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Monochloramine potently inhibits arachidonic acid metabolism in rat platelets

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Abstract

In the present study, the effects of hypochlorous acid (HOCl), monochloramine (NH_2Cl), glutamine-chloramine (Glu-Cl) and taurine-chloramine (Tau-Cl) on the formation of 12-lipoxygenase (LOX) metabolite, 12-HETE, and cyclooxygenase (COX) metabolites, TXB_2, and 12-HHT, from exogenous arachidonic acid (AA) in rat platelets were examined. Rat platelets (4×10^8/ml) were preincubated with drugs for 5 min at 37 °C prior to the incubation with AA (40 μM) for 2 min at 37 °C. HOCl (50–250 μM) showed an inhibition on the formation of LOX metabolite (12-HETE, 5–67% inhibition) and COX metabolites (TXB_2, 33–73% inhibition; 12-HHT, 27–74% inhibition). Although Tau-Cl and Glu-Cl up to 100 μM were without effect on the formation of 12-HETE, TXB_2 and 12-HTT, NH_2Cl showed a strong inhibition on the formation of all three metabolites (10–100 μM NH_2Cl, 12-HETE, 21–92% inhibition; TXB_2, 58–94% inhibition; 12-HHT, 36–92% inhibition). Methionine reversed a reduction of formation of LOX and COX metabolites induced by NH_2Cl, and taurine restoring that induced by both NH_2Cl and HOCl. These results suggest that NH_2Cl is a more potent inhibitor of COX and LOX pathways in platelets than HOCl, and taurine and methionine can be modulators of NH_2Cl-induced alterations in the COX and LOX pathways in vivo.

Keywords: Monochloramine; Hypochlorous acid; Arachidonic acid; 12-Lipoxygenase; Cyclooxygenase; Platelet

Stimulation of oxygen (O_2) of neutrophilic polymorphonuclear leukocytes (neutrophils) results in reduction of O_2 to superoxide anion radical ($O_2^{\bullet -}$). $O_2^{\bullet -}$ rapidly dismutates to yield hydrogen peroxide (H_2O_2), and neutrophils contain myeloperoxidase which catalyzes the oxidation of chloride (Cl^-) by H_2O_2 to yield hypochlorous acid (HOCl). Further, it has been shown that an incubation of stimulated neutrophils with primary amines, ammonium ion or other nitrogenous compounds results in reaction of HOCl with the N-compounds to yield derivatives containing the nitrogen–chlorine (N–Cl) bond [1]. N–Cl derivatives are powerful oxidizing agents as well as HOCl. However, there are some reports that N–Cl derivatives can be more powerful oxidants than HOCl on biological systems [1–3]. Myeloperoxidase is secreted from cytoplasmic granules in neutrophils into the intracellular phagolysosome compartment and the extracellular fluid [4], and so HOCl and N–Cl derivatives may be produced both inside and outside the neutrophils, influencing the functions of other blood cells.

In platelets, arachidonic acid (AA) is converted into thromboxane A_2 and 12-hydroxy-5,8,10-heptadecatrienoic acid (12-HHT) by the cyclooxygenase (COX) pathway and into 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) by the 12-lipoxygenase (LOX) pathway [5]. Thromboxane A_2 is a potent vasoconstrictor and inducer of platelet aggregation and rapidly breaks down to form the stable end-product thromboxane B_2 (TXB_2). 12-HETE has been shown to play a central role in the regulation of platelet aggregation [6,7].

Until now, there is no information concerning the relationship between chlorinated oxidants produced from neutrophils and platelet AA metabolism. Therefore, in the

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present study, we evaluated whether HOCl and N–Cl derivatives {monochloramine (NH_2Cl), glutamine-chloramine (Glu-Cl), and taurine-chloramine (Tau-Cl)} can affect the AA metabolism via COX and LOX pathways in platelets.

Materials and methods

Materials. TXB_2, L-glutamine, taurine, chlorogenic acid, and sodium salt of AA were obtained from Sigma Chemical Co., St. Louis, MO, USA, and NaOCl was from Wako Pure Chemical Industries, Limited, Osaka, Japan. 12-HHT was purchased from Cayman Chemical Co., Michigan, USA, and 12-HETE was from Cascade Biochem Ltd., Berkshire, England. 9-Anthryldiazomethane was obtained from Funakoshi Pharmaceutical Co., Tokyo, Japan. All other reagents were analytical grade.

Preparation of platelets. Blood was withdrawn into a 3.8% solution of trisodium citrate (9:1, v/v) from the abdominal aorta of male rats (150–200 g) under sodium pentobarbital anesthesia. Platelets were then collected by differential centrifugation. Whole blood was centrifuged for 10 min at 200*g* at room temperature and the platelet-rich plasma was withdrawn from above the pelleted erythrocytes. After the addition of EDTA (to a final concentration of 1 mM), the platelet-rich plasma was cooled to 0 °C and centrifuged at 2000*g* for 10 min. The platelet pellet was washed twice with and resuspended in 67 mM sodium phosphate buffer (pH 7.4).

Preparation of NH_2Cl, Glu-Cl, and Tau-Cl, and spectrophotometric assay for HOCl, NH_2Cl, Glu-Cl, and Tau-Cl. NH_2Cl, Glu-Cl, and Tau-Cl were prepared using the method of Thomas et al. [8]. A 20 ml of 200 mM ammonium chloride, 200 mM taurine or 300 mM L-glutamine in 0.9% NaCl was cooled while stirring with a magnetic stir bar and 2.7 ml of 740 mM NaOCl (220 mM NaOCl for ammonium chloride) was added dropwise over 1 min. The concentrations of HOCl NH_2Cl, Glu-Cl, and Tau-Cl were determined spectrophotometrically using published molar extinction coefficients (ε), for HOCl as $\varepsilon_{292} = 350\ M^{-1}\ cm^{-1}$, for NH_2Cl as $\varepsilon_{242} = 429\ M^{-1}\ cm^{-1}$, and for Glu-Cl and Tau-Cl as $\varepsilon_{252} = 429\ M^{-1}\ cm^{-1}$ [8,9]. All three chloramines were prepared, and the concentrations measured just before use.

Incubation conditions and measurement of 12-HETE, TXB_2, and 12-HHT. Incubation conditions using washed platelets with exogenous AA, and measurement of 12-HETE, TXB_2, and 12-HHT formed were performed as described by us [10–12], except that 67 mM sodium phosphate buffer (pH 7.4), in place of 15 mM Tris–HCl buffer (pH 7.4) containing 134 mM NaCl and 5 mM glucose, was used during a preincubation with platelets and chlorinated oxidants (HOCl, NH_2Cl, Glu-Cl, and Tau-Cl), because a N-moiety of Tris easily reacts with chlorinated oxidants [8]. Briefly, the washed platelet suspension (4×10^8 platelets) was preincubated for 5 min at 37 °C in 1 ml of 67 mM sodium phosphate buffer (pH 7.4) with or without the indicated concentrations of HOCl, NH_2Cl, Glu-Cl, and Tau-Cl. Then, platelets were cooled to 0 °C and centrifuged at 2000*g* for 10 min. The platelet pellet was washed twice with and resuspended in 15 mM Tris–HCl buffer (pH 7.4) containing 134 mM NaCl and 5 mM glucose. AA (40 μM) was subsequently added to the platelet suspension, and the mixture was incubated at 37 °C for 2 min. The reaction was terminated by quickly adding 20 μl of 0.25 M HCl to bring the pH of the reaction mixture to 3.0. The reaction mixture was then extracted with 3 ml of ethyl acetate. 12-HETE, TXB_2, and 12-HHT in the extracted lipid were simultaneously determined by a high-performance liquid chromatography (HPLC). 12-HETE and 12-HHT were separated by normal-phase chromatography and simultaneously quantitated by using a UV spectrophotometric detector. TXB_2 was measured after esterification with 9-anthryldiazomethane. TXB_2 esterified with 9-anthryldiazomethane was separated by reverse-phase chromatography and quantitated by using a fluorescence spectrofluorometer.

Statistics. Results are means ± SE. Statistical significance was determined by Student's *t* test.

Results and discussion

Washed rat platelets (4×10^8/ml) metabolized exogenously added AA (40 μM) to 12-HETE, TXB_2, and 12-HHT. Experiments utilizing quercetin, an inhibitor of LOX [13,14], and indomethacin, an inhibitor of COX [15], demonstrated that the movement of amounts of 12-HETE, and TXB_2 or 12-HHT produced from exogenously added AA in the present assay conditions reflects changes in the activities of platelet LOX and COX, respectively; Quercetin (1–100 μM) inhibited the formation of 12-HETE, but not TXB_2 and 12-HHT, and indomethacin (1–100 μM) reducing TXB_2 and 12-HHT formation without an effect on 12-HETE formation (data not shown). Fig. 1 shows the effects of HOCl (A) and NH_2Cl (B) on the formation of 12-HETE, TXB_2, and 12-HHT from exogenous AA. At concentrations ranging from 50 to 250 μM, HOCl reduced all three metabolites, and the concentrations required for 50% inhibition (IC_{50}) were

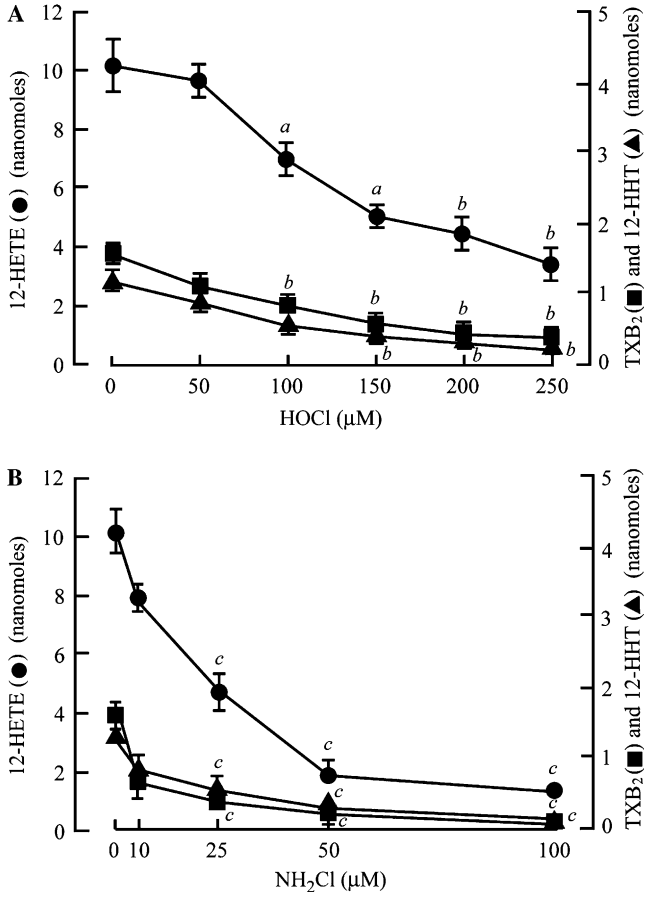

Fig. 1. Effects of hypochlorous acid [HOCl (A)] and monochloramine [NH_2Cl (B)] on the formation of 12-HETE, TXB_2 and 12-HHT in washed rat platelets. Platelets (4×10^8/ml) were preincubated with or without various concentrations of HOCl or NH_2Cl for 5 min at 37 °C prior to incubation with arachidonic acid (40 μM) for 2 min at 37 °C. Each point indicates the mean of 4–5 experiments; vertical lines show SE. (A) $^aP < 0.05$, $^bP < 0.01$; significantly different from the corresponding value in the absence of HOCl. (B) $^cP < 0.01$; significantly different from the corresponding value in the absence of NH_2Cl. ●, 12-HETE; ■, TXB_2; ▲, 12-HHT.

approximately 150 μM (Fig. 1A). NH_2Cl inhibited the formation of 12-HETE, TXB_2, and 12-HHT, and further the inhibitory potencies (IC_{50}, approximately 25 μM) being much stronger than that elicited by HOCl (Fig. 1B). On the other hand, Glu-Cl and Tau-Cl at concentrations of 25 and 100 μM had no significant effect on the formation of 12-HETE, TXB_2, and 12-HHT (Table 1).

In an attempt to clarify the mode of actions of HOCl as an inhibitor of the activities of LOX and COX in platelets, we investigated the effect of chlorogenic acid, a HOCl inhibitor [16] on the HOCl (Fig. 2A)- and NH_2Cl (Fig. 2B)-induced reductions of formation of 12-HETE, TXB_2, and 12-HHT. Chlorogenic acid completely nullified HOCl (150 μM)-induced inhibition on the 12-HETE, TXB_2, and 12-HHT formation at a concentration of 300 μM (the concentration ratio of HOCl and chlorogenic acid, 1:2) (Fig. 2A). In contrast, this compound had no significant effect on the NH_2Cl (25 μM)-induced alterations even at the concentration of 125 μM (the concentration ratio of NH_2Cl and chlorogenic acid, 1:5) (Fig. 2B). This finding demonstrates that HOCl inhibits the LOX and COX pathways in platelets.

Figs. 3 and 4 show the effects of methionine and taurine on the HOCl- and NH_2Cl-induced reduction of formation of 12-HETE, TXB_2, and 12-HHT. Methionine even at a concentration of 750 μM (the concentration ratio of HOCl and methionine, 1:5) weakly reversed the HOCl (150 μM)-induced inhibition of 12-HETE formation only (Fig. 3A). In contrast, even at a concentration of 25 μM (the concentration ratio of NH_2Cl and methionine, 1:1), this amino acid completely reversed the NH_2Cl (25 μM)-induced reduction of all three metabolites (Fig. 3B). Methionine contains both thiol and amine groups, and having a capacity to produce methionine chloramine or methionine sulfoxide by the incubation with HOCl or NH_2Cl [3,17]. Thus, it might be possible that the difference of potency of methionine against HOCl- or NH_2Cl-induced alterations in 12-HETE, TXB_2, and 12-HHT formation is partially due to a difference of product formed mainly during an incubation of methionine plus HOCl, or methionine plus NH_2Cl. On the other hand, taurine completely reversed HOCl (150 μM)-induced alterations in LOX and COX pathways at a concentration of 150 μM (the concentration ratio of HOCl and taurine, 1:1) (Fig. 4A). This amino acid also completely nullified NH_2Cl (25 μM)-induced reduction of formation of 12-HETE, TXB_2, and 12-HHT at a concentration of 125 μM (the concentration ratio of NH_2Cl and taurine, 1:5) (Fig. 4B). We further investigated the effects of taurine on HOCl and NH_2Cl using absorption spectra for HOCl, NH_2Cl, and Tau-Cl in the ultraviolet region; an incubation with HOCl and taurine resulted in a rapid loss of absorbance at 292 nm, a wavelength near the maximum (λ_{max}) exhibited by HOCl, and an appearance of absorbance at 252 nm, the λ_{max} exhibited by Tau-Cl, and when taurine was added to NH_2Cl solution, there was a rapid loss of absorbance at 242 nm, the λ_{max} exhibited by NH_2Cl, and an appearance of absorbance at

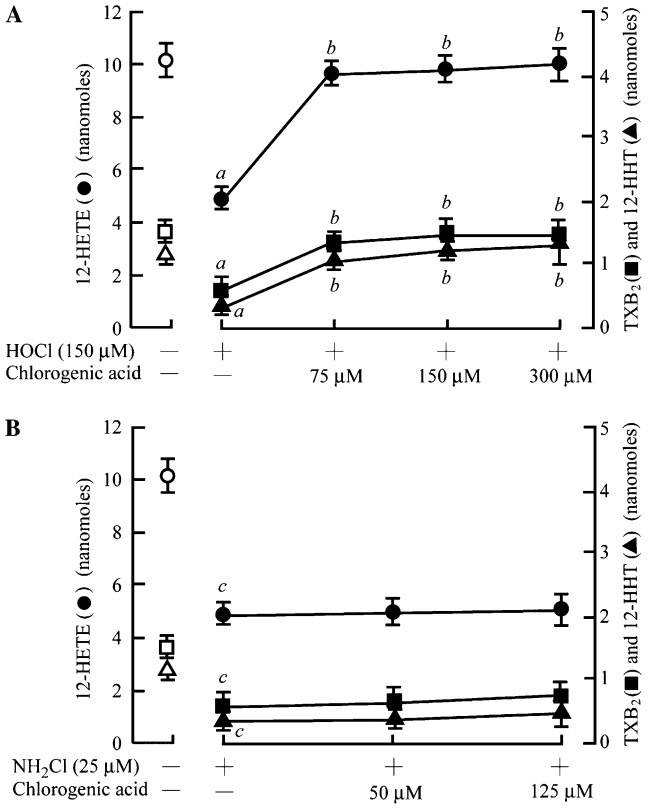

Fig. 2. Effect of chlorogenic acid in the presence of HOCl (A) and NH_2Cl (B) on the formation of 12-HETE, TXB_2 and 12-HHT in washed rat platelets. Platelets (4×10^8/ml) were preincubated with or without various concentrations of HOCl, NH_2Cl and chlorogenic acid for 5 min at 37 °C prior to incubation with arachidonic acid (40 μM) for 2 min at 37 °C. Each point indicates the mean of 4–5 experiments; vertical lines show SE. (A) $^{a}P < 0.01$; significantly different from the corresponding value in the absence of HOCl and chlorogenic acid. $^{b}P < 0.05$; significantly different from the corresponding value in the presence of HOCl alone. (B) $^{c}P < 0.01$; significantly different from the corresponding value in the absence of NH_2Cl and chlorogenic acid. ●, 12-HETE; ■, TXB_2; ▲, 12-HHT.

Table 1
Effects of glutamine-chloramine and taurine-chloramine on the formation of 12-HETE, TXB_2 and 12-HHT in washed rat platelets

Pretreatment	12-HETE (nanomoles)	TXB_2 (nanomoles)	12-HHT (nanomoles)
None	10.92 ± 0.86	3.78 ± 0.20	3.42 ± 0.17
NH_2Cl			
25 μM	4.59 ± 0.15*	1.86 ± 0.08*	2.34 ± 0.19*
Glutamine-chloramine			
25 μM	10.63 ± 0.98	3.69 ± 0.20	3.64 ± 0.25
100 μM	10.68 ± 0.63	3.62 ± 0.29	3.38 ± 0.13
Taurine-chloramine			
25 μM	10.42 ± 1.03	3.73 ± 0.22	3.78 ± 0.18
l00 μM	10.31 ± 0.77	3.82 ± 0.19	3.28 ± 0.17

Rat platelets (4×10^8/ml) were preincubated with or without NH_2Cl, glutamine-chloramine and taurine-chloramine for 5 min at 37 °C prior to the incubation with arachidonic acid (40 μM) for 2 min at 37 °C. Values are means ± SE ($n = 4$).

* $P < 0.01$; significantly different from the corresponding value in the absence of drugs.

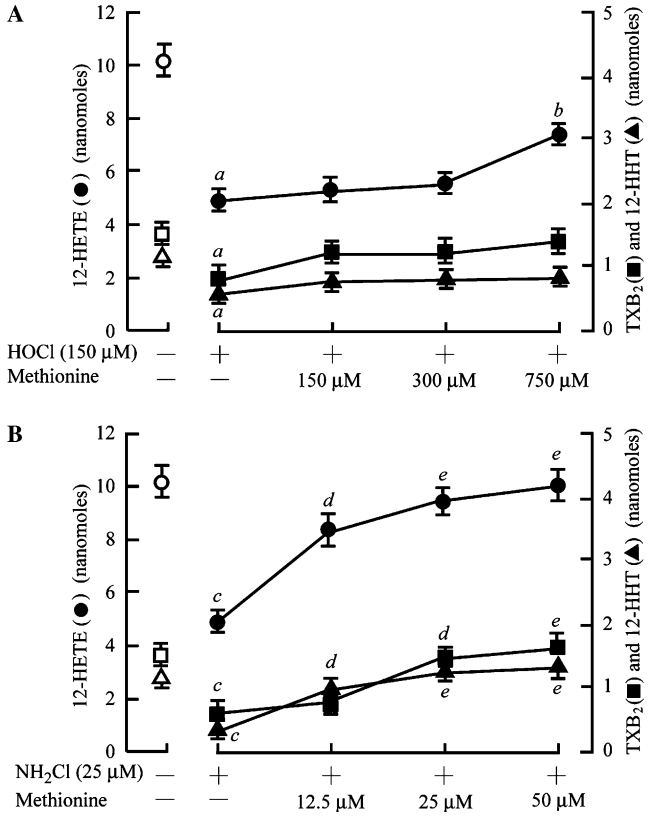

Fig. 3. Effect of methionine in the presence of HOCl (A) and NH_2Cl (B) on the formation of 12-HETE, TXB_2 and 12-HHT in washed rat platelets. Platelets (4×10^8/ml) were preincubated with or without various concentrations of HOCl, NH_2Cl and methionine for 5 min at 37 °C prior to incubation with arachidonic acid (40 μM) for 2 min at 37 °C. Each point indicates the mean of 3–5 experiments; vertical lines show SE. (A) $^{a}P < 0.01$; significantly different from the corresponding value in the absence of HOCl and methionine. $^{b}P < 0.05$; significantly different from the corresponding value in the presence of HOCl alone. (B) $^{c}P < 0.01$; significantly different from the corresponding value in the absence of NH_2Cl and methionine. $^{d}P < 0.05$, $^{e}P < 0.01$; significantly different from the corresponding value in the presence of NH_2Cl alone. ●, 12-HETE; ■, TXB_2; ▲, 12-HHT.

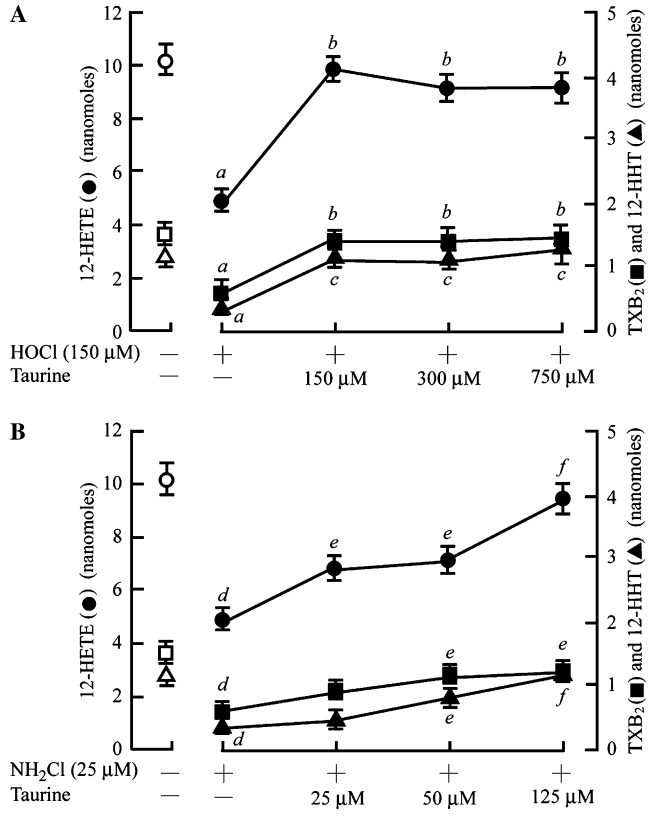

Fig. 4. Effect of taurine in the presence of HOCl (A) and NH_2Cl (B) on the formation of 12-HETE, TXB_2 and 12-HHT in washed rat platelets. Platelets (4×10^8/ml) were preincubated with or without various concentrations of HOCl, NH_2Cl and taurine for 5 min at 37 °C prior to incubation with arachidonic acid (40 μM) for 2 min at 37 °C. Each point indicates the mean of 3–4 experiments; vertical lines show SE. (A) $^{a}P < 0.01$; significantly different from the corresponding value in the absence of HOCl and taurine. $^{b}P < 0.05$, $^{c}P < 0.01$; significantly different from the corresponding value in the presence of HOCl alone. (B) $^{d}P < 0.01$; significantly different from the corresponding value in the absence of NH_2Cl and taurine. $^{e}P < 0.05$, $^{f}P < 0.01$; significantly different from the corresponding value in the presence of NH_2Cl alone. ●, 12-HETE; ■, TXB_2; ▲, 12-HHT.

252 nm, the λ_{max} exhibited by Tau-Cl. These findings together with the results shown in Table 1 indicate that taurine interferes with the inhibitory actions of HOCl and NH_2Cl on LOX and COX pathways in platelets by forming Tau-Cl from HOCl or NH_2Cl.

The present study first showed that NH_2Cl inhibits the LOX and COX pathways in platelets more potently than HOCl. The fact that Glu-Cl and Tau-Cl had no effect on the AA metabolism also may imply that the effect of NH_2Cl is specific among N–Cl derivatives. Grisham et al. [1] have reported that NH_2Cl can oxidize Fe^{2+} in erythrocyte hemoglobin to Fe^{3+}. Thus, it may be likely that NH_2Cl interacts with iron in LOX and COX, and inhibiting these two enzyme activities. The reason by which NH_2Cl is a stronger modulator in inhibiting the platelet AA metabolism than HOCl, Glu-Cl, and Tau-Cl cannot be explained clearly in the present results. However, N–Cl derivatives produced by HOCl, and primary amines or ammonium ions may be of two major types. Tau-Cl and Glu-Cl are hydrophilic derivatives [18]. In contrast, NH_2Cl is a lipophilic derivative, and having an ability to penetrate the hydrophobic barrier of biological membranes [1,18]. Thus, one feasible explanation would be guessed as follows: Glu-Cl and Tau-Cl could not easily pass through platelet cell membranes because of their hydrophilicity, and having no influence on the LOX and COX pathways in platelets, and NH_2Cl because of its hydrophobicity could penetrate the membranes, thus performing the strong modulatory effects on the AA metabolism. The low efficacy of HOCl appears to be due to the rapid reaction of HOCl with platelet surface N-compounds that are available to yield hydrophilic N–Cl derivatives or to weak permeability into cell membranes by itself [1].

Interest in chloramines has increased as a result of many studies indicating that these oxidizing agents are produced by neutrophils, monocytes, and perhaps also eosinophils and other leukocytes [8]. In leukocytes they are known to be an important class of bactericidal oxidants [19]. They

also induce the loss of cellular glutathione [20], which in neutrophils leads to impaired function [21]. They cause necrosis (lysis) of erythrocytes [1] and damage lung and upper respiratory epithelial cells [22]. Even though much of the literature on the cytotoxicity of chloramines is in regard to the induction of necrosis, chloramines are also known to induce apoptosis in gastric epithelium [23,24] and to enhance Fas-induced apoptosis in Jurkat T cells [25]. Binding of ligands to membrane-surface receptors of neutrophils stimulates the formation of NH_2Cl intracellularly and extracellularly. Grisham et al. [1] and Thomas et al. [18] have reported that phorbol myristate acetate (80 nM)-stimulated neutrophils (4×10^6/ml) with erythrocytes (2×10^7/ml) produce about 80 μM of HOCl and 50 μM of ammonium ions, and NH_2Cl thus produced is estimated to be 20 μM or over. Therefore, under pathophysiological conditions, several micromolar levels of NH_2Cl may exist in environments around platelets. Neutrophils and platelets are the predominant cell types found in the circulation after an acute inflammatory injury. Recent studies in patients and experimental animal models suggest that neutrophil–platelet interactions occur at sites of vascular injury [26]. Furthermore, inflammatory and thrombotic states are associated with circulating neutrophil–platelet aggregation [27]. Enhanced neutrophil–platelet adhesion has been observed in patients suffering from acute myocardial infarction and stroke, as well as those that have undergone coronary angioplasty [28]. Similarly, increased adhesion of monocyte and neutrophil to platelets has been reported after cardiopulmonary bypass [29,30]. Leukocyte–platelet adhesion has been reported to increase in parallel with the extent of platelet activation [31]. Therefore, the present findings that NH_2Cl is a more potent inhibitor of COX and LOX pathways in platelets than HOCl and that taurine and methionine can be inhibitors of NH_2Cl-induced alterations in the AA metabolism, together with these previous reports, may suggest that NH_2Cl formed from leukocytes-releasing HOCl, taurine, and methionine act as endogenous modulators of neutrophil–platelet adhesion involved in various vascular diseases. The present findings at least may give a new insight concerning interactions between leukocytes and platelet functions.

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