Droperidol inhibits tracheal contraction induced by serotonin, histamine or carbachol in guinea pigs

Tetsumi Sato MD,*† Kazuyoshi Hirota MD,‡
Akitomo Matsuki MD,‡ Elemer K. Zsigmond MD,*
Sara F. Rabito MD†

Purpose: Droperidol (D) is effective in the treatment of patients with status asthmaticus. It has been reported that D inhibits the bronchoconstriction induced by serotonin (5-HT) but not that by histamine (H) or acetylcholine. However, haloperidol, another butyrophenone, is known to interact with and inhibit calmodulin, an intracellular Ca^{++} -binding protein which is important in the contraction of smooth muscles. The present study was designed to investigate the effects of D on tracheal contractions induced by 5-HT, H or carbachol (C) and to determine the contribution of α -adrenoceptors to the relaxant effect of D in vitro.

Methods: Tracheas of female guinea pigs were cut spirally into strips and mounted in water-jacketed organ baths in Tyrode's solution, aerated with a mixture of 95% O_2 and 5% CO_2 at 37°C. The changes in isometric tension induced by each spasmogen in the strips were measured with a transducer and a polygraph.

Results: We found that D inhibited the tracheal contractions induced by 5-HT, H or C in a concentration-dependent manner. At 1.25×10^{-6} M D blocked the effect of 10^{-4} M 5-HT by

$44.1 \pm 4.3\%$ and at 2.5×10^{-6} M by $63.8 \pm 3.8\%$. Similarly, at 5.0×10^{-6} M concentration, D blocked the effect of 10^{-5} M H by $27.7 \pm 5.3\%$ and at 10^{-5} M by $56.2 \pm 2.6\%$. Furthermore, 5×10^{-6} M of D reduced the contractions produced by 10^{-7} M C by $37.1 \pm 3.0\%$ and 10^{-5} M of D by $76.1 \pm 3.2\%$. The inhibiting effect of D was strongest on contractions induced by 5-HT. Prazosin (10^{-6} M) affected neither 5-HT-induced contractions nor the inhibition by D.

Conclusion: Our data indicate that D partially blocks the contractile responses not only to 5-HT, an effect which would be mediated through a blockade of the 5-HT receptors, but also to H or C, probably through inhibition of calmodulin. Our data support previous reports indicating that droperidol may be an important therapeutic agent in the treatment of patients with hyperreactive airways.

Objectif: Le droperidol (D) constitue un traitement efficace du status asthmaticus. On a rapporté que D inhibait la bronchoconstriction induite par la sérotonine (5-HT) mais pas celle de l'histamine (H) ou de l'acétylcholine. Cependant on reconnaît que l'halopéridol, une autre butyrophénone, réagit avec la calmoduline et inhibe son action; la calmoduline, une protéine de liaison du Ca^{++} intracellulaire, est importante pour la contraction des muscles lisses. La présente étude vise à étudier les effets de D sur les contractions trachéales induites par 5-HT, H ou le Carbachol (C) et de déterminer la contribution des récepteurs α -adrénergiques sur l'effet relaxant de D in vitro.

Méthode: Des trachées de cobayes femelles ont été découpées en spirales et montées au bain-marie dans une solution de tyrode, aérées avec un mélange de 95% d' O_2 et de 5% de CO_2 à 37°C. Les changements de tension isométrique induits par chacun des spasmogènes sur les spirales ont été mesurés à l'aide d'un transducteur et d'un polygraphe.

Résultats: Les auteurs ont trouvé que D inhibait les contractions induites par 5-HT, H et C proportionnellement aux concentrations. A $1,25 \times 10^{-6}$ M, D bloquait l'effet de 10^{-4} M de 5-HT par $44 \pm 4,3$ et à $2,5 \times 10^{-6}$ par $63,8 \pm 3,8\%$. De la même façon, à $5,0 \times 10^{-6}$ M, D bloquait l'effet de 10^{-5} M H

Key words

ANAESTHETICS, INTRAVENOUS: droperidol;

SMOOTH MUSCLE: tracheal;

DRUGS: carbachol, histamine, serotonin.

From the Departments of Anesthesiology, University of Illinois College of Medicine at Chicago*, and Cook County Hospital†, Chicago, IL 60612, USA, and University of Hirosaki School of Medicine‡, Hirosaki, 036 Japan.

Address correspondence to: Dr. Sara F. Rabito, Department of Anesthesiology and Pain Management, Cook County Hospital, Durand Building, Room #427, 637 South Wood St., Chicago, Illinois 60612, USA.

Phone: (312) 633-7425. Fax: (312) 572-3822.

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par $27,7 \pm 5,3\%$ et à 10^{-5} par $56,2 \pm 2,6\%$. De plus, 5×10^{-6} M de D diminuait les contractions induites par 10^{-7} M de C par $37,1 \pm 3,1\%$ et 10^{-5} M de D par $76,1 \pm 3,2\%$. L'effet inhibiteur de D était à son plus fort sur les contractions induites par 5-HT. La prazosine (10^{-6} M) n'avait d'effet ni sur les contractions induites par 5-HT ni sur leur inhibition par D.

Conclusion: Ces données montrent que D inhibe partiellement les réponses contractiles non seulement au 5-HT, effet d'une médiation probable du bloc des récepteurs 5-HT, mais aussi à H et à C, vraisemblablement par inhibition de la calmoduline. Ces données confirment les études antérieures qui rapportent que le droperidol pourrait être un agent thérapeutique important contre l'hyperréactivité des voies aériennes.

Certain surgical manipulations or procedures associated with the administration of anaesthesia such as tracheal intubation can trigger bronchospasm in patients with hyperreactive airways. Since airway constriction can be a life-threatening event, particularly in the asthmatic patient, the choice of a safe anaesthetic and/or sedative is of paramount importance when caring for these patients.

Bronchial hyperresponsiveness and asthma have become recognized as inflammatory diseases.^{1,2} Histamine, serotonin (5-HT), neuropeptides, prostaglandins and leukotrienes are inflammatory mediators with potent bronchoconstrictor actions which play an important role in the pathogenesis of these diseases.^{2,3} Furthermore, acetylcholine and neuropeptides released from nerve terminals of the parasympathetic nervous system, also cause a variety of symptoms in asthmatic patients.⁴⁻⁷

Droperidol is a neuroleptic agent widely used to produce neuroleptanaesthesia and to prevent/treat emesis in many clinical situations. Prezant and Aldrich⁷ reported two patients with status asthmaticus unresponsive to conventional therapy, whose condition improved after receiving droperidol. Gentil *et al.*⁸ and Takeda *et al.*⁹ showed that droperidol prevented the bronchospasm induced by 5-HT, but not that induced by histamine or acetylcholine.⁹ In their studies, bronchoconstriction was evaluated by measuring airway conductance, an indirect method to estimate airway calibre which is not considered to be reliable.¹⁰ However, Otomo *et al.*¹¹ reported that droperidol is also effective in reversing the bronchoconstriction induced by histamine in dogs. These authors utilized an ultrafine fibroscope to evaluate directly the calibre of the airway.

Haloperidol, another butyrophenone derivative, can interact with the activity of calmodulin, an intracellular

receptor of Ca^{++} that plays an important role in the contraction of smooth muscles.¹²

The present study was designed to investigate the spasmolytic effects of droperidol on tracheal contractions induced by 5-HT, histamine or carbachol, because these mediators can cause airway constriction in patients with bronchial asthma. We also investigated whether the non-specific α -receptor blocking effect of droperidol might be involved in its mechanism of action on airway smooth muscle.

Methods

Preparation of guinea pig tracheal strips

This study was approved by our Institutional Animal Care and Use Committee. Female guinea pigs weighing 250–400 g were sacrificed with an overdose of sodium pentobarbital (Nembutal®, 75 mg · kg⁻¹, *ip*). The cervical trachea was removed, isolated free from surrounding connective tissues, and cut spirally into two strips of 3 mm width and 15 mm length. All dissecting procedures after removing the trachea were performed in ice-cold Tyrode's solution aerated through with a mixture of 95% O₂/5% CO₂. The composition of Tyrode's solution was (mM): NaCl 138, KCl 2.7, NaH₂PO₄ 1.05, MgCl₂ 1.05, glucose 5.5, NaHCO₃ 5.5, and CaCl₂ 1.8. The tracheal strip was mounted in a 10 ml organ bath filled with Tyrode's solution aerated through with a mixture of 95% O₂/5% CO₂ at 37°C. Each tracheal strip was fixed with two small clips, one attached to a force displacement transducer (FT 03, Grass Instruments Co, Quincy, MA), connected to a polygraph (Model 79D, Grass Instruments Co, Quincy, MA). Each strip was subjected to a load of 2 g for at least two hours before the beginning of each experiment. After each experimental step, the strip was washed ten times with Tyrode's solution. At the end of each washing procedure, each strip was subjected to a load of 2 g and left unstimulated for 20 min to recover the initial basal tone. Each drug was added to the bath in a volume of 100 µl. Drug concentrations are expressed as the final concentrations in the bath.

Effect of droperidol on 5-HT-induced tracheal contractions

After the equilibration phase, tracheal contractions were induced with 10^{-4} M 5-HT. Strips where peak responses varied by more than 10% were excluded from the study. Eight strips were studied in this set. Because the contractions induced by 5-HT are short-lasting, the effect of droperidol was evaluated by adding droperidol before 5-HT. The protocol used was as follows:

- 1 10^{-4} M 5-HT several times until reproducible contractions were obtained.
- 2 0.05% ethanol followed by 10^{-4} M 5-HT with a five minute interval.
- 3 1.25×10^{-6} M droperidol dissolved in ethanol followed by 10^{-4} M 5-HT with a five minute interval.
- 4 10^{-4} M 5-HT.
- 5 0.1% ethanol followed by 10^{-4} M 5-HT with a five minute interval.
- 6 2.5×10^{-6} M droperidol followed by 10^{-4} M 5-HT with a five minute interval.

The peak tension developed five to ten minutes after the addition of 5-HT to the bath. If the force of contraction in step 4 was <90% of that in step 1, the strip was excluded from the experiment. The mean of the maximal tensions developed in step 1 was taken as the control 100%, the maximal tensions obtained in step 2 and 3 were then compared with the one obtained in step 1. Likewise, the mean of the maximal tensions developed in step 4 was taken as 100%. The values from step 5 and 6 were compared to the one in step 4.

Effects of droperidol on histamine- or carbachol-induced tracheal contractions

Ten tracheal strips were studied with histamine and 11 with carbachol. Because the contractions induced by histamine or carbachol are sustained for more than one hour, the effect of droperidol on the contractions induced by these agonists was evaluated by cumulative additions of droperidol after full contraction by the agonist was attained. In this set we followed this protocol:

- 1 10^{-5} M histamine or 10^{-7} M carbachol.
- 2 10^{-5} M histamine or 10^{-7} M carbachol and 0.1% ethanol every ten minutes, up to a total of 0.4% ethanol concentration, immediately after the peak response to histamine or carbachol was obtained.
- 3 10^{-5} M histamine or 10^{-7} M carbachol and 2.5×10^{-6} M droperidol in ten minute intervals, to add up to a total of 10^{-5} M, immediately after the peak response to histamine or carbachol was obtained.

The effect of prazosin either on 5-HT-induced contraction or on the relaxing effect of droperidol

In this experimental set, cocaine (5 μ M) was added to the Tyrode's solution to reduce the reuptake of 5-HT. Ten tracheal strips were studied:

- 1 10^{-4} M 5-HT several times until reproducible contractions were obtained.
- 2 10^{-6} M prazosin followed by 10^{-4} M 5-HT with a ten minute interval.
- 3 10^{-4} M 5-HT.

- 4 1.25×10^{-6} droperidol followed by 10^{-4} M 5-HT with a five minute interval.

- 5 10^{-4} M 5-HT.

- 6 10^{-6} M prazosin followed by 1.25×10^{-6} M droperidol five minutes later and by 10^{-4} M 5-HT ten minutes later.

The mean of the maximal tensions developed in step 1, 3, and 5 were used as the basal control values to which the maximal tensions obtained in step 2, 4, and 6 were compared.

Drugs and solutions

Sodium pentobarbital (Nembutal®) was purchased from Abbott Laboratories (North Chicago, IL). Droperidol, 5-HT (creatinine sulfate complex), histamine hydrochloride, carbamylcholine (carbachol) and prazosin were purchased from Sigma (St. Louis, MO). Ethanol was purchased from Fisher (Pittsburgh, PA). Cocaine hydrochloride was obtained from the University of Illinois Hospital pharmacy. Other chemicals were obtained from Sigma or Fisher. Twice distilled and deionized water was used for all solutions.

Each drug solution was prepared fresh on the day of the experiment. Droperidol was dissolved in ethanol (Fisher) as a 2.5×10^{-3} M solution and then diluted with Tyrode's solution to the appropriate working concentrations. The final concentrations of ethanol with 1.25 or 2.5×10^{-6} M droperidol in the organ bath were 0.05% and 0.1%. 5-HT (10^{-2} M) was dissolved in distilled water. Histamine and carbachol (10^{-1} M) were dissolved in distilled water and then diluted with Tyrode's solution to the appropriate concentrations. Solutions containing droperidol or 5-HT were protected from light.

Data analysis

All results, presented as percentages of the control values, were expressed as mean $\pm$ SEM. The data were analyzed with one way analysis of variance and Bonferroni multiple comparison test. $P < 0.01$ was considered to be statistically significant.

Results

Contractile responses of the tracheal strips to 5-HT, histamine and carbachol

The maximal tracheal tensions developed by the addition of 5-HT, histamine and carbachol were 965 ± 85 , 855 ± 60 , and 1010 ± 100 mg, respectively.

Effect of droperidol on 5-HT-induced tracheal contraction

The previous addition of droperidol, 1.25 and 2.5×10^{-6}

FIGURE 1 Effect of droperidol on serotonin-induced contraction in isolated guinea pig tracheal strips ($n = 8$). Droperidol (reticulated bars) prevented the tracheal contraction induced by 10^{-4} M serotonin in a concentration-dependent manner. White bars indicate the effects of ethanol (0.05% and 0.1%) used as a solvent of droperidol. Asterisk indicates $P < 0.01$ vs control and ethanol.

M, reduced tracheal contractions induced by 10^{-4} M 5-HT by $44.1 \pm 4.3\%$ ($P < 0.001$) and $63.8 \pm 3.8\%$ ($P < 0.001$), respectively. Ethanol, in concentrations attained in the bath after adding droperidol, had no significant effect on the contractions (Figure 1).

Effect of droperidol on histamine-induced tracheal contractions

Droperidol 2.5×10^{-6} M, did not affect the contractions induced by 10^{-5} M histamine significantly. However, droperidol at 5.0 , 7.5 and 10.0×10^{-6} M concentration reversed the tracheal contraction to 10^{-5} M histamine by $27.7 \pm 5.3\%$ ($P < 0.001$), $47.2 \pm 7.4\%$ ($P < 0.001$), and $56.2 \pm 5.5\%$ ($P < 0.001$), respectively. Ethanol (0.1, 0.2, 0.3, or 0.4%) did not alter the tension induced by histamine (Figure 2).

Effect of droperidol on carbachol-induced tracheal contractions

Droperidol, 2.5 , 5.0 , 7.5 , and 10.0×10^{-6} M, reversed the contractions induced by 10^{-7} M carbachol by $12.5 \pm 3.0\%$ ($P < 0.01$), $37.1 \pm 3.0\%$ ($P < 0.001$), $59.3 \pm 3.6\%$ ($P < 0.001$), and $76.1 \pm 3.2\%$ ($P < 0.001$), respectively. Ethanol, the solvent of droperidol in concentrations of 0.1, 0.2, 0.3, and 0.4% reduced the carbachol-induced contractions by $7.3 \pm 1.4\%$ ($P < 0.05$), $10.2 \pm 1.3\%$ ($P < 0.01$), $11.9 \pm 2.2\%$ ($P < 0.001$), and $9.2 \pm 3.3\%$ ($P < 0.01$), respectively. However, at concentrations 5 – 10×10^{-6} M droperidol was more effective than ethanol

FIGURE 2 Effect of droperidol on histamine-induced contraction in guinea pig isolated tracheal strips ($n = 10$). Droperidol (reticulated bars) reversed the tracheal contraction induced by 10^{-5} M histamine in a concentration-dependent manner. White bars indicate the effects of ethanol (0.1, 0.2, 0.3, and 0.4%) used as a solvent of droperidol. Asterisk indicates $P < 0.01$ vs control and ethanol.

FIGURE 3 Effect of droperidol on carbachol-induced contraction in isolated guinea pig tracheal strips ($n = 11$). Droperidol (reticulated bars) reversed the tracheal contraction induced by 10^{-7} M carbachol in a concentration-dependent manner. White bars indicate the effects of the vehicle ethanol (0.1, 0.2, 0.3, and 0.4%). Asterisk indicates $P < 0.01$ vs control and ethanol.

reducing the tracheal contractions induced by carbachol (Figure 3).

Effect of prazosin on either 5-HT-induced contractions or the relaxing effect of droperidol

Prazosin, 10^{-6} M, did not alter the contractile response

FIGURE 4 The effects of prazosin (P) on serotonin-induced contraction and on the relaxation of the isolated guinea pig tracheal strips by droperidol (DROP) ($n = 10$). 10^{-6} M prazosin altered neither the response to 10^{-4} M serotonin nor the effect of 1.25×10^{-6} M droperidol on the contraction induced by serotonin.

to 10^{-4} M 5-HT ($90.2 \pm 3.8\%$, $P > 0.05$) (Figure 4). Furthermore, on the contraction induced by 10^{-4} 5-HT, 10^{-6} M prazosin did not alter the relaxing effect of 1.25×10^{-6} M droperidol ($45.3 \pm 3.2\%$ with prazosin vs $44.4 \pm 4.4\%$ without prazosin, $P > 0.05$).

Discussion

We report here that droperidol inhibits the contractions of guinea pig tracheal smooth muscle induced not only by 5-HT but also by histamine or carbachol. Prezant *et al.*⁷ successfully treated with droperidol two patients with status asthmaticus whose condition had worsened in spite of receiving adequate "conventional" therapy. They speculated that the bronchodilating property of droperidol was the result of its ability to block α -adrenergic receptors. On the other hand, Gentil *et al.*⁸ and Takeda *et al.*⁹ reported that droperidol prevented the bronchospasm induced in guinea pigs by 5-HT, an important inflammatory mediator. It is recognized that droperidol acts as a neuroleptic agent because of its dopaminergic¹³ and serotonergic¹⁴ blocking properties. However, Gentil *et al.*⁸ found that the prevention of the bronchoconstriction by 5-HT was independent of the effect of droperidol on the autonomic nervous system and strongly suggested a competitive antagonism for droperidol at the level of 5-HT₂ receptors. Takeda *et al.*⁹ also suggested that droperidol reverses both the bronchospasm and the pulmonary vasoconstriction induced by 5-HT at the level of the 5-HT receptor. In addition, in an *in vivo* model using guinea pigs, Gentil *et al.*⁸ found that droperidol did not alter the contractile responses to

histamine or acetylcholine. However, if droperidol is as effective, as shown for the treatment of severe status asthmaticus, it may have reversed airway contractions induced not only by 5-HT but also by other spasmogens.

In our study, droperidol inhibited the tracheal contractions not only by 5-HT but also by histamine and carbachol in a concentration-dependent manner. The effect of droperidol in relaxing the trachea was strongest against 5-HT. These results indicate that droperidol can inhibit some common pathways in the signal transduction mechanism of a variety of spasmogens, in addition to its interaction with 5-HT receptors in the airway smooth muscle. For instance, some antipsychotic drugs can inhibit calmodulin,¹² which plays an important role in the contractile response of smooth muscles as an intracellular receptor of calcium ion and as an activator of myosin light chain kinase.^{15,16} Furthermore, phenothiazine derivatives, which are antipsychotic agents and inhibit calmodulin, also block smooth muscle contractions.^{17,18} Haloperidol, like droperidol, is a butyrophenone derivative that also inhibits calmodulin.¹³ The non-specific effect of droperidol relaxing tracheal contractions induced by 5-HT, histamine and carbachol may be explained by the fact that pharmacological properties of droperidol are similar to that of haloperidol. On the other hand, neuroleptics such as droperidol exert their central nervous system effects by interacting with 5-HT receptors.¹⁴ Therefore, it was strongly suggested that droperidol prevents 5-HT-induced contractions by interacting with 5-HT receptors in the airway smooth muscle.

Droperidol has α -adrenergic blocking effects¹⁹ and α -adrenoceptors mediate, directly^{20,21} and indirectly,^{22,23} the signal transduction evoked by 5-HT in smooth muscle cells. Presumably, the droperidol inhibition of the tracheal contractions induced by 5-HT could have been due to blockade of α -adrenoceptors. However, our result show that α -adrenergic blockade with prazosin does not alter either the 5-HT-induced contraction or the relaxing effect of droperidol. Nonetheless, an α -blocking effect of droperidol cannot be excluded as a mechanism of the relaxing effect of droperidol because Barnes *et al.* have reported that pulmonary α -adrenoceptor concentration increased in experimental asthma²⁴ and that it is higher in the distal segments of the airway.²⁵

Since droperidol increases blood catecholamine concentrations,²⁶ the bronchodilation by droperidol *in vivo* could be mediated by an indirect β -adrenergic stimulation. However, Gentil *et al.*⁸ showed that pretreatment with propranolol did not alter the beneficial effect of droperidol on 5-HT-induced airway contraction. Our present study *in vitro* supports their findings.

Droperidol is one of the safest intravenous anaesthetic

agents used in clinical practice because of its wide therapeutic range and few adverse effects. Furthermore, droperidol, when administered with fentanyl, inhibits histamine release from synovial mast cells.²⁷ Therefore, our data as well as the previous reports indicate that droperidol may be an important therapeutic agent in the treatment of patients with hyperreactive airways. In this regard, droperidol (molecular weight: 379.4) administered to humans at the dose of 150–200 $\mu\text{g} \cdot \text{kg}^{-1}$ resulted in a plasma concentration of around 200 $\text{ng} \cdot \text{ml}^{-1}$,^{26,28} a concentration that is similar to that used in our experiments. However, comparisons of this nature should be taken with caution because isolated, denervated tissue preparations could have increased or decreased sensitivity to agonists or antagonists.

In conclusion, we found that droperidol inhibits tracheal contractions induced by histamine and carbachol as well as those induced by 5-HT in the guinea pig *in vitro*. Droperidol prevents the tracheal contractions induced by 5-HT probably by interacting with 5-HT receptors in the airway smooth muscle. Our findings also suggest that droperidol might inhibit histamine- and carbachol-induced contractions by interacting with and inhibiting calmodulin.

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