BETA-ADRENERGIC BLOCKER, 2-(2-HYDROXY-3-TERT-BUTYLAMINOPROPOXY) CHLOROBENZENE
HYDROCHLORIDE (D-69-12)

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The concept of two adrenergic receptor mechanisms or α - and β -adrenergic receptor systems, originally proposed by Ahlquist (1) was based on orders of potency of a series of catecholamines. Since dichloroisoprenaline (DCI) was introduced as a new category of drugs that selectively blocked the response due to β -adrenergic activation, several β -adrenergic blockers were found. In this paper 2-(2-hydroxy-3-tert-butylaminopropoxy) chlorobenzene hydrochloride (D-69-12) has been found to be a potent β -adrenergic blocker. However, D-69-12 in very high concentrations relaxed the smooth muscle preparations. So mode of action of D-69-12 was examined. Furthermore, the dual action of D-69-12 on the smooth muscle preparations has been discussed in this paper.

MATERIALS AND METHODS

A piece of the taenia caecum (or taenia coli), atrium and tracheal muscle (2) from the male guinea pig, weighing 350 to 400 g were suspended in a 30 ml organ bath. The responses of the taenia caecum and tracheal muscle to drugs were recorded through an isotonic lever. The movement of the atrium was isometrically recorded through a mechano-electrical transducer (RCA-5734). Locke Ringer solution gassed with a mixture of 95% O₂ and 5% CO₂ and kept at 32°C was used as a bath fluid. Locke Ringer solution used contained 9.0 g of NaCl, 0.4 g of KCl, 0.2 g of CaCl₂, 0.2 g of MgCl₂, 0.5 g of NaHCO₃ and 0.5 g of glucose in a litre. In experiments with the isolated atrium, tension increased by isoprenaline was used as a response (3). The competitive antagonistic activities of drugs were expressed as the pA₂ values, which were calculated from the parallel shift of the concentration action curve of isoprenaline (4, 5). The results in this paper were presented as means of at least 7 experiments.

Drugs used: butyltrimethylammonium bromide (BuTMA), 1-isoprenaline hydrochloride, papaverine hydrochloride, dibenamine hydrochloride, propranolol hydrochloride, dichloroisoprenaline (DCI) and 2-(2-hydroxy-3-tert-butylaminopropoxy) chlorobenzene hydrochloride (D-69-12) whose chemical structure is shown in Fig. 1.

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RESULTS

1. β -adrenergic blocking activity of D-69-12

All the concentration action curves of l-isoprenaline tested on the taenia caecum, tracheal muscle and atrium were parallelly shifted towards its higher concentrations by D-69-12, indicating a competitive antagonism between l-isoprenaline and D-69-12. The pA_2 values (mean $\pm$ s.d.) of D-69-12 and propranolol were 7.7 ± 0.1 and 7.3 ± 0.2 on the tracheal muscle, 7.4 ± 0.2 and 7.2 ± 0.2 on the taenia caecum, and 7.3 ± 0.2 and 7.3 ± 0.2 on the atrium.

2. Inhibitory action of D-69-12 on the taenia caecum and tracheal muscle

The tracheal muscle was relaxed by D-69-12 (10^{-4} to 10^{-3} g/ml), as shown in Fig.

FIG. 1. Inhibitory action of D-69-12 on the tracheal muscle from the guinea pig in the presence and absence of propranolol (10^{-6} g/ml).

Note that inhibitory action of D-69-12 is unaffected by propranolol.

FIG. 2. Effects of dibenamine and propranolol on the relaxations of the guinea pig taenia caecum produced by l-isoprenaline, DCI and D-69-12.

—: in the presence of dibenamine 10^{-6} g/ml and propranolol 10^{-6} g/ml.

1. D-69-12 (10^{-6} to 10^{-5} g/ml) also relaxed the taenia caecum. The maximum relaxation produced by D-69-12 was the same as that by 1-isoprenaline. However, these relaxations of the both smooth muscle preparations were unaffected by 10^{-6} g/ml of propranolol, which was enough concentration to block the action of 1-isoprenaline (Fig. 1). Furthermore, relaxations of the taenia caecum produced by DCI and D-69-12 were little affected by pretreatment with dibenamine 10^{-8} g/ml and propranolol 10^{-6} g/ml (Fig. 2). D-69-12 in the concentrations of 10^{-5} g/ml or more depressed the maximum height of the concentration action curve of BuTMA, an acetylcholine-like drug. This phenomenon is similar to antagonism between BuTMA and papaverine.

DISCUSSION

The adrenergic blocking potency ratio of D-69-12 relative to propranolol is one or more in the organ preparations used. D-69-12 in very high concentrations relaxed the smooth muscles. It is known that some β -adrenergic blockers in their high concentrations relax the smooth muscles. Takagi and Takayanagi (3) have presented the evidence that relaxation of the smooth muscle preparations produced by DCI is due to its papaverine like action. It is indicated in this paper that D-69-12 as well as DCI has the dual action and the relaxation of the smooth muscle by D-69-12 is unaffected by the adrenergic blockers. Furthermore, D-69-12 as well as papaverine non-competitively inhibited the concentration action curve of BuTMA, an acetylcholine-like drug. These facts indicate the possibility that the inhibitory action of D-69-12 is due to its papaverine-like action.

It is considered as one of explanations of the dual action that D-69-12, being in the racemic forms, conceivably consists of a mixture with the two opposite actions residing in two optical isomers. Therefore, a concentration action curve of a mixture of an agonist and its antagonist is theoretically analysed. If the agonist A and its antagonist B compete for the same receptor, the concentration action curve of the agonist A in the presence of the antagonist B is given by Gaddum's equation (1).

$$\frac{y}{y'} = \frac{\frac{[A]}{K_A}}{1 + \frac{[A]}{K_A} + \frac{[B]}{K_B}} \quad (1)$$

Where [A] and [B] represent the concentrations of the agonist A and its antagonist B in the equilibrium with their receptors. K_A , K_B , y and y' indicate the dissociation constants of A and of B, the response to [A] and the maximum response. A concentration action curve of a equivalent mixture of the agonist A and its antagonist B is given by equation (1), where $[A]=[B]$. Equation (1) in this case indicates that the smaller K_B is, the smaller the maximum of the concentration action curve of the equivalent mixture is. A concentration action curve of the equivalent mixture in the presence of a certain concentration $[B_1]$ of the antagonist B is given by equation (2).

$$\frac{y}{y'} = \frac{\frac{[A]}{K_A}}{1 + \frac{[A]}{K_A} + \frac{[B+B_i]}{K_B}} \quad (2)$$

Where $[A]=[B]$.

The concentration action curve of the agonist A ($K_A=10^{-8}$) is parallelly shifted towards its 10 times higher concentration by 10^{-7} of the competitive antagonist B ($K_B=10^{-8}$), as shown in Fig. 3. The maximum of the concentration action curve of the equivalent mixture of the agonist A ($K_A=10^{-8}$) and its antagonist B ($K_B=10^{-8}$) is 50% of that produced by the agonist A. The parallel shift of the concentration action curve of the equivalent mixture by 10^{-7} of the antagonist B is practically same as that of the curve of the agonist A by the same concentration of B, as shown in Fig. 3.

FIG. 3. Theoretical concentration action curves of an agonist A ($K_A=10^{-8}$) and of an equivalent mixture of the agonist A and its competitive antagonist B ($K_B=10^{-8}$) in the presence and absence of a constant concentration (10^{-7}) of B.

A=agonist A alone, B=agonist A with B (10^{-7}), C=equivalent mixture, D=equivalent mixture plus B (10^{-7}).

One of two optical isomers of D-69-12 is assumed to be an agonist and another a competitive antagonist. But the maximum relaxation of the smooth muscles produced by D-69-12 is the same as that by 1-isoprenaline. The inhibitory action of D-69-12 is unaffected by propranolol. These phenomena are quite different from the results of the theoretical consideration on the mode of action of the equivalent mixture of the agonist and its competitive antagonist.

It is given as a conclusion that the inhibitory action of D-69-12 on the smooth muscle preparations is due to its non-specific action or papaverine-like action.

SUMMARY

Beta-adrenergic blocking potency ratio of D-69-12 relative to propranol is one or more. D-69-12 in very high concentrations relaxed the smooth muscle preparations. This inhibitory action seems to be due to its papaverine-like action.

REFERENCES

- 1) AHLQUIST, R.P.: *Am. J. Physiol.* **153**, 586 (1948)
- 2) TAKAGI, K. AND TAKAYANAGI, I.: *Chem. Pharm. Bull.* **6**, 716 (1958)
- 3) TAKAGI, K. AND TAKAYANAGI, I.: *Jap. J. Pharmac.* **20**, 92 (1970)
- 4) VAN ROSSUM, J.M.: *Archs int. Pharmacodyn. Thér.* **143**, 299 (1963)
- 5) TAKAYANAGI, I.: *Pharmacometrics* **2**, 131 (1968) (*in Japanese*)