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LG 30435, a new potential antiasthmatic agent

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LG 30435, a new potential antiasthmatic agent. F. Berti, L. Daffonchio, F. Magni, C. Omini, G. Rossoni, A. Subissi.

ABSTRACT: LG 30435 is a new quaternary phenothiazine derivative with H_1–antihistaminic and antimuscarinic properties. The ability of LG 30435 to prevent changes in respiratory mechanics, induced by different mediators and the immunological reaction, was monitored together with biological and radioimmunological determination of circulating thromboxane–A_2 (TxA_2) in anaesthetized guinea-pigs. LG 30435 dose-dependently reduces the bronchoconstriction and TxA_2 generation caused by different stimuli such as histamine, acetylcholine, leukotriene C_4 (LTC_4) and PAF-acether. In addition *i.v.* and aerosol administration of LG 30435 causes a dose-dependent reduction of the increase in airway resistance and TxA_2 generation induced by ovalbumin challenge in actively sensitized animals. LG 30435 infused at different concentrations through the isolated guinea-pig lungs inhibits the TxB_2 generation caused by different anaphylactic mediators, but not by arachidonic acid. These data, which further substantiate the bronchodilator activity of LG 30435 against a variety of stimuli and demonstrate its protective properties on lung anaphylaxis, suggest that this compound has a potential therapeutic value in the treatment of asthma.

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Both mediator release and the responsiveness of airway smooth muscle to mediators are of importance in the clinical manifestation of asthma. Therefore, compounds capable of controlling the effects of neuronal and immunological agents that lead to obstruction and hyperreactivity of airway smooth muscles may have therapeutic value. LG 30435, 1-methyl-3-(10H-phenothiazine-10-ylmethyl)-1-azoniabicyclo (2.2.2) octane iodide, is a new quaternary phenothiazine derivative with H_1–antihistaminic and antimuscarinic properties and a pharmacological profile suggesting therapeutic potential in human airway diseases [1]. Thus, LG 30435 has activity against PAF–acether (PAF), inhibiting PAF–induced platelet aggregation and bronchoconstriction [2], which may be of particular value since it has been suggested that PAF plays a role as a putative mediator of anaphylaxis and inflammation, together with its ability to induce airway hyperreactivity [3]. We now have new evidence that LG 30435 counteracts the effects of different autacoids in the airways, including the ability of such agents to amplify their pulmonary actions *via* activation of the eicosanoid system with preferential generation of thromboxane A_2 (TxA_2). Furthermore, LG 30435 possesses antiallergic activity in passive anaphylaxis reactions of lung and skin [4]. This observation prompted us to investigate the protection by LG 30435 against pulmonary responses induced by antigen challenge in actively sensitized guinea-pigs.

Materials and methods

Bronchopulmonary effects of autacoids in the guinea-pig

Male Hartley strain guinea-pigs (300–400 g) were anaesthetized with urethane (1.2 $g \cdot kg^{-1}$ *i.p.*), paralysed with pancuronium bromide (2 $mg \cdot kg^{-1}$ *i.v.*) and prepared for recording pulmonary mechanics and arterial blood pressure [5]. Dynamic compliance ($C_{L}dyn$), lung resistance (R_L) and transpulmonary pressure (Ptp.) were recorded using Hewlett-Packard instruments.

Guinea-pigs were also arranged for extracorporeal circulation following the blood-bathed organ technique [6], in order to detect circulating thromboxane A_2–like activity (TxA_2-la). Blood derived from the left carotid artery superfused a helical strip of rabbit aorta (RbA) which was maintained overnight under Krebs-bicarbonate buffer superfusion, containing a mixture of receptor antagonists [7] and indomethacin (1 $\mu g \cdot ml^{-1}$) in order to increase both the specificity for TxA_2–la and the sensitivity of the RbA. Aliquots (0.2 ml) of arterial blood were also taken for radioimmunological determination of TxB_2 [8].

Bronchospasm was induced by *i.v.* injections of histamine (50 $nmol \cdot kg^{-1}$), acetylcholine (ACh, 50 $nmol \cdot kg^{-1}$), PAF (0.2 $nmol \cdot kg^{-1}$) and leukotriene C_4 (LTC_4, 1.6 $nmol \cdot kg^{-1}$). The effects of these doses on R_L and $C_{L}dyn$ were of comparable magnitude. In experiments with PAF,

changes of blood pH, carbon dioxide tension (P_{CO_2}) and oxygen tension (P_{O_2}) were conducted utilizing a blood/pH/gas analyser (IL-1302). Different doses of LG 30435 (0.01–0.1 μmol·kg^{-1} in the case of histamine and ACh, 0.1–3 μmol·kg^{-1} in the case of LTC_4 and PAF) were injected 3 min before mediator challenge and pulmonary changes were evaluated at the peak effect. Antagonistic activity of LG 30435 was expressed in terms of median effective dose (ED_{50}), which was calculated from dose-effect regression function [9]. In order to avoid tachyphylaxis of PAF, this autacoid was injected only once in groups of control and LG 30435-treated animals.

Active lung anaphylaxis in the guinea-pig

Male Hartley strain guinea-pigs (250–350 g) were actively sensitized to ovalbumin (100 mg·kg^{-1} *i.p.* plus 100 mg·kg^{-1} *s.c.*) [10]. Twenty one days after ovalbumin treatment the animals were anaesthetized with urethane (1.2 g·kg^{-1} *i.p.*) and resistance to lung inflation was evaluated by the KONZETT and RÖSSLER technique [11] using Hewlett-Packard instruments. Systemic blood pressure (carotid artery) was also recorded and respiration was fully arrested with pancuronium bromide (2 mg·kg^{-1} *i.v.*). The animals were arranged for extracorporeal circulation as previously described and blood pH, P_{O_2} and P_{CO_2} were also monitored. The anaphylactic reaction was induced with ovalbumin (5 mg·kg^{-1} *i.v.*) in control guinea-pigs and in groups of animals treated with graded doses of LG 30435 (0.1–3 μmol·kg^{-1} *i.v.*) three min before antigen challenge. The severity of the bronchoconstriction was evaluated [12] and the protective activity of LG 30435 was expressed as percentage of maximal bronchoconstriction in control animals.

In another series of experiments the anaphylactic reaction was triggered in actively sensitized guinea-pigs by ovalbumin inhalation (aerosol, 10 mg·ml^{-1} × 5 s) according to the ovalbumin macroshock procedure [13]. Bronchoconstriction and systemic blood pressure were measured as reported above. LG 30435 was administered by aerosol (0.65 and 6.5 mM for 30 s) 3 min before antigen challenge.

Guinea-pig perfused lungs

Lungs removed from both normal and ovalbumin sensitized guinea-pigs (300–400 g) were perfused through the pulmonary artery with Krebs-bicarbonate solution at a flow rate of 10 ml·min^{-1} [14]. The pulmonary outflow superfused a set of RbA in cascade to monitor TxA_2-la during the immunological and autacoid response of the pulmonary tissues [6]. As reported above, the bioassay tissues were treated with a mixture of receptor antagonists and indomethacin to increase their specific response [7]. The resting tension of the RbA was 1 g and tension changes were measured with isometric transducers. Histamine (27 nmol), PAF (0.2 nmol), arachidonic acid (16 nmol) and ovalbumin (1 mg, in sensitized tissues) were injected as bolus through the pulmonary artery, and lung formation of TxA_2 was evaluated as the maximal increase of RbA tension in g. Aliquots of perfusates (1 min sample) were collected before and after challenge, in order to evaluate the concentration of TxB_2 [8].

Different concentrations of LG 30435 (0.01–0.1 μM against histamine; 0.3–3 μM against PAF; 1–10 μM against ovalbumin; 0.1–1 mM against arachidonic acid) were infused through the lungs for 15 min before agonist or antigen challenge. The antagonistic activity of this compound on TxB_2 generation was expressed as IC_{50} evaluated from the dose-effect regression function [9].

Drugs

The following drugs were used: histamine dihydrochloride (Sigma Chemical Co., St. Louis, MO, USA); acetylcholine bromide (Sigma); LTC_4 (Ono Pharmaceutical Co., Ltd, Osaka, Japan); PAF-acether (C_{18}, Bachem Inc., Torrance, CA, USA); arachidonic acid sodium salt (Sigma); ovalbumin (Sigma, grade II) and LG 30435 (Laboratori Guidotti S.p.A., Pisa, Italy). LTC_4 and PAF-acether were dissolved in ethanol and appropriately diluted with normal saline or Krebs-bicarbonate solution. All the other compounds were dissolved in normal saline or Krebs-bicarbonate solution.

Results

Bronchopulmonary effects of autacoids in the guinea-pig

The intravenous injection to anaesthetized guinea-pigs of histamine, LTC_4 and PAF brings about a severe bronchospasm with an increase in R_L and a decrease in C_{Ldyn} which are associated with a rise of the blood levels of immunoreactive TxB_2 (fig. 1a, figs. 2b and c,). Therefore, these results suggest that TxA_2 may take part in the overall effect observed with the above autacoids in anaesthetized guinea-pigs. On the contrary, the cardiopulmonary activity of ACh (fig. 2a) is not accompanied by TxB_2 formation indicating that the modifications of respiratory mechanics are mediated exclusively by muscarinic receptor activation.

LG 30435 dose-dependently antagonizes the changes in R_L and C_{Ldyn} caused by ACh, histamine and LTC_4; moreover the increase in blood TxB_2 induced by histamine and LTC_4 is significantly reduced (fig. 2). However, LG 30435 is more potent in antagonizing histamine than ACh or LTC_4; ED_{50} values and 95% confidence limits being 19 (17–22) nmol·kg^{-1}, 32 (29–36) nmol·kg^{-1} and 180 (156–207) nmol·kg^{-1}, respectively. At higher doses, LG 30435 counteracts the bronchoconstriction induced by PAF (ED_{50}: 284 (236–343) nmol·kg^{-1}), and the concomitant increase in blood TxB_2 is also dose-dependently decreased (fig. 1a). The severity of the pulmonary effects of PAF correlates well with the modifications of blood pH, P_{CO_2} and P_{O_2}. In fact, according to the dose used, LG 30435 maintains the values of blood pH (data not shown) and blood gases (fig. 1b) closer to control levels.

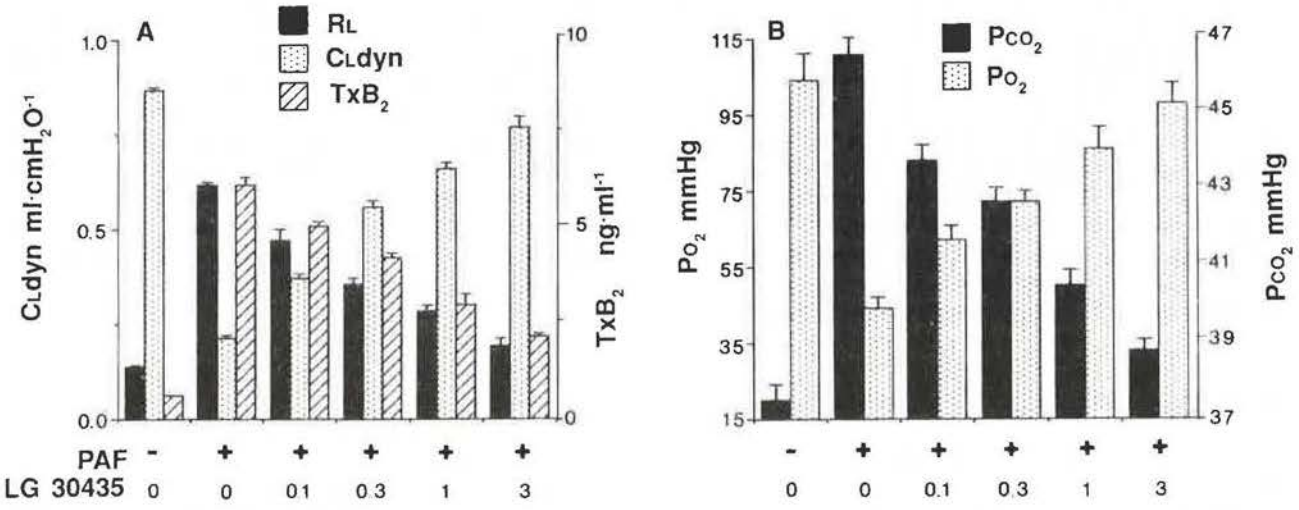

Fig. 1. – Protective effects of LG 30435 against the bronchoconstriction and the release of TxB_2 (a) and the blood changes of Pco_2 and Po_2 (b) induced by PAF (0.2 nmol·kg^{-1} *i.v.*) in the anaesthetized guinea-pig. LG 30435 was administered 3 min before PAF at the doses indicated (μmol·kg^{-1} *i.v.*). Values are mean ±SEM of at least 6 experiments. RL: lung resistance; CLdyn: dynamic compliance; Pco_2: carbon dioxide tension; Po_2: oxygen tension; TxB_2: thromboxane B_2.

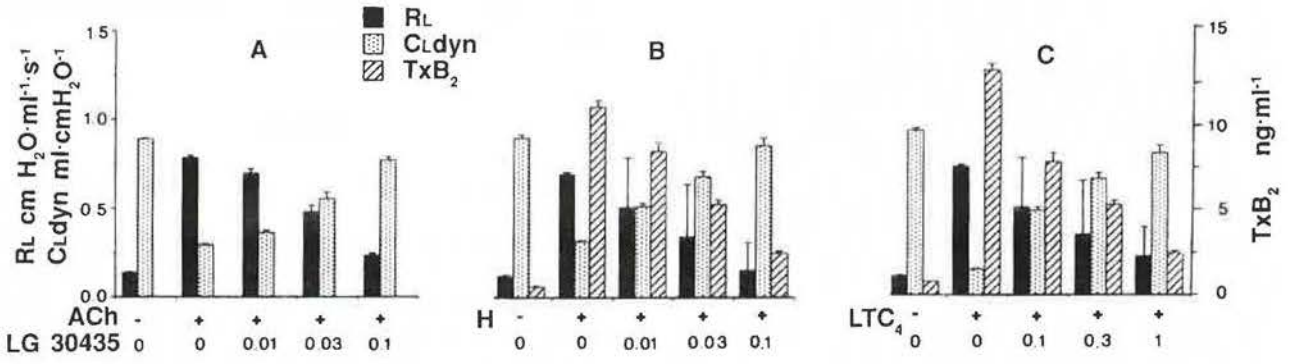

Fig. 2. – Protective effects of LG 30435 against the bronchoconstriction induced by acetylcholine (ACh) (a), histamine (H) (b) and leukotriene C_4 (LTC_4) (c) and against the release of TxB_2 induced by H (b) and LTC_4 (c) in the anaesthetized guinea-pig. LG 30435 was administered 3 min before the challenge at the doses indicated (μmol·kg^{-1} *i.v.*). Values are mean ±SEM of at least 5 experiments. RL: lung resistance; CLdyn: dynamic compliance; TxB_2: thromboxane B_2.

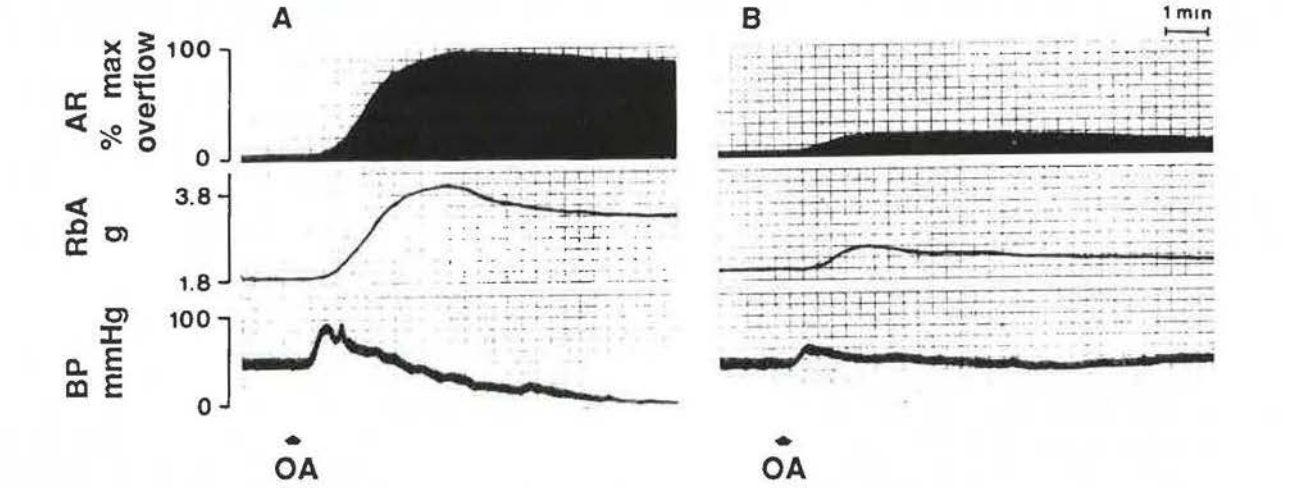

Fig. 3. – Protective effects of LG 30435 in actively sensitized anaesthetized guinea-pigs from the anaphylactic reaction caused by antigen challenge (ovalbumin (OA) 5 mg·kg^{-1} *i.v.*). A=Vehicle or B=LG 30435 (3 μmol·kg^{-1} *i.v.*) was injected 3 min before the antigen challenge. AR: airway resistance; RbA: strip of rabbit aorta monitoring TxA_2-like activity in superfusing blood; BP: blood pressure; TxA_2: thromboxane A_2.

Lung anaphylaxis in the guinea-pig

The administration of ovalbumin (5 mg·kg^{-1} *i.v.*) to actively sensitized guinea-pigs brings about a sustained and irreversible bronchoconstriction and a progressive fall in systemic blood pressure, associated with a prompt tension increase in RbA, indicating the release of TxA_2–la during the immunological response (figs. 3 and 4). A marked reduction of blood pH and Po_2 and increase in Pco_2 accompanies the pulmonary dysfunction and the animals die in less than 10 min. Graded doses of LG 30435 (0.1–3 µmol·kg^{-1} *i.v.*), administered 3 min before ovalbumin challenge, cause a dose-dependent protection against the anaphylactic response (ED_{50}: 599 (548–655) nmol·kg^{-1}) and all of the animals, except those treated with the lowest dose, survive the anaphylactic shock.

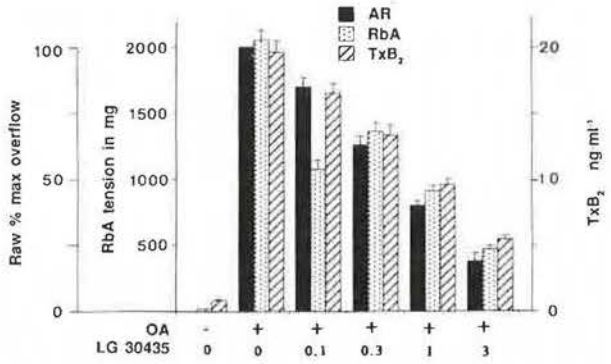

Fig. 4. – Protective effects of LG 30435 in actively sensitized anaesthetized guinea-pigs from the anaphylactic reaction caused by antigen challenge (ovalbumin (OA) 5 mg·kg^{-1} *i.v.*). LG 30435 was administered 3 min before the challenge at the doses indicated (µmol·kg^{-1} *i.v.*). Values are mean ±SEM of at least 7 experiments. Raw: airway resistance; RbA: strip of rabbit aorta monitoring TXA_2-like activity in superfusing blood; TxB_2: thromboxane B_2.

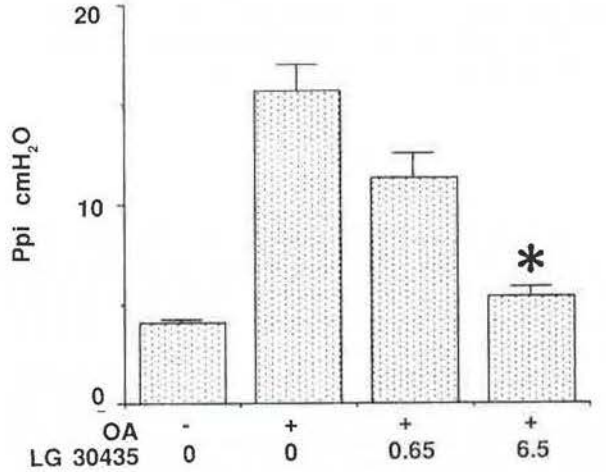

Fig. 5. – Protective effects of LG 30435, administered by aerosol, against the increase in pulmonary inflation pressure (Ppi) evoked by aerosolized ovalbumin (OA, 10 mg·ml^{-1} for 5 s) in actively sensitized anaesthetized guinea-pigs. LG 30435 (0.65 and 6.5 mM for 30 s) was given 3 min before OA. *:$p<0.01$ by Student's t-test.

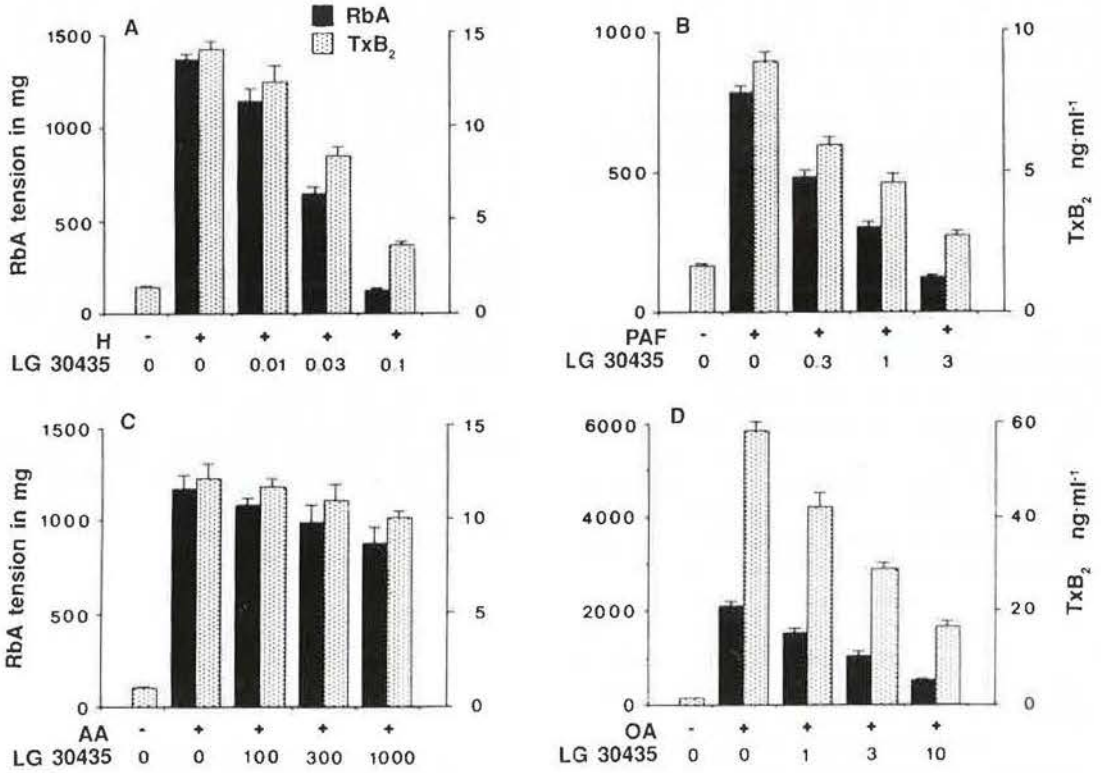

Fig. 6. – Prevention by LG 30435 of TxA_2 generation induced by histamine (H) (a), PAF (b), arachidonic acid (AA) (c) and ovalbumin (OA) (d) in isolated perfused guinea-pig lungs. LG 30435 was infused through the lungs for 15 min at the concentrations (µM) indicated before the releasing challenge. Values are mean ±SEM of at least 6 experiments. RbA: strip of rabbit aorta monitoring TxA_2-like activity in superfusing blood; TxB_2: thromboxane B_2.

The protective activity of LG 30435 on anaphylactic bronchoconstriction correlates well with the reduction in release of TxB_2 (fig. 4, ED_{50}: 730 (665–802) $nmol \cdot kg^{-1}$) and the modification of blood pH and blood gases (data not shown).

The challenge of actively sensitized guinea-pigs with ovalbumin given by aerosol (10 $mg \cdot ml^{-1} \times 5$ s) induces an immediate and reversible bronchoconstriction. The administration of LG 30435 by aerosol 3 min before antigen is also effective in this model; in particular almost complete protection from bronchoconstriction is achieved at the dose of 6.5 mM for 30 s (fig. 5).

Guinea-pig perfused lungs

The bolus injection of histamine and PAF through the lungs causes generation and release in the pulmonary effluent of a significant amount of TxA_2-la, as indicated by the increase of RbA tension, and of TxB_2 immunoreactivity in the perfusate.

The bolus injection of ovalbumin (1 mg) through the lungs obtained from actively sensitized guinea-pigs also induces a fast and sustained increase in tension development of superfused RbA and in TxB_2 immunoreactivity in the pulmonary effluent (fig. 6).

The infusion of the lungs with graded concentrations of LG 30435 for 15 min inhibits, in a concentration-dependent manner, both the tension increase of RbA and the increase of perfusate TxB_2 caused by the two autacoids and by antigen challenge (fig. 6). The IC_{50}s and 95% confidence limits, calculated for TxB_2 inhibition, are 0.035 (0.030–0.041) μM against histamine, 0.53 (0.45-0.61) μM against PAF and 2.9 (2.6–3.3) μM against ovalbumin. TxA_2–la or TxB_2 formation induced by arachidonic acid (17 nmol) administration to the lungs is poorly affected by LG 30435 even at the concentration of 1 mM (fig. 6).

Discussion

The present results underline the ability of LG 30435 to antagonize the pulmonary effects of various mediators believed to be involved in the clinical manifestations of asthma; they also suggest different sites of action, all useful in the control of reversible airway obstruction. The efficacy of LG 30435 in preventing bronchoconstriction induced by ACh, histamine and leukotrienes is already known [1], but the ability of this new compound to inhibit arachidonic acid metabolism and generation of TxA_2 represents a new insight into its mode of action. This is important since the pulmonary effects of leukotrienes [15] and PAF [16] are amplified by the formation of TxA_2 and other bronchoactive eicosanoids. Another point of interest emerging from these experiments is the ability of LG 30435 to affect the pulmonary changes due to PAF. There are several reasons to believe that PAF is involved in human asthma: this alkylphospholipid not only provokes bronchoconstriction and inflammation in various animal species but also causes bronchial hyperreactivity [3, 17]. Therefore, inhibition of the acute respiratory smooth muscle response to PAF observed with LG 30435 in guinea-pigs represents a good starting point for further investigations concerned with immediate and late anaphylactic responses. In this regard the ability of LG 30435 to inhibit systemic anaphylaxis, decreasing both the immediate bronchoconstriction and the concomitant TxB_2 generation, as shown with the present experiments, reinforces the potential value of the compound in asthma therapy.

The experiments carried out with guinea-pig perfused lungs substantiate the results obtained with anaesthetized animals and demonstrate that LG 30435 consistently reduces the formation of TxA_2 induced by histamine, PAF and antigen challenge in the pulmonary tissues, contributing to the bronchodilator and antiallergic properties of the compound.

Our data, taken together, suggest that the mode of action of LG 30435 in protecting guinea-pigs from anaphylactic shock may result from this complex pharmacological profile. In fact LG 30435 has pronounced peripheral antihistaminic and antimuscarinic activity and also antagonizes the pulmonary effects of LTC_4 and PAF, including those mediated through release of eicosanoids. On the other hand the phenothiazine nature of LG 30435 allows another possible interpretation of the mode of action of this compound.

Phenothiazines may selectively bind and inhibit the action of calmodulin [18, 19], an ubiquitous intracellular calcium-receptive protein involved in mechanisms of stimulus-response coupling (such as muscle contraction, mediator release and inflammatory cell recruitment) as well as in phospholipase A_2 (PLA_2) activation [20]. The latter is a crucial point since not only eicosanoid, but also PAF biosynthesis, requiring PLA_2 activation [17], could be affected by LG 30435. Preliminary experiments show that this compound does bind to calmodulin, indicating a possible inhibitory interference of LG 30435 with calmodulin-activated phospholipase A_2. This is in agreement with the inhibition of TxA_2 release induced by different agents (histamine, LTC_4, PAF and antigen), which are believed to activate PLA_2, but the lack of effect on the conversion of exogenously administered arachidonic acid, suggesting that neither cyclo-oxygenase nor thromboxane synthase are affected by the compound.

In conclusion, the multiple actions shown by LG 30435 reinforce its potential therapeutic value, since the effects of several mediators and their resultant interactions contribute to the pathology of asthma, especially allergen-induced bronchospasm.

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RÉSUMÉ: LG 30435 est un nouveau dérivé quaternaire de la phénothiazine doué de propriétés anti-histaminiques (anti H_1) et de propriétés anti-muscariniques. Nous avons étudié la capacité du LG 30435 pour prévenir des modifications de la mécanique respiratoire ainsi que la réaction immunologique induites par différents médiateurs. Nous avons également déterminé par voie biologique et radioimmunologique la thromboxane A_2 circulante chez des cobayes anesthésiés. LG 30435 réduit de manière dose dépendante la bronchoconstriction et la production de TxA_2 générés par différents stimuli comme histamine, acétylcoline, LTC_4 et PAF acéther. Par ailleurs, l'administration intra-veineuse ou en aérosol de LG 30435 provoque une réduction dose-dependante de l'augmentation de la résistance des voies aériennes et de la production de TxA_2 induite par une provocation à l'ovalbumine chez des animaux activement sensibilisés. LG 30435, infusé à différentes concentrations dans les poumons isolés de cobayes, inhibe la production de TxB_2 provoquée par différents médiateurs de l'anaphylaxie mais pas celle due à l'acide arachidonique. Ces données qui confirment l'activité broncho-dilatatrice de LG 30435 contre une variété de stimuli démontrent sa valeur protectrice sur l'anaphylaxie pulmonaire et suggèrent que ce composé pourrait avoir une valeur thérapeutique potentielle dans le traitement de l'asthme.

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