muscarinic potency but replacement of alcoholic oxygen by sulphur in anticholinergic compounds has little effect on anticholinergic potency (Barlow, 1964).

Thus, apart from the observation that the anticholinergic drugs discussed above are formally derived from acetylcholine by the replacement of acetyl by a bulky substituent,



VII



VIII

the stereochemical requirements for high cholinergic and high anticholinergic potency bear no other resemblance and make it unlikely that the two types of drugs share a common receptor. A similar conclusion may be reached from the observation that in the cholinergic 2-methyl-4-trimethylammoniummethyl-1,3-dioxolan iodides (VII) it is the configuration of C-4 on which cholinergic potency depends, whereas in the anticholinergic drugs derived from VII such as the 2-phenyl-2-cyclohexyl derivative VIII the configuration at C-4 is of little importance and anticholinergic potency depends only on the configuration at C-2 (Brimblecombe & Inch, 1970). However against these facts must be weighed the results that *R*(−)-quinuclin-3-yl acetate is a more potent agonist than its *S*-enantiomer (Robinson, Belleau & Cox, 1969; Belleau & Pauling, 1970) and *R*(−)-quinicludin-3-yl diphenylacetate is a much more potent antagonist than its *S*-enantiomer (Randall, Benson & Stefko, 1952).

If the idea that antagonists interact with a different receptor site to the agonist and merely alter the affinity of the agonist for the receptor is correct, it appeared to us to be unlikely that the affinity of all agonists would be altered to the same extent and thus using different agonists and the same antagonist, different affinity constants for that antagonist might be obtained. Using acetylcholine, carbachol, (*R*)-acetyl β-methylcholine and (*S*)-acetyl-β-methylcholine and oxotremorine the same value for the atropine affinity constant was obtained in experiments on guinea-pig ileum although with oxotremorine considerable changes in the rate of reactions on the ileum were apparent.

It appears therefore that anticholinergic drugs act at different receptors to the cholinergic drugs and do not allosterically modify the nature of the cholinergic receptor yet in many respects anticholinergic drugs appear to be competitive antagonists of cholinergic drugs (for example by causing a parallel shift in dose response curves). This seems to us to provide evidence for the view that there must be a large receptor reserve and that maximum biological response must be elicited by fractional receptor occupancy.

Moran & Triggle (1970) have reached a similar conclusion that the agonist and antagonist receptor sites are different but their experiments seem to indicate the absence of a receptor reserve.

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