Communications of the Editor

Chemicophamacological Studies on the Antispasmodic Action : Competitive and Non-competitive Acetylcholine Antagonism.

Recently, studies on the mode of action of atropine (Atr) and other synthetic antispasmodics have been reported.[1~3] All these studies have the same object as that of our research, but their consideration is confined to the Gaddum's equation (1).[4] From the equation (1) we derived equation (2) by an algebraic rearrangement.

$$e^{X_A} = K_A(1+e^{nX_B}/K_B)\,y/y'-y \quad \cdots\cdots (1)$$

$$e^{nX_B} = \frac{K_B(e^{X_A}+K_A)}{K_A} \cdot \frac{y''-y}{y} \quad \cdots\cdots (2\text{-}1)$$

$$y'' = \frac{e^{X_A} \cdot y'}{e^{X_A}+K_A} \quad \cdots\cdots (2\text{-}2)$$

X_A, X_B are log concentration of the active drug A, and of the antagonist B, y the response by X_A in the presence of X_B, y' the maximum response, and y'' is the response at X_A without the antagonist.

Non-competitive antagonism to active drug would be expressed by equation (3).

$$e^{mX_C} = K_C(y''-y)/y \quad \cdots\cdots (3\text{-}1)$$

$$y'' = y'e^{X_A}/e^{X_A}+K_A \quad \cdots\cdots (3\text{-}2)$$

where X_C is the log concetration of antagonist C and y'' the height of contraction by X_A without C. Both equations (2) and (3) are logistic sigmoids, from which reaction orders n and m can be estimated.

The experimental method was the same as reported before[5] using excised ileum of mice.

(1) Competitive antagonism between acetylcholine (ACh) and atropine (Atr) — A-action : The log concentration-action curves by ACh were obtained in a constant concentration of Atr. There was no depression of the maximum at each Atr level. The reaction order between ACh and receptor did not change significantly from 1. These results indicate the competitive nature of antagonism between ACh and Atr.

(2) The reaction order n of Atr with ACh-receptor—The estimate of n was not significantly different from 1.5 according to our results on the concentration-inhibition curve of Atr against a constant concentration of ACh (Fig. 1).

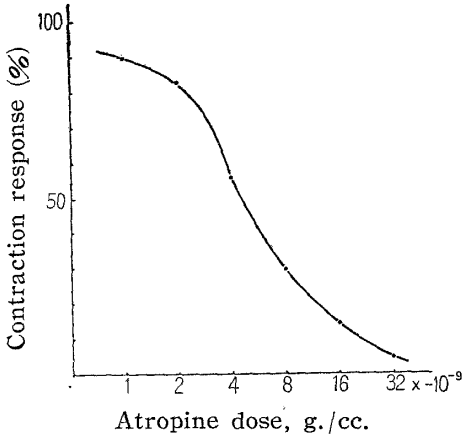

Fig. 1. Concentration-Inhibition Curve of ACh-Contraction (4×10^{-7} g./cc.) by Atropine

1) Marshall : Brit. J. Pharmacol., **10**, 354(1955).
2) Timms : *Ibid.*, **11**, 273(1956).
3) Chihara : Fol. Pharmacol. Japon., **52**, 141(1956).
4) Gaddum : J. Physiol., **89**. 7(1937).
5) K. Takagi, M. Kimura : This Bullutin, **4**, 444(1956).

(3) Non-competitive antagonism to ACh — P-action : Antagonism of papaverine to ACh is non-competitive. Synthetic antispasmodics usually have competitive and non-competitive activity, but if the effective concentration of A-action is close to that of P-action in one compound, the discrimination between them will be difficult. According to equation (2), effective concentrations exhibiting A-action shift to lower or higher levels of the antagonist, corresponding to ACh doses. On the other hand, effective concentration of P-activity, being indifferent to X_A levels, can be estimated without consideration of A-action, when higher concentration of ACh is used. If lower concentrations of ACh are applied, the A-action can be separated from P-action, although responses may become smaller. In this way we were able to reveal definitely an A-action in papaverine that had been partially recognized by Chihara[3] (Fig. 2).

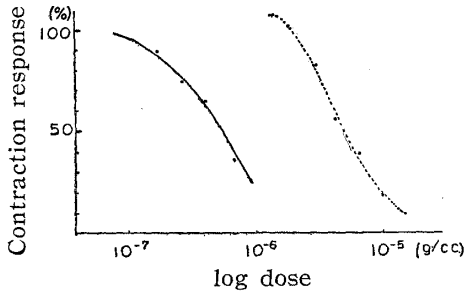

Fig. 2. Competitive and Non-competitive Inhibition by Papaverine Hydrochloride against ACh-Contraction in Excised Ileum of Mice

Dotted line : Non-competitive inhibition of the contraction induced by ACh, 1.1×10^{-4}g./cc.
Solid line : Competitive inhibition at ACh, 10^{-7} g./cc. The contraction height elicited by each ACh level is adopted as the 100% response.

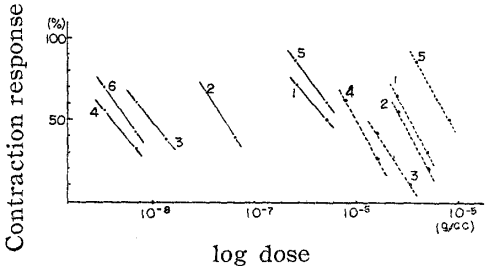

Fig. 3. Competitive and Non-competitive Inhibition by Several Antispasmodics against Ach-contraction in Excised Ileum of Mice

Solid lines : Inhibition curves at ACh, 4×10^{-8} g./cc.
Dotted lines : Inhibition curves at ACh 1.1×10^{-4} g./cc. The contraction height elicited by each ACh level is adopted as the 100% response.

1 : Papaverine hydrochloride
2 : Avacan (Isoamyl β-dimethylaminoethylaminophenylacetate hydrochloride)
3 : Aspaminol (1,1-Diphenyl-3-piperidinobutanol hydrochloride)
4 : Benactyzine(Diethylaminoethyl benzilate hydrochloride)
5 : Dihydroneupaverine (1-Piperonyl-3-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline)
6 : Atropine sulfate

All the compounds used by us have a common $n=1.5$ as A-action and m is 2.2 in the case of P-action (Fig. 3).

The papaverine-like potencies thus obtained are shown in Table I. The discrepancies from the usual potency ratios estimated by antagonism to $BaCl_2$ were comparatively small.

Table I. Comparison of Non-competitive Antiacetylcholine Activity with Anti-Barium Activity by Mouse Ileum

	(1)	(2)	(3)	(4)	(5)
Non-competitive anti-Ach activity	1.00	1.17	2.35	3.20	0.24
Anti-barium activity	1.00	1.00	1.48	1.50	0.25

(4) The pA method, proposed by Schild[6] can be applied only when the antagonism is competitive and when the reaction orders of the two compounds are both 1. In the case of ACh-Atr antagonism it was proved that reaction order of Ach was 1 and n of Atr was 1.5. If n is 1.5, the theoretical value of pA_2-pA_{10} must be $(\log 9)/1.5=0.636$, which agrees fairly well with that obtained experimentally by Timms[2] or by Marshall[1].

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6) Schild : Brit. J. Pharmacol., **2**, 189(1947).