■ LABORATORY INVESTIGATIONS

Anesthesiology
82:102–107, 1995
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Carbachol, Norepinephrine, and Hypocapnia Stimulate Phosphatidylinositol Turnover in Rat Tracheal Slices

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Background: **The intracellular mechanisms involved in the α-adrenoceptor- or hyperventilation-induced bronchoconstriction remain unknown. Because there is a direct relationship between phosphatidylinositol (PI) metabolism and airway smooth muscle contraction induced by muscarinic agonists, the authors examined the effects of carbachol (CCh), norepinephrine (NE), and hypocapnia on PI turnover in the airway smooth muscle.**

Methods: **Rat tracheal slices were incubated in Krebs-Henseleit solution containing LiCl and [^{3}H]myo-inositol in the presence of NE, CCh, or neither. The P_{CO_2} in the solution was 36 ± 3 mmHg (normocapnia), 19 ± 2 mmHg (moderate hypocapnia), or 5 ± 2 mmHg (severe hypocapnia), respectively. [^{3}H]inositol monophosphate (IP_1) formed was counted with a liquid scintillation counter.**

Results: **Basal IP_1 formed was greater at severe hypocapnia than at normocapnia. Norepinephrine- and CCh-induced IP_1 formation were also greater at hypocapnia than at normocapnia.**

Conclusions: **These results indicate that CCh, NE, and hypocapnia stimulate PI turnover in the airway smooth muscle, which would cause bronchoconstriction, and hypocapnia also augments NE- and CCh-induced PI turnover, which could cause worsening of exercise-induced asthma and vagotonic asthma, respectively. (Key words: Lungs, hyperventilation: hypocapnia. Phosphatidylinositol turnover: inositol monophosphate. Sympathetic nervous system, catecholamines: norepinephrine.)**

BOTH muscarinic receptors and α-adrenoceptors have been shown to exist in airway smooth muscle.[1] Baron *et al.*[2] reported that phosphatidylinositol (PI) metabolism plays a role in the pharmacomechanical coupling of muscarinic receptor-mediated airway smooth muscle contraction. Hashimoto *et al.* demonstrated that inositol 1,4,5-triphosphate (IP_3) may initiate smooth muscle contraction in dogs.[3] Meurs *et al.*[4] demonstrated evidence for a direct relationship between PI metabolism and airway smooth muscle contraction induced by muscarinic agonists. On the other hand, some studies have reported that α-adrenoceptor agonists stimulate human airway smooth muscle contraction,[5–7] that α-adrenoceptors play a role in exercise-induced bronchoconstriction,[8] and that plasma norepinephrine (NE) increases in normal and asthmatic subjects during exercise.[9] However, the intracellular mechanisms involved in the α-adrenoceptor-induced bronchoconstriction remain unknown.

It is known that hyperventilation[10–13] provokes bronchoconstriction and worsens exercise-induced asthma. Several investigators reported that bronchoconstriction occurs in asthmatic patients during exercise more readily when they breathe cold dry air than when they breathe warm moist air, and suggested that either heat loss or water loss worsened exercise-induced asthma.[14–18] Thus, Freed *et al.*[19] speculated that drying of the bronchial mucosa may inactivate an epithelial dependent relaxant process and simultaneously stimulate release of bronchoactive mediators from osmosensitive cells, and that cooling *per se* would tend to offset the effect of hyperventilation to provoke bronchoconstriction. On the other hand, hyperventilation could not induce airway obstruction when end-tidal CO_2 was maintained at a normal resting level.[11] Thus, it seems probable that hypocapnia plays an essential role in the genesis of hyperventilation-induced bronchoconstriction.[10–13]

Although both NE and hypocapnia seem to play essential roles in exercise-induced asthma, the mecha-

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Received from the Department of Anesthesiology, Nagasaki University School of Medicine, Nagasaki, Japan. Submitted for publication February 7, 1994. Accepted for publication August 8, 1994. Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 17–21, 1992.

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nisms remain unknown. The current study was designed using rat tracheal slices to clarify whether NE or hypocapnia could stimulate PI turnover, which is an important physiologic step in the bronchoconstriction process.

Materials and Methods

The technique of Brown *et al.*[20] was used. Inositol 1,4,5-triphosphate is rapidly degraded into inositol monophosphate (IP_1), which is recycled back to phosphatidylinositol (PI) *via* free inositol. Li^+ inhibits the conversion of IP_1 into inositol. Thus, in the presence of Li^+, the accumulation rate of IP_1 reflects the extent of PI turnover.[21] We measured ^{3}[H]IP_1 in tracheal slices incubated with [^{3}H]myo-inositol (Amersham, Tokyo, Japan). The studies were conducted under guidelines approved by the Animal Care Committee of Nagasaki University School of Medicine. Ninety-four male Wistar rats (Charles River, Yokohama, Japan) weighing 250–350 g were used for experiments. The rats were stunned by cervical dislocation and decapitated, and the tracheas were rapidly isolated. For tissue preparation without epithelium, epithelium was removed by rubbing with cotton gauze. Trachea with or without epithelium was cut longitudinally and chopped into 1-mm-wide pieces with a McIlwain tissue chopper (The Mickle Laboratory Engineering, Gomshall, England). Briefly, three pieces of the tracheal slice were placed in small flat-bottomed tubes and preincubated for 15 min in Krebs-Henseleit (K-H) solution (composition in mM: NaCl 118, KCl 4.7, $CaCl_2$ 1.3, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, glucose 10, and Na_2-EDTA 0.05) containing 5 mM LiCl. The solution was continuously aerated with 95% O_2/5% CO_2. An aliquot of 0.5 μCi [^{3}H]myo-inositol was then added to each tube (final concentration 0.1 μM in 300 μl incubation volume) and the tubes were flushed with 95% O_2/5% CO_2, capped, set in a shaking bath at 37°C, and incubated for 30 min (time 0).

Effects of Norepinephrine and Carbachol on IP_1 Formation

The reaction was started at time 0 when NE, carbachol (CCh), or neither (basal) was added. The tubes were reaerated with 95% O_2/5% CO_2, recapped, and reincubated for 0, 15, 30, 45, and 60 min. The reaction was stopped with 940 μl chloroform:methanol (1:2 v/v). Chloroform and water were then added (310 μl each) and the phases were separated by centrifugation with 90*g* for 5 min. [^{3}H]IP_1 was separated from [^{3}H]myo-inositol in the water phase by column chromatography using Dowex AG 1-X8 resin (Bio Rad, Richmond, CA) in the formate form. The "n" refers to the number of experiments and one experiment includes the mean value of duplicate results. The [^{3}H]IP_1 formed in the tracheal slices was counted with a liquid scintillation counter and presented by disintegration per minute (DPM). The counts in DPM of two samples were averaged and the average DPMs of the blank values (no slices present) were subtracted to obtain the experimental data.

The Effect of Hypocapnia on Monophosphate Formation

The tracheal slices were taken out at time 0, washed, wiped, and put into new K-H solution, containing 0.5 μCi [^{3}H]myo-inositol. The conditions of aeration and *p*H of solution were fourfold, *i.e.*, 95% O_2/5% CO_2 (*p*H 7.48), 97.5% O_2/2.5% CO_2 (*p*H 7.84), 100% O_2 (*p*H 8.37), or 95% O_2/5% CO_2 (*p*H 8.37 titrated with NaOH) (table 1). The *p*H and partial pressure of CO_2 and O_2 were assayed with an ABL Acid Base Analyzer (Radiometer, Copenhagen, Denmark). The reaction was started by adding NE, CCh, or neither 15 min after putting into the new K-H solution. The tubes (300 μl incubation volume) were reaerated, recapped, and reincubated for an additional 45 min. The reaction was stopped with 940 μl chloroform:methanol (1:2 v/v), followed by the same procedure described above.

Statistical Analysis

Data were expressed as mean ± SE. The results of repeated measures and multiple groups were analyzed by one-way ANOVA. Multiple pairwise comparisons between groups were assessed by Scheffe's test. A comparison between two groups was assessed by Student's *t* test. A P value < 0.05 was considered significant.

Table 1. Gas Analysis of the Solution of Normocapnia, Moderate Hypocapnia, and Severe Hypocapnia

	Normocapnia	Moderate Hypocapnia	Severe Hypocapnia
*p*H	7.48 ± 0.10	7.84 ± 0.08	8.37 ± 0.02
P_{CO_2} (mmHg)	36 ± 3	19 ± 2	5 ± 2
P_{O_2} (mmHg)	535 ± 53	512 ± 43	552 ± 65

Values are mean ± SE; n = 4 for each value.

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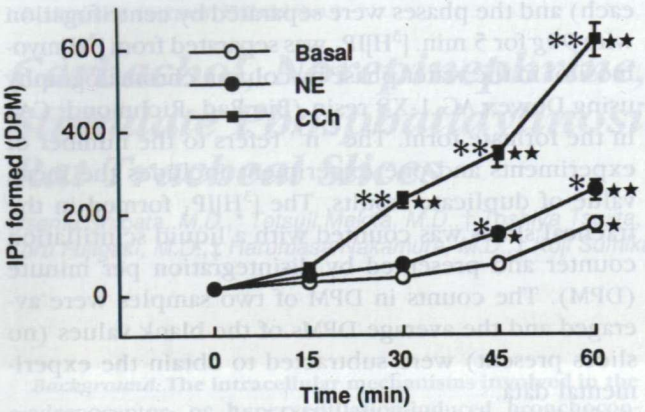

Fig. 1. Time course of IP_1 formation by 2.5 μM norepinephrine (NE), 5.5 μM carbachol (CCh), or neither (Basal) under normocapnia in rat tracheal slices (mean ± SE; n = 6–9 for each value). *$P < 0.05$ *versus* time 0. **$P < 0.01$ *versus* time 0. *$P < 0.05$ *versus* basal. **$P < 0.01$ *versus* basal.

Results

Time course of IP_1 formation after adding NE (2.5 μM), CCh (5.5 μM), or neither (basal) are shown in figure 1. Basal IP_1 formation reached a level of 168 ± 12 DPM after 60 min and, in the presence of NE or CCh, IP_1 formed was 252 ± 23 DPM and 615 ± 39 DPM, respectively. The effects of hypocapnia on IP_1 formation were shown in figures 2 and 3. Basal IP_1 formation was 150 ± 8 DPM under normocapnia and 245 ± 18 DPM under severe hypocapnia, respectively, and there was a significant difference between normocapnia and severe hypocapnia. Monophosphate formed in the presence of 2.5 μM NE was 272 ± 21 DPM under normocapnia and 356 ± 23 DPM under severe hypocapnia, respectively, and there was a significant difference between normocapnia and severe hypocapnia. Monophosphate formed in the presence of 0.55 μM CCh was 300 ± 10 DPM under normocapnia and 412 ± 25 DPM under severe hypocapnia, respectively, and there was a significant difference between them. Monophosphate formed in the presence of 5.5 μM CCh was not significantly different between normocapnia and hypocapnia. As shown in figure 4, removal of the epithelium did not influence basal IP_1 formation under either normocapnia or hypocapnia. Figure 5 shows roles of the

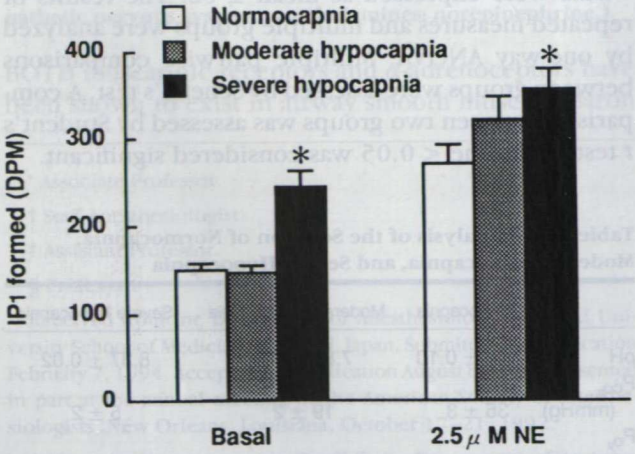

Fig. 2. The effects of hypocapnia on basal and norepinephrine (NE)-induced IP_1 formation in rat tracheal slices (mean ± SE; n = 7–11). *$P < 0.05$ *versus* normocapnia.

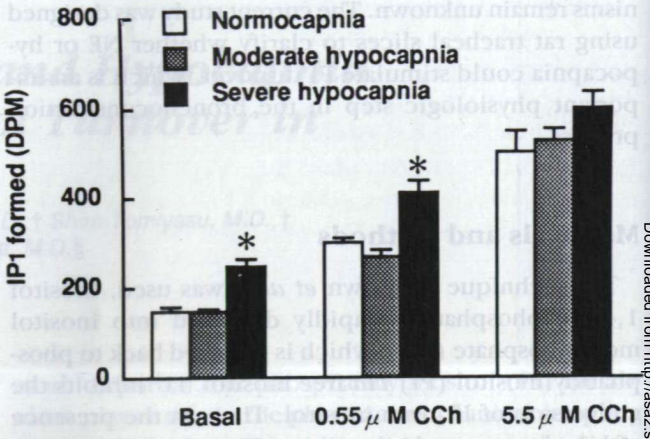

Fig. 3. The effects of hypocapnia on basal, carbachol (CCh)-induced IP_1 formation in rat tracheal slices (mean ± SE; n = 7–11). *$P < 0.05$ *versus* normocapnia.

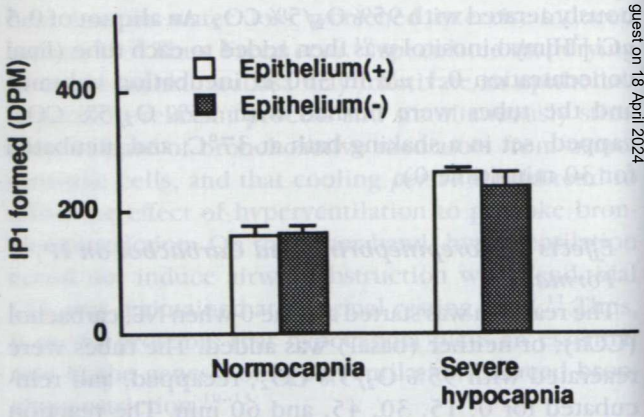

Fig. 4. Basal IP_1 formation under normocapnia and severe hypocapnia in the presence and absence of epithelium (mean ± SE; n = 6).

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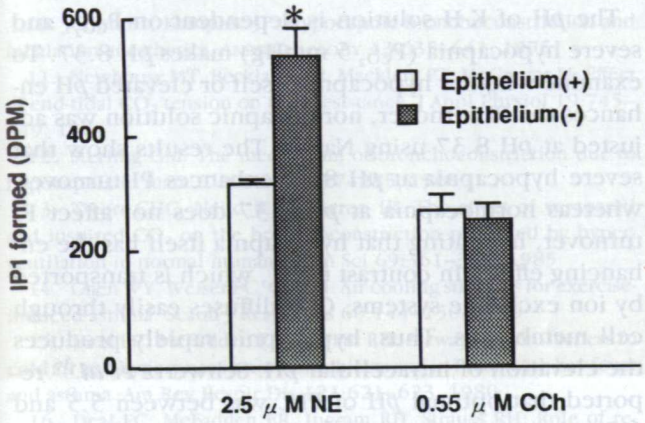

Fig. 5. Norepinephrine (NE)- and carbachol (CCh)-induced IP_1 formation in the presence and absence of epithelium (mean ± SE; n = 6). *$P < 0.05$ *versus* presence of epithelium.

epithelium in the IP_1 formation stimulated by NE or CCh. Monophosphate formation stimulated by NE was 315 ± 7 DPM in the presence of epithelium and 535 ± 48 DPM in the absence of epithelium. Thus, removal of the epithelium significantly enhanced NE-stimulated IP_1 formation. In contrast, IP_1 formation stimulated by CCh was not influenced by removal of the epithelium. The effects of *p*H and severe hypocapnia on basal IP_1 formation were shown in figure 6. The basal IP_1 formation was not influenced by an increase in extracellular *p*H under normocapnia, whereas it was enhanced by severe hypocapnia.

Discussion

Histochemical analysis of human airways reveals a dense network of parasympathetic fibers.[22] Acetylcholine released from parasympathetic nerve terminals activates muscarinic receptors in airway smooth muscle cell membrane, and contracts airway smooth muscle. Carbachol was also shown to stimulate IP_3 formation in animal tracheal smooth muscle,[3] and the present results also show that CCh stimulates IP_1 formation. When muscarinic receptors are stimulated to activate the phospholipase C (PLC), phosphatidylinositol-4,5-bisphosphate (PIP_2) is hydrolyzed into IP_3 and diacylglycerol. Inositol 1,4,5-triphosphate mobilizes Ca^{++} from sarcoplasmic reticulum,[23] whereas diacylglycerol activates protein kinase C (PKC), which may also be a mechanism of modulating or controlling smooth muscle tension.[24] Subsequently, the increase in cytoplasmic Ca^{++} concentration and activation of PKC may cause smooth muscle contraction.

Park and Rasmussen[25,26] have reported that the contractile response of tracheal smooth muscle strips to CCh stimulation reaches the plateau within 2–3 min and is sustained with no loss of tension after many hours of incubation with the agonist. Giembycz and Rodgers[27] have provided evidence that a rapid, short-lived increase in IP_3 induced by CCh stimulation precedes the development of tension. Phosphatidylinositol-4,5-bisphosphate, precursor of IP_3, formation decreases rapidly and remained at this new steady state level in the continued presence of CCh,[28] indicating that IP_3 production is sustained even after a rapid, short-lived increase. Thus, IP_3 would have an important role for initiating and maintaining contraction of airway smooth muscle. In the current study, we measured the tissue content of IP_1 as an index of IP_3 generation, because IP_3 is rapidly degraded into IP_1 and the tissue content of IP_1 increases in a linear manner over 60 min in the presence of CCh.[29] Wills-Karp[30] observed both the contraction and the PI response in tracheal tissues of guinea pigs and found that IP_1 accumulation incubated for 30 min with CCh between 1 μM and 1 mM is between 150 and 250% of basal. Our results show that IP_1 accumulation for 60 min with 5.5 μM CCh is 370% of basal. The magnitude of IP_1 accumulation in our study is consistent with their values. Thus, this magnitude of the PI response would be enough to cause the physiologic effect.

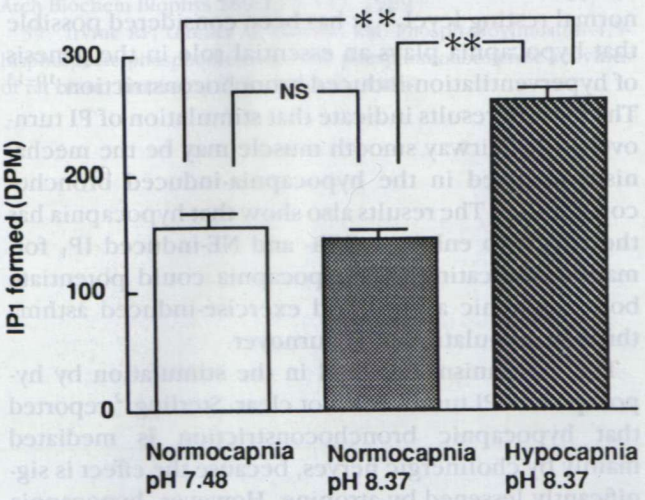

Fig. 6. Effects of severe hypocapnia (P_{CO_2} 5 mmHg) and metabolic alkalosis (*p*H 8.37) on basal IP_1 formation in rat tracheal slices (mean ± SE; n = 6). **$P < 0.01$. NS = not significant.

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α-Adrenoceptors also have been shown to exist in rat airways by autoradiographic analysis.[1] Catecholamine administration after β-receptor blockade induces asthma in normal subjects, as well as in patients with asthma.[31] Although inhalation of prazosin, a specific α_1-adrenergic antagonist, had little effect on resting airway tone in asthmatics, it partially inhibited exercise-induced asthma in asthmatic subjects.[32,33] Barnes *et al.* demonstrated that the plasma concentration of NE increases in normal and asthmatic subjects during exercise[9] and it is considered probable that NE released during exercise would play a significant role in causing exercise-induced asthma. The current results indicate that the stimulation of PI turnover through α_1-adrenoceptor activation would be the mechanism involved in the NE-induced bronchoconstriction during exercise. We have also examined the roles of epithelium in the NE- or CCh-induced PI turnover. The results show that NE-induced PI turnover is enhanced in the absence of epithelium, whereas CCh-induced PI turnover is not influenced. Farmer *et al.*[34] reported that epithelium removal enhances the sensitivity of guinea-pig isolated trachea to the bronchodilator, isoproterenol, and they have indicated that airway epithelium would play a significant role in the uptake and metabolism of catecholamines. Our results would also support this mechanism, and indicate that exercise-induced asthma may occur easily in patients who have the airway epithelium damaged by inflammation.

Airway smooth muscle contraction cannot be induced by hyperventilation if end-tidal CO_2 is maintained at a normal resting level.[11] It has been considered possible that hypocapnia plays an essential role in the genesis of hyperventilation-induced bronchoconstriction.[10–13] The current results indicate that stimulation of PI turnover in the airway smooth muscle may be the mechanism involved in the hypocapnia-induced bronchoconstriction. The results also show that hypocapnia has the effects to enhance CCh- and NE-induced IP_1 formation, indicating that hypocapnia could potentiate both vagotonic asthma and exercise-induced asthma through stimulation of PI turnover.

The mechanism involved in the stimulation by hypocapnia of PI turnover is not clear. Sterling[12] reported that hypocapnic bronchoconstriction is mediated mainly by cholinergic nerves, because the effect is significantly lessened by atropine. However, hypocapnia (P_{CO_2} less than 14 mmHg) causes bronchoconstriction that cannot be prevented by atropine.[35]

The *p*H of K-H solution is dependent on P_{CO_2}, and severe hypocapnia (P_{CO_2} 5 mmHg) makes *p*H 8.37. To examine whether hypocapnia itself or elevated *p*H enhances the PI turnover, normocapnic solution was adjusted at *p*H 8.37 using NaOH. The results show that severe hypocapnia at *p*H 8.37 enhances PI turnover, whereas normocapnia at *p*H 8.37 does not affect PI turnover, indicating that hypocapnia itself has the enhancing effect. In contrast to H^+, which is transported by ion exchange systems, CO_2 diffuses easily through cell membranes. Thus, hypocapnia rapidly produces the elevation of intracellular *p*H. Schwertz *et al.*[36] reported that optimal *p*H of PLC was between 5.5 and 6.8, whereas Irvine *et al.*[37] observed that optimal *p*H was 5.5–6.8 and 7.5–8.0. Therefore, hypocapnia may activate PLC, and may stimulate PI turnover by increasing intracellular *p*H to 7.5–8.0.

In conclusion, CCh, NE, and hypocapnia stimulate PI turnover in the airway smooth muscle, which causes bronchoconstriction. Hypocapnia also augments NE- and CCh-induced PI turnover, which may cause worsening of exercise-induced asthma and vagotonic asthma, respectively.

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