Attached are 6 abstracts submitted by Dr. David Eastmond for consideration regarding the possible oral effects of ammonium hydroxide
Ammonia (NH4OH) generated by urease from urea in the Helicobacter pylori (Hp)-infected stomach is considered as one of the major pathogenic factors in the Hp-associated gastritis but the mechanism of the deleterious action of NH4OH on gastric mucosa has not been fully explained. In this study, the gastric mucosa was exposed to topical NH4OH in various concentrations (15-250 mM) (series A) and to NH4OH in a small concentration followed by a high concentration (250 mM) of NH4OH (series B) or to the combination of urea and urease to generate NH4OH (series C) followed by 250 mM NH4OH in order to determine the "mild irritant" and protective properties of this substance on the mucosa. Administration of NH4OH alone resulted in a concentration-dependent mucosal damage starting at 30 mM and reaching at 250 mM the degree similar to that obtained with 100% ethanol. The acute mucosal damage by NH4OH was accompanied by the fall in gastric blood flow reaching nadir at 250 mM NH4OH of about 30% of the normal value. When the mucosa was first exposed to low concentration of NH4OH (15 mM) and then insulted with its larger concentration (250 mM), the lesion area was markedly reduced as compared to that obtained with 250 mM NH4OH alone and this effect was accompanied by a significant rise in the GBF. This adaptive cytoprotection by 15 mM NH4OH was reversed, in part, by the pretreatment with indomethacin to inhibit prostaglandins (PG) or L-NAME to suppress nitric oxide (NO) formation or after capsaicin-induced denervation of sensory nerves. Blockade of endogenous sulfhydryls (SH) by N-ethylmaleimide (NEM) eliminated this adaptive cytoprotection but the suppression of ornithine decarboxylase (ODC), a key enzyme in polyamine biosynthesis, by alpha-difluoro methylornithine (DFMO) failed to influence the protection and accompanying hyperemia afforded by NH4OH in low concentration. The combination of urea (2%) and urease (100 U), which raised the gastric luminal NH4OH concentration by about 5-folds, also reduced significantly the lesions provoked by 250 mM NH4OH. This protection and accompanying hyperemia induced was significantly attenuated by the pretreatment with indomethacin or hydroxyurea, a potent urease inhibitor. Hydroxyurea abolished completely the rise in luminal NH4OH produced by the combined treatment of urea plus urease. We conclude that 1) NH4OH in high concentration damages the gastric mucosa but when applied at lower concentration or generated in the stomach by urea-urease system, acts as local mild irritant to induce adaptive cytoprotection that probably involves PG, sensory nerves and arginine-NO-pathway.
Adaptive cytoprotection by ammonia and urea-urease system in the rat gastric mucosa.

Brzozowski T(1), Konturek P, Sliwowski Z, Szlachcic A, Hahn EG, Konturek SJ.

Author information:
(1)Institute of Physiology Jagiellonian University Medical School, Cracow, Poland.

Urease and ammonia (NH4OH) have been proposed to be play a major role in the pathogenesis of the the Helicobacter pylori (Hp)-associated gastric damage but the mechanism of this damage has not been fully explained. This study was designed to determine whether topical application with NH4OH at low concentration or the generation of the NH4OH in gastric lumen by the hydrolysis of urea in the presence of urease can induce adaptive cytoprotection. Single insult of NH4OH alone in various concentrations (15-500 mM) caused the mucosal damage starting at 30 mM and reaching at 250 mM the value similar to that obtained with 100% ethanol and being accompanied by the fall in gastric blood flow to about 30% of the normal value. When the mucosa was first exposed to the low concentration (15 mM) of NH4OH, causing by itself only small microscopic damage of surface epithelium, but then insulted by a high concentration (250 mM) of NH4OH, the extent of mucosal damage was greatly attenuated as compared to that caused by NH4OH alone. This "adaptive" cytoprotection, accompanied by the rise in the GBF, was reversed in part, after the pretreatment with indomethacin to inhibit PG-cyclooxygenase, with L-NAME to suppress NO-synthase or with capsaicin to induce deactivation of sensory nerves. The combined topical pretreatment with urea (2%) and urease (100 U) to generate NH4OH in the stomach, also significantly reduced the severity of gastric lesions induced by 100% ethanol and this was also accompanied by a significant rise in the gastric blood flow. The protective and hyperemic effects of urea and urease were significantly attenuated by the pretreatment with indomethacin or suppression of NO-synthase by L-NAME. The functional ablation of sensory nerves by the pretreatment with capsaicin also reversed, in part, the protective effect of the combination of urea plus urease and abolished completely the mucosal hyperemia accompanying this protection. We conclude that 1) NH4OH alone at higher concentrations damages the gastric mucosa but when applied at lower concentration corresponding to that in the stomach of Hp-infected patients, or generated by the urea in the presence of urease, NH4OH acts like "mild irritant" to induce adaptive cytoprotection, 2) this adaptive cytoprotection is mediated, in part, by endogenous PG, sensory nerves and arginine-NO-dependent pathway.

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Mucosal irritation, adaptive cytoprotection, and adaptation to topical ammonia in the rat stomach.

Brzozowski T(1), Konturek PC, Konturek SJ, Ernst H, Sliwowski K, Hahn EG.

Author information:
(1)Institute of Physiology, Jagiellonian University School of Medicine, Cracow, Poland.

BACKGROUND: The urease-ammonia (NH₄OH) system has been proposed to play a major role in the pathogenesis of the Helicobacter pylori-associated gastritis, but the mechanism of the mucosal damage has not been fully explained. This study was designed to examine possible adaptive cytoprotection and the adaptation of rat gastric mucosa to the irritant action of NH₄OH and urease.

METHODS AND RESULTS: Single application of NH₄OH alone in various concentrations (15-500 mM) caused concentration-dependent mucosal damage starting with 30 mM and reaching a maximum at 250 mM NH₄OH, similar to that obtained with 100% ethanol; it was accompanied by a decrease in gastric blood flow (GBF) to approximately 30% of the normal value. When the mucosa was first exposed to the low, non-damaging concentration (15 mM) of NH₄OH and then insulted with 100% ethanol, the extent of ethanol damage was greatly attenuated as compared with that caused by ethanol alone. This adaptive cytoprotection was accompanied by the rise in GBF and reversed, in part, by the pretreatment with indomethacin, an inhibitor of prostaglandin (PG)-cyclooxygenase; with L-NAME, a blocker of NO-synthase; or with capsaicin deactivating the sensory nerves. Damaging concentrations of NH₄OH (125 mM) caused widespread mucosal damage after the first application, but with repeated insults with 125 mM NH₄OH a gradual reduction in the mucosal lesions, accompanied by enhanced mucosal cell proliferation and over-expression of epidermal growth factor (EGF) (using immunocytochemistry) and mRNA of EGF (using trans-reverse polymerase chain reaction), were observed.

CONCLUSIONS: NH₄OH alone damages gastric mucosa only at the concentration exceeding that found in H. pylori-infected stomachs, whereas at lower concentrations it acts as 'mild' irritant to induce adaptive cytoprotection. This adaptive cytoprotection appears to be mediated, in part, by endogenous PG, sensory nerves, and an arginine-NO-dependent pathway, and repeated applications of NH₄OH induce gastric adaptation, probably mediated by enhanced expression of EGF and its receptors and by an increased cell proliferation.

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Products of neutrophil metabolism increase ammonia-induced gastric mucosal damage.

Murakami M(1), Asagoe K, Dekigai H, Kusaka S, Saita H, Kita T.

Author information:
(1)Department of Geriatric Medicine, Kyoto University Hospital, Japan.

Recent studies have indicated that ammonia is involved in the pathophysiology of Helicobacter pylori-associated gastric mucosal damage. Helicobacter pylori-associated chronic active gastritis is characterized by an invasion of neutrophils. We investigated the interrelationship among hypochlorous acid (oxidant produced by neutrophil), ammonia (product of Helicobacter pylori urease), and monochloramine (product of ammonia and hypochlorous acid) in the development of gastric mucosal damage in rats. Gastric mucosal lesions were produced by exposure of the gastric mucosa to ammonia, urea with urease, or urea with Helicobacter pylori in rats subjected to ischemia. Pretreatment with taurine (scavenger of hypochlorous acid) or antineutrophil serum significantly attenuated gastric mucosal lesions induced by the above test agents. Ammonia-induced gastric mucosal lesions were exacerbated in the presence of hypochlorous acid with concomitant generation of monochloramine. These results suggest that the ammonia, hypochlorous acid, and monochloramine triad may be important in Helicobacter pylori-mediated gastric mucosal damage.

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Implications of gastric topical bioactive peptides in ammonia-induced acute gastric mucosal lesions in rats.

Mori S(1), Kaneko H, Mitsuma T, Hayakawa T, Yamaguchi C, Uruma M.

Author information:
(1)Fourth Dept. of Internal Medicine, Aichi Medical University, Japan.

BACKGROUND: Ammonia, one of the pathogenic factors in Helicobacter pylori-induced mucosal injury, induces acute mucosal lesions in the rat glandular stomach.

METHODS: The effect of ammonia administered intragastrically on gastric peptides was investigated in urethane-anesthetized rats.

RESULTS: Gastric mucosal lesions were observed 5 min after 0.3% ammonia (4 ml/kg, intragastrically). Immunoreactive endothelin-1 (ET-1) and immunoreactive thyrotropin-releasing hormone (TRH) concentrations in the gastric wall decreased significantly 2 min and 5 min after ammonia, respectively. A significant increase in gastric juice immunoreactive ET-1 and TRH levels was reciprocally observed. The severity of gastric mucosal injury and changes in gastric immunoreactive ET-1 and TRH concentrations were shown to be concentration-dependent 30 min after ammonia. Atropine (5 mg/kg, intraperitoneally, -20 min) prevented ammonia-induced injury accompanied by a block of changes in gastric immunoreactive ET-1 and TRH concentrations. BQ-485 (ET(A) receptor antagonist; 2 mg/kg, subcutaneously) also abolished ammonia-induced lesions and gastric immunoreactive TRH changes.

CONCLUSIONS: These findings suggested that gastric ET-1 and TRH play a role in ammonia-induced gastric mucosal injury mediated via a muscarine and an ET(A) receptor.

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Irritant and protective action of urea-urease ammonia in rat gastric mucosa. Different effects of ammonia and ammonium ion.

Takeuchi K(1), Ohuchi T, Harada H, Okabe S.

Author information:
(1)Department of Applied Pharmacology, Kyoto Pharmaceutical University, Japan.

The effects of urea-urease-ammonia on the rat gastric mucosa were examined and compared with those of NH4OH and NH4Cl. The mucosal application of urea with urease produced a reduction in potential difference (PD) in a dose-related manner for urea, and a significant drop was observed by > 0.1% urea in the presence of 100 units urease. Such PD reduction was also observed when the mucosa was exposed to either NH4OH (> 0.03%) or NH4Cl (> 1%); delta PD (20 mV) caused by 0.3% NH4OH and 3% NH4Cl was equivalent to that induced by 0.5% urea+urease (100 units). The combined oral administration of urea (approximately 6%) and urease (100 units) did not induce any macroscopic damage in the gastric mucosa. NH4Cl given orally had no or little effect on the mucosa at any dose levels even at 10%, while NH4OH given orally caused hemorrhagic lesions in the mucosa at the dose of > 0.3%. In contrast, both urea+urease and NH4Cl given prior to HCl/ethanol protected the gastric mucosa against damage in a dose-related manner, and a significant effect was obtained by urea at > 0.5% and by NH4Cl at > 1%. NH4OH was also effective in reducing the severity of HCl/ethanol-induced gastric lesions at lower dose (0.3%). The protective effect of urea+urease was attenuated significantly by prior administration of indomethacin or coadministration of hydroxyurea, while that of NH4Cl or NH4OH was mitigated by indomethacin.(ABSTRACT TRUNCATED AT 250 WORDS)