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ANTAGONISM OF ACETYLCHOLINE BY (+)- AND (−)-HYOSCYAMINE

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Atropine is generally accepted as a competitive antagonist of acetylcholine (ACh) at cholinergic nerve endings. Quantitative investigation of the antagonism of ACh contractions of isolated guinea-pig ileum by atropine, however, indicated that the antagonism was non-competitive. This observation confirmed similar studies of ACh-atropine antagonism reported by Schild (1947). In a recent paper (Marshall, 1955) a compound was reported of which the (−)-isomer is a competitive and the (+)-isomer a non-competitive antagonist of histamine. It was thought that this might also apply to (+)- and (−)-hyoscyamine, antagonizing ACh, and that atropine, or (±)-hyoscyamine, might thus be predominantly non-competitive. The competition between these isomers and ACh has accordingly been investigated.

METHODS

Guinea-pig ileum was suspended in oxygenated Tyrode solution at 37° C. in an automatic organ bath of the type described by Boura, Mongar and Schild (1954). Determinations of pA_2 and pA_{10} against ACh contractions were made on samples of atropine and of (+)- and (−)-hyoscyamine by the method of Schild (1947). The nature of the antagonism was assessed as described by Marshall (1955).

RESULTS

Table I shows the pA values and type of antagonism of ACh by the three compounds examined.

The results show that, whereas ACh antagonism by atropine and (+)-hyoscyamine is non-competitive, that by (−)-hyoscyamine is competitive. The (−)-isomer has the most potent anti-ACh action, and the potency of the racemic compound, atropine, lies between those of the two optical isomers. These results agree with those previously reported for an optically active antihistamine compound (Marshall, 1955), and offer an explanation of the non-competitive antagonism found in atropine. Since atropine is a mixture of the two optical isomers—one competitive and the other non-competitive—its antagonism against ACh might be expected to mediate between the two types. In subsequent experiments using guinea-pig ileum in Tyrode solution containing sodium acetate instead of glucose, and with rat ileum in both glucose and acetate Tyrode, I have found atropine to be competitive, though the results were always on the border-line between the two types of antagonism.

TABLE I

ANTAGONISM OF ACh CONTRACTIONS OF GUINEA-PIG ILEUM

(ACh concentrations: 0·01, 0·02, 0·1 μg./ml.)

Antagonist	pA_2	pA_{10}	(pA_2-pA_{10})	Significance of Deviation from $(pA_2-pA_{10})=0·95$ (P=0·05)
Atropine ..	8·82	8·12		
	8·77	8·12		
	8·76	8·22		
	9·02	8·05		+(Non-competitive)
	8·89	8·10		
	8·76	8·06		
	Mean 8·84	Mean 8·11	0·73	
(+)-Hyoscyamine	7·79	7·39		
	7·95	7·12		
	7·76	7·12		
	7·97	7·08		+(Non-competitive)
	7·78	7·02		
	7·83	7·11		
	Mean 7·85	Mean 7·14	0·71	
(−)-Hyoscyamine	9·67	8·32		
	9·10	8·38		
	9·32	8·45		
	9·37	8·68		−(Competitive)
	9·45	8·67		
	9·20	8·43		
	9·36	8·44		
	Mean 9·35	Mean 8·48	0·87	

DISCUSSION

These observations offer a possible explanation of the variable results, with regard to type of

antagonism, obtained previously between histamine and four samples of promethazine (Marshall, 1955). Since all the samples were shown to be optically inactive, and therefore racemic mixtures, the (pA_2–pA_{10}) difference would be expected to lie on the border-line between competitive and non-competitive types of action. If it were shown that the resolved isomers of promethazine had different types of antagonism, this suggestion would be strongly supported by analogy with the foregoing results for atropine and its stereo-isomers.

Summary

1. Studies of ACh antagonism by hyoscyamine show that (−)-hyoscyamine is 30 times more potent than (+)-hyoscyamine, whereas the potency of the racemic compound, atropine, falls between the values for the stereo-isomers.

2. With atropine and (+)-hyoscyamine the antagonism is non-competitive, whereas antagonism by (−)-hyoscyamine is competitive.

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