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ANTIBRADYKININ AND ANTIHISTAMINIC ACTIONS OF HALOPERIDOL, CHLORPOMAZINE AND TRIFLUOPERAZINE-II: THEIR INEFFECTIVENESS ON THE BRONCHOCONSTRICTOR ACTION OF BRADYKININ IN THE IN VIVO GUINEA - PIG LUNG IN CONTRAST WITH HISTAMIN

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SUMMARY:

It is known that haloperidol, chlorpromazine and trifluoperazine posses antibradykinin effects. In addition, it has been previously shown the antihistaminic actions of chlorpromazine and trifluoperazine. This study was carried out for further characterization of the mentioned pharmacologic effects. In the present study it is observed that chlorpromazine and trifluoperazine but not haloperidol are able to inhibit the bronchoconstrictor responses to histamine in the guinea-pig lung. These inhibitions were competitive in nature. In contrast to histamine, it was determined that none of these compounds exers antagonistic action on the bradykinin-induced bronchoconstriction. Under the light of the results obtained in this study, it is supposed that chlorpromazine and trifluoperazine, in the therapeutic doses, have considerable antihistaminic actions possibly through H_1-receptors. Conversely, these compounds were found to be ineffective on the brochocontriction elicited by bradykinin.

HALOPERİDOL, KLORPROMAZİN VE TRİFLUOPERAZİN'İN ANTİBRADİKİNİN VE ANTİHİSTAMİNİK ETKİLERİ-II: İNVİVO KOBAY AKCİĞERİNDE HİSTAMİNİNKİNİN AKSİNE BRADİKİNİNİN BRONKOKONSTRÜKTÖR TESİRİNE ETSİSİZLİKLERİ

ÖZET:

Haloperidol, Klorpromazin ve trifluperazin'in antibradikinin etkilerinin varlığı bilinmektedir. Buna ilaveten klorpromazin ve trifluoperazinin antihistaminik etkileri daha önce gösterilmişti. Bu çalışma, bu etkilerin daha detaylı incelenmesi için yapılmıştır. Bu çalışmada haloperidol'un değil ama klorpromazin ve trifluoperazinin kobay akciğerinde histamin'in bronkokonstrüktör etkisini inhibe etme yetenekleri olduğu gözlenmiştir. Doğal olarak bu inhibisyon kompetitiftir.

Bu maddelerin hiçbiri histamine karşı çalışıldığında, bradikinin indüklediği bronkokonstrüksiyona antogonist etki yapmazlar. Bu çalışmanın sonuçlarına göre klorpromazin ve trifluoperazin tedavi edici dozlarda, muhtemelen H_1 reseptörleri üzerinden dikkate değer antihistaminik etki göstermektedirler. Tersine bu bileşiklerin bradikininin oluşturduğu bronkokonstrüksiyonda etkisiz olduğu bulunmuştur.

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INTRODUCTION

Bradykinin and histamine influence mammalian lungs both in vivo and in vitro inducing powerful bronchoconstrictor responses. The histamine-induced bronchoconstriction is specifically inhibited by H_1-antagonists(1). But, there is no specific antagonist for the bradykinin-induced brochoconstriction, even though some investigators have been making considerable endeavor to find out a clinically useful antibradykinin agent(2,3,4). On the other hand, some aspirinlike analgesic-antipyretic agents are able to inhibit this bronchoconstriction, non-specifically(5,6, 7).

Haloperidol, chlorpromazine and trifluoperazine which are used in treatment in pychosis have been reported to exert antibradykinin actions on various preparations(8,9.10,11). Confirmatively, we examined the effects of these compounds on the isolated guinea-pig ileum in a previous study observing their antibradykinin and antihistaminic actions having been concluded as a conseguenee of cal inhibition in a dose-dependent manner(12). In the present study, we aimed to investigate possible interactions of haloperidol, chlorpromazine and trifluoperazine with bradykinin and histamine on the guinea-pig lungs in vivo. In this way it is likely to obtain some information on the spectrum of the antibradykinin and antihistaminic actions of these antipsychotic agents.

METHODS

Guinea-Pig Lungs In Vivo

Resistance of inflation of guinea-pig lungs in vivo was measured in a manner consistent with the method described by (13) and modified(7).

Instead of the piston recorder, a bronchospasm transducer (Ugo Basile, No. 7020) was used. Male and female guinea-pigs weighing 250 to 450 g were anaesthetized using 1.0 to 1.25 g/kg urethane i.p. Further urethan was given intraperitonally when necessary to maintain supression of spontaneous respiratory movements. The trachea was immediately cannulated and inflated by a Palmer respiration pump (5 to 10 ml stroke volume, generally at 72 strokes per minute). The cannula was connected to the bronchospasm transducer by means of a side arm. The side arm permitted some air to escape through a water valve in the transducer, offering a resistence of 10 cm water. The changes due to bronchoconstriction were recorded on a recording microdynamometer (Ugo Basile, No. 7050) connected to the bronchospasm transducer.

The experiments were started 30 minutes after setting up, meanwhile 1.0 to 2.0 ml saline was given to substitute fluid loss. After this period, dose-response relationships were obtained before and after the administration of antagonists, in which two different doses of bradykinin and histamine were used. The antagonists were haloperidol, chlorpromazine and trifluoperazine. The bronchoconstrictor actions of bradykinin and histamine were evaluated using at least two individual dose-response procedures in all experiments.

Fresh solutions of bradykinin and histamine in saline (0.1 to 0.2 ml) were injested at 15 minutes intervals through a cannula in the external jugular vein and washed in with 0.4 ml saline containing 10 units/ml heparin.

Analysis of Data

All values reported are the mean of the individual experiment. The dose-response relationships performed before and after administration of the antagonists were evaluated by the help of linear regression analysis. When indicated, significance of differences between the mean values were estimated by Student t-test(14).

Drugs Used

Bradykinin triacetate (Sigma), Chlorpromazine hydrochloride (Eczacıbaşı),

Haloperidol hydrochloride (Janssen), Heparine (Luquemine®, Roche), Histamine diphosphate (Sigma), Trifluoperazine hydrochloride (SKF) and Urethane (Schering). All dilutions were prepared with fresh saline.

RESULTS

Haloperidol, in a dose range of 0.10 to 4.00 mg/kg, caused no significant alteration on the bronchoconstrictions elicited by bradykinin and histamine in the guinea-pig luns. Chlorpromazine and trifluoperazine were also ineffective on the bronchoconstrictor responses to bradykinin confirming a previous study(15). Conversely, it has been reported that chlorpromazine inhibits bradykinin-induced bronchoconstriction(11). In the present study it was, however, observed that chlorpromazine and trifluoperazine inhibit the histamine-induced bronchoconstriction. According to regression analysis it was determined as a competitive inhibition (Figure 1).

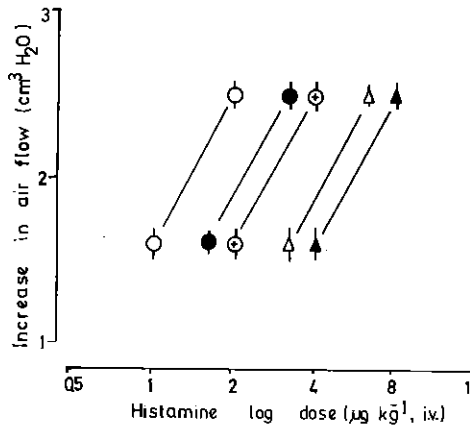

Figure 1 Inhibition of histamin-induced bronchoconstriction by chlorpromazine and trifluoperazine in the guinea-pig. (○) histamine control (n:19), in the presence of trifluoperazine (▲) 0.1 mg/kg (n:5), (△) 1.0 mg/kg (n:5), in the presence of chlorpromazine (⊕) 0.5 mg/kg (n:5), (●) 5.0 mg/kg (n:5).

DISCUSSION

It has been proposed that raised resistance of the lungs to inflation after bradykinin is due to constriction of bronchiols. By the way, bradykinin action on the Konzett-Rössler's preparation has been found to be different from those of acetylcholine, histamine, serotonin, substance P and angiotensin in that aspirin-like analgesic-antipyretic agents antagonize it(5,6,7). Furthermore, it has been reported that the slope of dose-response curve of bradykinin on this preparation is flatter and maximum response is lower than that for histamine(16,17).

Further evidences on the differences between bradykinin and some other bronchospastic agents such as serotonin and histamine have been obtained in the previous studies. First, vitamin K_1 and K_3 have been shown to inhibit the bradykinin-induced bronchoconstriction and to potentiate the histamine-induced bronchoconstriction in the guinea-pig(18,19). Second, it has been demonstrated that the bronchoconstrictor responses to histamine bradykinin and serotonin in the guinea-pig lungs were inhibited by captopril (SQ 14225) which is a well-known angiotensin converting enzyme inhibitor. Since the inhibition percentage of bradykinin has been found less than those of serotonin and histamine, it has been concluded that the bronchospastic action of bradykinin is different from these agents in terms of its mechanism(20).

Confirmatively, our results showed that bradykinin bronchoconstriction occurs with a different mechanism regarding to histamine. Seeing that haloperidol, chlorpromazine and trifluoperazine failed to inhibit the bradykinin-induced broncho-

constriction in contrast with that of histamine, it might be suggested that the bradykinin-induced bronchoconstriction is not due to histamine release and histamine-like action on the guinea-pig lungs. Apart from this, it is concluded that haloperidol, chlorpromazine and trifluoperazine possess only non-specific antibradykinin actions depending on the biological properties of the tissues.

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