Characteristics of the muscularis mucosae in the acid-secreting region of the rabbit stomach

W. H. PERCY, J. M. WARREN, AND J. T. BRUNZ
Department of Physiology and Pharmacology, School of Medicine, University of South Dakota, Vermillion, South Dakota 57069–2390

Percy, W. H., J. M. Warren, and J. T. Brunz. Characteristics of the muscularis mucosae in the acid-secreting region of the rabbit stomach. Am. J. Physiol. 276 (Gastrointest. Liver Physiol. 39): G1213–G1220, 1999.—It has been suggested that muscularis mucosae excitation may augment gastric acid secretion, implying that this muscle should contract to secretagogues or stimulation of its motor innervation. The aim of this study was to characterize in vitro the responses of the muscularis mucosae in the rabbit gastric corpus to substances that modulate acid release and to intrinsic nerve stimulation. Muscularis mucosae from both fundic and antral ends of the corpus had identical mechanical properties, contracted to ACh, ADP, ATP, and histamine but relaxed to vasoactive intestinal polypeptide. Fundic but not antral muscularis mucosae contracted to bombesin and PGE2 and PGF2α, whereas adenosine, AMP, CCK, gastrin, secretin, and somatostatin were without effect on any preparation. In both regions electrical field stimulation evoked TTX-sensitive responses consisting of an atrine-resistant contraction followed by an N-nitro-L-arginine methyl ester- and indomethacin-resistant relaxation. It is concluded from the regional variability in the pharmacological properties of the gastric muscularis mucosae that if its motor activity is linked to acid secretion this would be achieved by a neurally mediated relaxation rather than a paracrine- and/or endocrine-induced alteration in tone.

smooth muscle contraction; gastric acid secretion; gastric pit; innervation; smooth muscle relaxation

THAT THE MUCOSA, SUBMUCOSA, and muscularis mucosae could be separated from the intestinal muscularis propria was demonstrated in 1904 by Magnus (18), yet this muscle has been the subject of fewer than 120 publications since that time. For this reason, the muscularis mucosae is the least well-understood muscle in the gut, and its role in any region of the gastrointestinal tract has never been empirically established. Suggested roles for this tissue include its involvement in maintaining structural integrity (14), modulating mucosal blood flow (31), promoting lymph flow (47), physically expelling acid from the gastric glands (38), modulating gastric gland pressure (41, 42), and promoting epithelial secretion (25).

The muscularis mucosae of the stomach has received singularly little attention, and the few studies of this tissue performed to date have not yet provided a complete picture of its pharmacological profile or its potential physiological function. In the first pharmacological study of the gastric muscularis mucosae Walder (45) noted that in the human stomach the mechanical and pharmacological characteristics of the muscularis mucosae varied considerably between regions. Thus, whereas ACh contracted and norepinephrine relaxed tissues from all areas, responses to epinephrine ranged from a relaxation followed by contraction in the region of the lesser curvature, to monophasic contraction at the greater curvature. Considerable variations were also noted in the responses of these tissues to nicotine, which provided the first indirect evidence that the submucosal plexus in the stomach contained both excitatory and inhibitory nerves.

Almost 30 years later a study of the canine gastric muscularis mucosae showed that electrical field stimulation of the submucosal plexus elicited pronounced phentolamine- plus propranolol-insensitive relaxations of the muscle. Based on analysis of the superfusate bathing the tissue it was suggested that the transmitter mediating this phenomenon was vasoactive intestinal polypeptide (VIP). Substance P, whose release was also detected, caused only contractions of the muscle. An inhibitory role for endogenous VIP was further suggested by the observation that both electrical field stimulation and exogenous VIP hyperpolarized individual muscle cells of this tissue in vitro (19). These authors also provided evidence that ATP was unlikely to be an inhibitory neurotransmitter in this system because it was without effect on their preparations. However, the canine gastric muscularis mucosae is not refractory to all purines, and subsequently it has been shown to possess excitatory adenosine A2 receptors (23). This paradoxical purine-induced excitation is characteristic of the muscularis mucosae throughout the gastrointestinal tract of several species (3, 28, 30) but contrasts with their predominantly inhibitory actions on other intestinal smooth muscles (e.g., Ref. 5).

From the few studies performed to date it is clear that the properties of the muscularis mucosae in the stomach are not well understood and its potential role in gastric function has yet to be established. The name muscularis mucosae literally means “muscle of the mucosa,” and this has been taken to mean that throughout the gut its contractile activity is somehow linked to mucosal function. If, as suggested for the stomach, this muscle acts to compress or relax the gastric glands in a manner that influences acid secretion (38, 41, 42), it might then be expected that it would produce the corresponding mechanical event in vitro in response to agents that are associated with promotion or inhibition of acid release. Alternatively, the gastric muscularis mucosae may produce such a pattern of contractile activity following stimulation of the neural elements that regu-
late its function. In view of the existing body of literature concerning rabbit intestinal muscularis mucosae (10, 25, 28–30) and the known characteristics of its gastric epithelium (e.g., Refs. 9, 32), the rabbit was chosen as an appropriate model system in which to test this hypothesis. The aim of the present study was to do this by characterizing the responses of rabbit gastric muscularis mucosae to agents that are known to influence acid secretion and also to stimulation of its intrinsic innervation.

METHODS

Male New Zealand White rabbits were euthanized with pentobarbital (60 mg/kg ip). After laparotomy, full thickness, circumferentially oriented segments 3 cm × 4 mm were excised from the fundic and antral ends of the gastric corpus (Fig. 1) in an attempt to assess if the muscularis mucosae throughout the acid-secreting region of the stomach is pharmacologically homogeneous. Throughout the text these preparations are referred to as “fundic” and “antral” tissues, respectively. Circumferentially oriented preparations were utilized because in preliminary experiments it was found that longitudinally oriented tissues were relatively unresponsive to pharmacological stimuli. Preparations were then pinned out mucosal surface down in a Sylgard (Dow Corning, Midland, MI)-coated 7-in. petri dish in oxygenated Krebs solution. The muscularis propria of each strip was separated from the mucosa-muscularis mucosae by sharp dissection, and the mucosa was then cleaned of adherent mucus and food particles.

Strips of muscularis mucosae with mucosa attached were prepared using the “sutured edge” technique originally described by Percy and Christensen (26). Briefly, strips of mucosa, muscularis mucosae, and submucosa 3 cm in length were tied together to form a loop. Inasmuch as curling of the preparation flat and ensures that the submucosa and muscularis mucosae are fully exposed to the bathing medium but does not compromise its ability to contract. Strips prepared in this way were mounted in 2- or 10-ml organ baths at 37 ± 0.5°C, and one end of the tissue was connected to a stationary mounting point on the bottom of the bath. The other end was connected to a Grass FT03D force-displacement transducer under a tension equivalent to a 1.0-g load (9.8 mN). Based on preliminary experiments a load of this magnitude stretched this muscle to approximately the optimal length (Lₒ) for the generation of active tension.

For electrical stimulation of intrinsic nerves platinum wire electrodes were placed on either side of each preparation. Rectangular electrical pulses were delivered via a Grass S88 stimulator. Stimulus parameters used throughout this series of experiments (30–50 Hz, 0.5- to 0.7-ms duration, 120 mA for 10 s) were those found to elicit consistent, well-defined responses in these preparations. Responses from all preparations were recorded on a Grass model 7D polygraph.

Responses to pharmacological agents. After a 30-min equilibration period the viability of each tissue preparation was assessed by constructing an initial concentration-response curve to ACh (10⁻⁴–10⁻² M) and all subsequent contractile events were expressed as a percentage of each tissue’s maximum response to this agent. The few tissues (1–3%) that did not exhibit concentration-dependent responses to ACh were discarded. When inhibition was being measured, responses were expressed in terms of the maximum relaxation of each tissue to sodium nitroprusside (10⁻⁴ M). In addition, because responses to higher concentrations of several pharmacological agents tended to persist and subsequent responses were then often highly variable, antagonist studies were performed on matched tissues from the same animal, where one served as a control and each of the others was pretreated with one of the antagonists under investigation.

Concentration-response curves were constructed in a non-cumulative manner. The order in which drugs were applied was changed daily, and not all drugs were applied to each individual tissue. At least 30 min were allowed to elapse between the additions of different drugs. All drugs were administered in amounts not exceeding 1% of the total bath volume.

Drugs and solutions. All experiments were performed in Krebs solution of the following composition (in mM): 118.5 NaCl, 4.75 KCl, 2.54 CaCl₂, 1.19 NaH₂PO₄, 1.19 MgSO₄, 25 NaHCO₃, 11 glucose, gassed with a mixture of 95% O₂-5% CO₂.

ACh chloride (Sigma, St. Louis, MO) was dissolved in a 5% NaH₂PO₄ solution and serially diluted with Krebs solution taken to pH 4.0 by the addition of 0.1 N HCl. Atropine sulfate, famotidine, sodium nitroprusside, pyrilamine maleate (Sigma), PGE₂, and PGF₂α (Perceptive Biorheology Products, Cambridge, MA) were dissolved in and serially diluted with a modified Krebs solution of the following composition (in mM): 143 NaCl, 4.75 KCl, and 2.54 CaCl₂. Histamine acid phosphate (British Drug Houses, Poole, UK) was dissolved in and diluted with modified Krebs solution to which ascorbic acid (0.15 mM) was added to act as an antioxidant. Adenosine, ADP, AMP, ATP, bombesin, CCK, gastrin, secretin, somatostatin, VIP polypeptide (Sigma), and N⁶-nitro-L-arginine methyl ester (L-NAME) (Research Biochemicals, Natick, MA) were dissolved in and diluted with distilled water. Stock solutions were frozen, and dilutions of all drugs were made daily. These were kept on ice during experiments. Indomethacin (Sigma) was dissolved in 5% Na₂CO₃ and diluted with modified Krebs. TTX (Sigma) was dissolved in a 50 mM citric acid-48 mM

![Fig. 1. Locations of preparations of muscularis mucosae (gray bars) taken from fundic and antral ends of gastric corpus. Note that these 3 cm × 4 mm strips were cut parallel to circumferential axis of stomach.](image-url)
NaH$_2$PO$_4$ buffer. Final dilutions of TTX were made at the time of use.

Statistical analysis. When appropriate, data were analyzed using either a paired Student's t-test, a nonpaired Student's t-test, or in the case of nonparametric data a Mann-Whitney U test. In all cases n equals the number of tissues from separate animals used to derive means ± SE; P < 0.05 was considered to represent a significant difference.

RESULTS

Intrinsic mechanical properties. Muscularis mucosae from the fundic and antral ends of the gastric corpus were found to be mechanically similar under these experimental conditions. Resting tone (means ± SE) in fundic tissues was 7.22 ± 0.40 mN (n = 42) and that in antral preparations was 7.88 ± 0.32 mN (n = 42). In 15 of 33 (45%) fundic and 17 of 37 (46%) antral preparations, spontaneous contractile activity was exhibited that was TTX (10^{-6} M) resistant in each region. When measured the frequencies of these were found to be 4.70 ± 0.71 (n = 12) contractions per minute (cpm) and 4.55 ± 0.32 (n = 12) cpm, respectively. None of these values differed significantly between the fundic and antral tissues when compared by either a paired Student's t-test (resting tone) or a Mann-Whitney U test.

Responses to agents that promote acid secretion. Fundic and antral muscularis were contracted by ACh at concentrations ranging between 10^{-9} and 10^{-5} M; from 10^{-5} to 10^{-3} M; responses to ACh declined in amplitude (Fig. 2) and were frequently followed by marked relaxations. In both regions these responses to ACh were atropine sensitive (not shown), and in separate experiments those to 10^{-3} M were significantly enhanced by a 5-min prior exposure to TTX (10^{-6} M): fundus 31.0 ± 12.1 to 61.1 ± 9.4% antrum 37.2 ± 9.7 to 104.7 ± 11.4%, n = 5, P < 0.05 in each case.

Fundic muscularis mucosae was only minimally responsive to gastrin (4.76 × 10^{-12}–4.76 × 10^{-6} M), whereas that from the antral region was refractory to this agent (Fig. 2). CCK (3.76 × 10^{-12}–3.76 × 10^{-6} M) had no measurable motor effect on preparations from either region (Fig. 2).

Bombesin (3.08 × 10^{-12}–3.08 × 10^{-6} M) caused contractions of the fundic muscularis mucosae that reached 119.6 ± 24.4% (n = 6) of the ACh maximum at 3.08 × 10^{-8} M. As the concentration of bombesin was further increased, the responses of this muscularis mucosae declined (Fig. 2). These responses were both atropine (10^{-6} M) and TTX (10^{-6} M) resistant (not shown). Antral muscularis mucosae was refractory to bombesin across the entire concentration range studied (n = 6; Fig. 2).

Muscularis mucosae from both regions was contracted by histamine (10^{-9}–10^{-3} M) in a concentration-dependent manner. In the antrum the concentration-response curve for this agent lay to the right of that for ACh (Fig. 2). All gastric muscularis mucosae responses to histamine were attenuated by a 30-min pretreatment with, and in the continuous presence of the H1-receptor antagonist, pyrilamine (10^{-6} M) but not the H2-receptor antagonist famotidine (10^{-6} M; Fig. 3).

Responses to agents that depress acid secretion. Secretin (3.27 × 10^{-12}–3.27 × 10^{-6} M) and somatostatin (3.05 × 10^{-12}–3.05 × 10^{-6} M) were each without effect on either fundic or antral muscularis mucosae at any concentration (n = 6 each; Fig. 4).

VIP (3.0 × 10^{-12}–3.0 × 10^{-6} M) elicited concentration-dependent relaxations of muscularis mucosae from both the fundic and antral ends of the corpus. In both regions the largest VIP-induced inhibitory responses were equal to maximum relaxation of each tissue to sodium nitroprusside (10^{-4} M; Fig. 4).

Fundic and antral muscularis mucosae both responded in a similar fashion to all purines tested. Both types of preparations were refractory to adenosine and AMP (10^{-9}–10^{-3} M; Fig. 5). In contrast, tissues from both the fundic and antral regions were contracted by ADP and ATP in the same concentration range (Fig. 5). There were no significant differences in the maximum responses evoked by ATP relative to those produced by ACh.
ADP. Compared with each tissue’s maximum response to ACh, fundic contractions to these purines were at least twice as large as those in the antral region.

Both PGE$_2$ and PGF$_{2\alpha}$ (2.8 × 10$^{-2.8}$ to 2.8 × 10$^{-6}$ M) caused marked contractions of fundic tissues over the concentration range studied. In contrast, on antral muscularis mucosae PGE$_2$ had a weak inhibitory effect that was seen at the highest concentration utilized. Similarly, only the highest PGF$_{2\alpha}$ concentration elicited an antral response, and this was seen as small contractions (Fig. 6).

Responses to stimulation of intrinsic nerves. Both fundic and antral muscularis mucosae responded to electrical field stimulation (10-s trains, 30–50 Hz, 120 mA, 0.7-ms duration pulses) with a biphasic response that consisted of a small initial contraction followed by a pronounced relaxation that persisted for several minutes (Fig. 7). Both the excitation and the inhibition were abolished by a 5-min pretreatment with TTX (10$^{-6}$ M) but were resistant to atropine (10$^{-6}$ M; 30-min exposure), indomethacin (10$^{-6}$ M; 30-min exposure), and L-NAME (10$^{-4}$ M; 30-min exposure).

### DISCUSSION

The data obtained in the present study illustrate that, as previously noted for both the rabbit gastric muscularis propria (8) and mucosal epithelium (32), the muscularis mucosae is a pharmacologically complex tissue that is not homogeneous throughout the stomach. In addition, in several instances the muscularis mucosae was found to be pharmacologically distinct from the muscularis propria in the same organ.

Although it has been previously shown that the muscularis mucosa of the human stomach exhibits different properties in the regions of the greater and lesser curvatures (45), the present study adds to that observation by demonstrating the presence of several oral-aboral changes in the pharmacological profile of this muscle in the rabbit stomach. These changes included simple differences in muscle sensitivity to particular agents (e.g., histamine, PGF$_{2\alpha}$, purines), responses to individual agents that were present in one region but absent in another (e.g., bombesin), and the same pharmacological stimulus producing strong exci-
It has been suggested for both the muscularis propria (8) and the muscularis mucosae (10) that one factor contributing to the variability of such preparations to pharmacological stimuli is their resting tone at the time when the agent under study is applied. However, under the experimental conditions utilized here, the mechanical characteristics of muscularis mucosae preparations from the fundic and antral ends of the gastric corpus were identical. It could also be argued that a proportion of the regional variations seen in this study reflects components of drug action that are indirect and mediated via the tissues' intrinsic innervation. Again, the results of the present study do not support such a conclusion. The intrinsic innervation of the muscularis mucosae from the fundic and antral ends of the corpus appeared to be indistinguishable from each other. Not only were the mechanical events following electrical stimulation exactly alike, they were also found to be equally resistant to a wide variety of pharmacological manipulations. Thus variations between preparations from these two regions to excitatory and inhibitory stimuli appear to reflect true pharmacological differences, rather than being artifacts arising from the mechanical characteristics or innervation of the tissues.

Fundic and antral muscularis mucosae responses to ACh were biphasic at higher concentrations, with relaxation following excitation. Both components of this response were atropine sensitive, and responses to higher ACh concentrations were enhanced by TTX pretreatment. This suggests that in these preparations cholinergic stimulation evokes a direct muscle excitation at low concentrations, coupled to a muscarinic stimulation of intrinsic inhibitory submucosal neurons at higher concentrations. The presence of excitatory muscarinic receptors on autonomic ganglia is a well-characterized phenomenon (24, 27), and, in addition, these responses reflect the original observations of Walder (45) regarding cholinergic stimulation of inhibitory neurons associated with the gastric muscularis mucosae.

In contrast to the mucosa in this region (32), the results from the present study make it appear unlikely that the actions of ACh on the gastric muscularis mucosae include a gastrin-mediated component. This may be concluded because, in contrast to its excitatory
actions on the rabbit gastric muscularis propria (21), this peptide was without a significant effect on muscularis mucosae preparations from either the fundic or antral ends of the corpus. These observations also exclude a role for bombesin in ACh-induced muscularis mucosae responses because ACh elicited excitatory effects on both fundic and antral tissues, whereas bombesin affected only fundic preparations. Furthermore, as the effects of bombesin on fundic muscularis mucosae were atropine and TTX resistant and because of the lack of effect of gastrin on preparations from either region, it may be concluded that bombesin itself has a direct action on fundic tissue via receptors that are absent in the antral region. The presence of such receptors on gastric smooth muscle has been described previously (16, 39), and the biphasic nature of the bombesin concentration-response curve suggests that in fundic muscularis mucosae they are easily desensitized to the effects of this peptide.

Unlike its H$_2$ receptor-mediated excitatory effects on the gastric mucosa (32), histamine-induced contraction of the fundic and antral muscularis mucosae arose via the activation of H$_3$ receptors. Although this contrasts with the reported presence of inhibitory H$_2$ receptors on the canine gastric muscularis mucosae (22), it is in agreement with the mechanism underlying the corresponding responses of the rabbit colonic muscularis mucosae to this agent (30). In contrast to the colon, however, muscularis mucosae from both the fundic and antral regions of the gastric corpus were relatively insensitive to even high concentrations of histamine.

One characteristic of the two muscularis mucosae preparations used in these studies was the greater sensitivity of fundic tissue to pharmacological agents compared with the corresponding antral responses. However, although purine-induced fundic responses were always larger than those in the antrum, based on the lack of effect of either adenosine or AMP, these appeared to be mediated via P$_2$ receptors in both regions. This observation is in agreement with the types of purinoceptors found in the rabbit esophagus (28) and colon (30) but contrasts to the inhibitory actions of these compounds on gastric acid secretion that is thought to be mediated via activation of adenosine receptors on somatostatin-releasing D cells (15). P$_2$ receptor-induced excitation of the muscularis mucosae is also in stark opposition to the previously demonstrated inhibitory actions of purines on the rabbit gastric muscularis propria (2) that are mediated by P$_1$ receptors (11).

A comparable difference in responses between fundic and antral preparations was also noted for PGE$_2$ and PGF$_{2\alpha}$. Thus, whereas each of these had marked excitatory effects on fundic muscularis mucosae, on antral tissues they were inactive except at high concentrations. Under these conditions PGE$_2$ appeared to produce a weak inhibitory response, whereas PGF$_{2\alpha}$ evoked small contractions. The gradient in the effects of these prostaglandins on tissues from the fundic and antral ends of the corpus makes it appear likely that their proposed role in increasing gastric gland pressure in response to different stimuli (42) may be region specific, rather than a global gastric phenomenon. However, the sensitivity of fundic tissues to these arachidonic acid metabolites also suggests that they play a unique role in its function because muscularis mucosae from the esophagus (28) and from the antral end of the corpus are essentially refractory to the actions of these agents.

A number of peptides that have marked effects on the gastric mucosa and/or exert effects on other intestinal smooth muscles were without effect on either muscularis mucosae preparation used in the present study. These included CCK, a peptide that elicits excitation of several types of gastrointestinal smooth muscle (20, 33, 40) including rabbit gastric muscularis propria (21, 44), somatostatin, an endogenous agent that stimulates enteric neurons (6), and secretin, a structural relative of VIP (35). However, this cannot be interpreted as an idiosyncratic feature of the muscularis mucosae in all species because it has been known for some time that canine small intestinal muscularis mucosae exhibits well-defined motor responses to a variety of such substances, including CCK, gastrin, and secretin (43). These data suggest that in the rabbit stomach the muscularis mucosae and its intrinsic innervation lack the appropriate receptors for certain of these substances. This also implies therefore that differences in
sensitivity between the fundic and antral muscularis mucosae to other pharmacological agents may be due to relative receptor densities at these locations.

Although muscularis mucosae motor responses to the test substances utilized in this study were highly variable, the responses of this muscle to stimulation of its intrinsic innervation were regionally uniform and extremely consistent. Of all substances evaluated in the present study only VIP mimicked this effect in both fundic and antral tissues, and, as in the canine and rat stomach (1, 41) it remains a candidate as a neurotransmitter involved in the neurally evoked inhibitory response. This conclusion is further strengthened by the observations that the field stimulation-evoked inhibitory response was L-NAME resistant and that norepinephrine has only excitatory actions on rabbit fundic and antral muscularis mucosae (29). These observations further highlight the pharmacological uniqueness of the muscularis mucosae in this region, because nitric oxide is known to play a significant role in relaxation of the rabbit gastric muscularis propria (7, 12).

One of the principal aims of this study was to try to determine if there is a potential relationship between muscularis mucosae contraction and gastric acid secretion, as originally proposed by Seelig et al. (38). In the rabbit stomach it has been shown that acid release is directly stimulated by ACh and histamine and indirectly by ACh eliciting gastrin (32) and histamine (9) release. In the present study both ACh and histamine evoked muscularis mucosae contraction in each region studied, and these data at first appear to add support to the suggestion that muscularis mucosae excitation could be linked to acid secretion and its subsequent expulsion from the gastric pits. However, several additional pieces of evidence make it appear unlikely that agents associated with the promotion or inhibition of gastric acid secretion utilize muscularis mucosae contraction to complement their actions on the mucosa itself. This conclusion is based on the following observations:

First, several endogenous agents that modulate acid secretion, including CCK (17, 36), gastrin (32), secretin (13), somatostatin (37), and adenosine (34, 46), were without a measurable effect on muscularis mucosae from either region of the gastric corpus. Second, PGE₂ and PGF₂α, substances that are capable of inhibiting acid secretion (4, 32), contracted fundic muscularis mucosae while eliciting trivial responses in antral preparations. Third, throughout the acid-secreting region of the stomach the predominant response of the muscularis mucosae to stimulation of its intrinsic innervation was a pronounced relaxation.

Based on these results, the highly consistent nature of the responses of this muscle to electrical field stimulation and to exogenous VIP suggests the potential for muscularis mucosae relaxation, rather than contraction, to be allied to acid secretion. This is supported by the recent demonstration of VIP-containing neurons associated with the gastric muscularis mucosae (41), hyperpolarization of canine gastric muscularis mucosae cells by application of this peptide (19), and its ability to decrease gastric gland pressure in the rat stomach (41). These observations and the data from the present study support the idea that a neurally mediated relaxation of the gastric muscularis mucosae may facilitate acid release by opening the gastric glands (41).

In addition to its potential relationship with acid secretion, the results presented here do not exclude additional roles for the muscularis mucosae in modulating other aspects of gastric epithelial function such as the secretion of mucus or of water and HCO₃⁻. Furthermore, the data strongly suggest that this muscle is not designed to perform one simple task throughout the entire stomach. The present study therefore provides additional evidence to support the belief that the muscularis mucosae has a different physiological role at successive locations within the gastrointestinal tract and that it undergoes large regional changes in its pharmacological profile to enable it to perform these functions.

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