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Review article: rebamipide and the digestive epithelial barrier

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SUMMARY

Rebamipide exerts a positive effect on the digestive epithelial barrier by reinforcing its integrity in normal and in inflammatory conditions, and by normalizing the macromolecular transport across this barrier, increased by Helicobacter infection. Moreover, in mice, rebamipide is capable of diminishing allergic sensitization and of counteracting the inhibitory effect of *Helicobacter pylori* on oral tolerance to dietary antigens. These properties of rebamipide could explain its anti-inflammatory activity with respect to the digestive mucosa and could provide protection against allergic sensitization to foreign antigens in susceptible individuals.

INTRODUCTION

The digestive epithelial barrier serves to separate the digestive lumen in communication with the external world from the internal compartments of the organism. Its roles are to maintain a selective exchange of different substances (secretions, nutrients, etc.) between these two compartments, and to assure the protection of the organism against the penetration of micro-organisms and other exogenous antigens, essentially contained in food. These functions are assured by two crucial elements of the digestive epithelial barrier—the epithelial cells and the intercellular junctions—which provide two pathways for transepithelial transport: transcellular and paracellular (Figure 1). The gastric barrier constitutes an important part of the digestive epithelial barrier, and its protective role against the deleterious effect of different endogenous and exogenous compounds, e.g. hydrochloric acid, pepsin, bile salts and other chemicals, has been recognized since the middle of the 20th century.[1–5]

Modifications of digestive barrier function, reflected by an increase in paracellular and/or transcellular permeabilities are found in many diseases, such as inflammatory bowel disease,[6–8] colonic cancer,[9] infectious diarrhoea,[10, 11] food allergy,[12, 13] reflux oesophagitis,[14] and the gastric lesions (erosions and ulcers) induced by various gastrotoxic agents.[15, 16]

Many factors can alter the epithelial barrier, the most important of which are bacteria and their products, immune cells and inflammatory mediators, as well as different chemical compounds. *Helicobacter pylori*, the main etiopathogenic factor of chronic gastritis and other gastric diseases, is able to increase both paracellular and transcellular epithelial permeability, *in vitro* and *in vivo*.[17–21] Its effects on the gastric barrier could be an important mechanism of the pathogenesis of gastro-duodenal, and probably also some extra-digestive diseases related to *H. pylori* infection.

Rebamipide is a gastroprotective agent which accelerates gastric ulcer healing in an experimental model,[22] and has been shown to be effective in the treatment of chronic[23] and acute[24] gastritis in humans. It also attenuates the indices of colitis in DSS-induced colitis formation in the rat[25] and has an anti-inflammatory effect on the proctitis type of ulcerative colitis in humans.[26] The mechanisms of the gastroprotective and anti-inflammatory actions of rebamipide are not completely understood, but may be partly due to the various properties of this drug such as scavenging of

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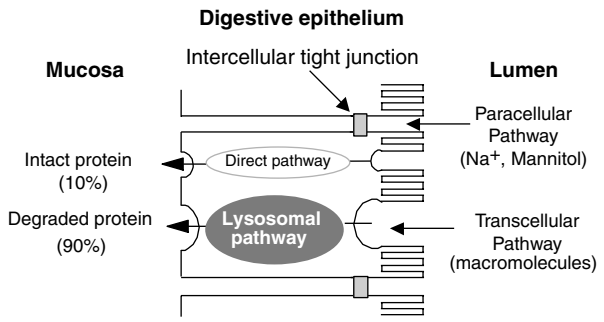

Figure 1. Transepithelial transport across the digestive epithelium in physiological conditions. Small molecules (mannitol, Na^+) cross the epithelium along the paracellular pathway, e.g. through the intercellular tight junctions and intercellular spaces. Macromolecules (proteins) cross the epithelium along the transcellular pathway, e.g. across the cells. During their transcellular passage, a major fraction of the protein (90%) is degraded in the lysosomal system and only a small fraction (10%) passes the epithelium in intact form.

cytokine-induced reactive oxygen species,[27] induction of prostaglandin production,[28] or inhibition of the pro-inflammatory cytokine secretion by immune cells.[29, 30]

The anti-inflammatory and gastro-protective actions of rebamipide could also be related to its beneficial effect with respect to the epithelial barrier. This aspect has been well studied, and all data suggest that rebamipide has a protective effect on the digestive epithelial barrier. The general principles of the transepithelial transport, data concerning the effect of rebamipide on the epithelial barrier *in vitro* and *in vivo*, and some arguments in favour of the possible consequences of its effect on the host immune responses, are presented in this review.

PARACELLULAR VS. TRANSCELLULAR TRANSPORT ACROSS THE DIGESTIVE EPITHELIUM (FIGURE 1)

The paracellular pathway is mainly used by small molecules which diffuse through the thin intercellular spaces. Paracellular permeability reflects epithelial integrity and can be measured by transepithelial electrical resistance (or its inverse, ionic conductance) and by mannitol fluxes, a reference marker for this pathway. In physiological conditions, the paracellular pathway is not accessible to macromolecules which cross the barrier via the transcellular pathway, i.e. transcytosis, as demonstrated by immunohistochemistry[31] and by *ex vivo* and *in vitro* studies performed in Ussing chambers with animal tissues,[32, 33] human intestinal biopsies,[34] or cultured enterocytes.[35] Horseradish peroxidase (HRP) is a reference marker frequently used to measure transepithelial macromolecular transport. There are two distinct pathways of macromolecular transport across the epithelial cell: a minor direct transcellular pathway (<10% of protein) which allows the passage of intact proteins, and a major pathway (>90% of protein) corresponding to the proteins which undergo lysosomal degradation during the transcellular passage.[33, 36] When the epithelium is damaged, a paracellular passage of protein may occur.

IN VITRO EFFECT OF REBAMIPIDE ON THE EPITHELIAL BARRIER

This effect was studied in Ussing chambers using the HT29-19A intestinal epithelial cells grown as monolayers, mounted as a model of the epithelial barrier.

In basal conditions, rebamipide at concentrations of 1 mM and 2 mM increased the integrity of the monolayer as reflected by increased electrical resistance and decreased mannitol fluxes across the epithelium. The reinforcement of the barrier in basal conditions may play an important role in the protective action of rebamipide on the epithelium of the digestive tract. It is known that rebamipide can protect the gastric mucosa against different damaging factors such as NSAIDs,[37] ischaemia-reperfusion injury,[38] platelet-activating factor-induced gastric injury,[39] ethanol-induced injury,[28] and oxygen radical-mediated gastric injury.[40]

Rebamipide also has a positive effect on epithelial barrier function in inflammatory conditions. This effect concerns both the paracellular and transcellular pathways. At a dose of 2 mM, rebamipide prevents the disruption of epithelial integrity by IL-1β, as shown by the higher electrical resistance of monolayers treated with IL-1β and rebamipide compared with monolayers treated only with IL-1β (Figure 2). IL-1β is putatively a major pro-inflammatory cytokine, playing an important role in the induction and maintenance of inflammation, including the gastric inflammation associated with *H. pylori* infection.[41] Recently, a genetic polymorphism of IL-1β has been discovered, and some of its genotypes have been associated with an increased risk of gastric cancer.[42] The protection by rebamipide against the deleterious effect of IL-1β on the epithelium may be an important element of its anti-inflammatory properties on the gastric mucosa, and could be related in part to its anti-apoptotic effects. Apoptosis, expressed as an

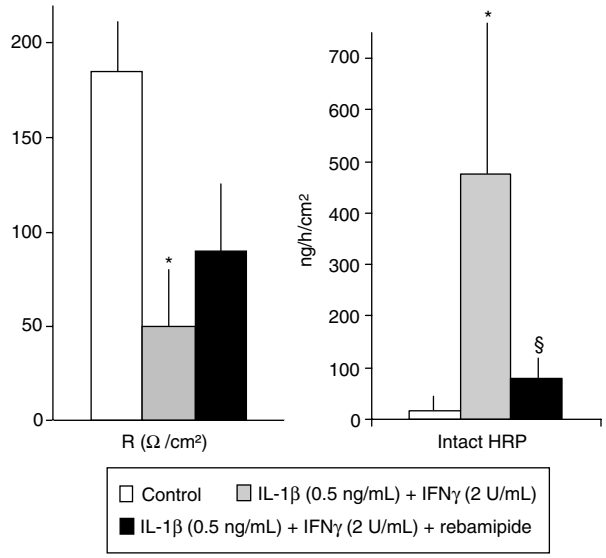

Figure 2. Effect of IL-1β (0.5 ng / mL) + stimulating dose (2 U / mL) of IFNγ and rebamipide on the integrity of the epithelial barrier and macromolecular transport across this barrier. IL-1β decreased the electrical resistance (R) of the cell layer, attesting the disruption of epithelial integrity; this effect was prevented by rebamipide. IL-1β also increased the intact horseradish peroxidase (HRP) flux across the epithelium and this increase was prevented by rebamipide. * and §: significantly different from controls and from IL-1β-treated cells, respectively ($P < 0.006$).

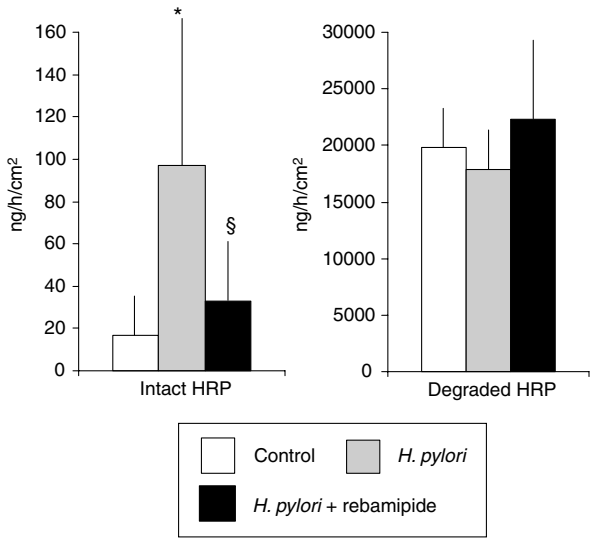

Figure 3. Effect of *H. pylori* and rebamipide on macromolecular transport across the epithelium. *H. pylori* increased the intact horseradish peroxidase (HRP) fluxes across the barrier without modifying the degraded HRP fluxes. Rebamipide restored the normal intact HRP fluxes. * and §: significantly different from controls and from *H. pylori*-treated cells, respectively. ($P < 0.007$).

apoptotic index, was increased in cells treated with IL-1β compared with control cells, and prevented by rebamipide.

At a concentration of 1 mM, rebamipide restores the normal intact horseradish peroxidase fluxes across the barrier, increased either by the infection with CagA(+) and VacA(+) wild strain of *H. pylori* (Figure 3), or by treatment of the cells with IL-1β (Figure 2). In the case of IL-1β, this effect could be simply explained by reinforcement of the integrity of the barrier by rebamipide, since the increase in intact horseradish peroxidase fluxes by IL-1β is mainly related to the induction of a paracellular leakage of protein by this cytokine. However, *H. pylori* increases the passage of intact protein through the transcellular pathway without modifying the paracellular permeability of the epithelium.[20, 43] In this case, the mechanisms of action of rebamipide are not clear, but the inhibition of bacterial adherence to the epithelial cells, as previously demonstrated,[44] may play a role. Indeed, a direct interaction between the bacterium and epithelial cells seems to be mandatory for the effect of *H. pylori* on the intact protein fluxes.[20]

Taken together, these results provide evidence which suggests that rebamipide exerts its protective effect on the gastric mucosa *in vitro* by reinforcing the epithelial barrier in normal conditions, and by counteracting the deleterious effect of *Helicobacter* and IL-1β on macromolecular permeability.

IN VIVO EFFECT OF REBAMIPIDE ON THE EPITHELIAL BARRIER

The beneficial effects of rebamipide on the digestive epithelial barrier were also found *in vivo*. This effect was again expressed on two levels: an improvement in epithelial integrity (paracellular permeability), and the restoration of normal transcellular macromolecular transport (transcellular permeability).

In normal C3H / He mice treated with rebamipide, reinforcement of the integrity of the intestinal epithelium was demonstrated by an increase in the transepithelial electrical resistance of intestinal fragments mounted in an Ussing chamber. The reinforcement was independent of the presence or absence of *H. felis* infection (Figure 4) (Matysiak-Budnik *et al. Infect Immun* 2003, in press). This result shows that rebamipide also acts on intestinal tissue and may

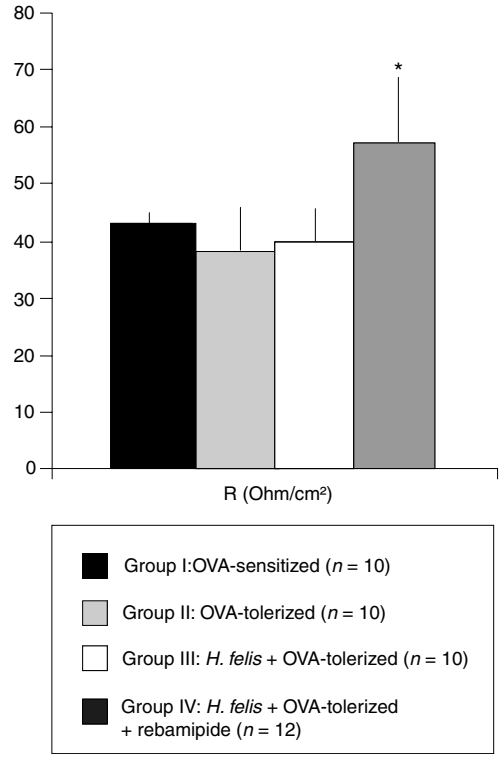

Figure 4. Electrical resistance (R) of the intestinal mucosa in mice sensitized or tolerized to ovalbumin (OVA) and infected or not with *H. felis*, measured in Ussing chamber. Mice treated with rebamipide present a significantly higher R than the mice from all other groups, attesting to an improvement in intestinal epithelial integrity by rebamipide. *Significantly different from all other groups ($P < 0.01$).

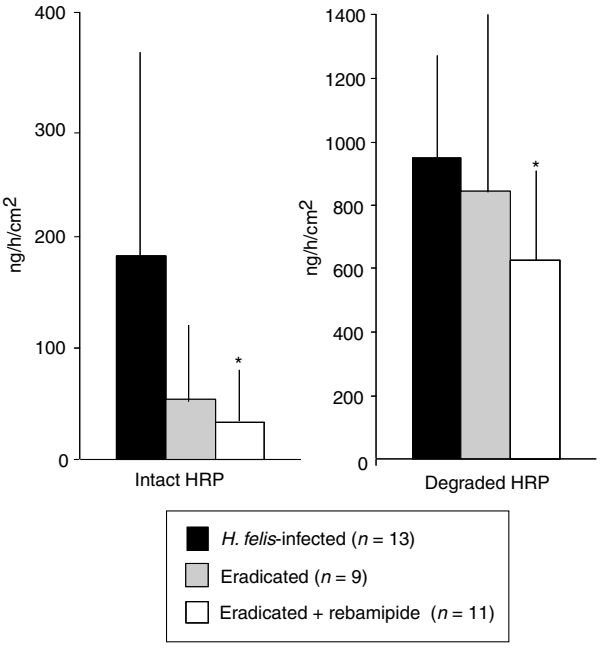

Figure 5. Effect of eradication of *H. felis* and of subsequent treatment with rebamipide on horseradish peroxidase (HRP) transport across the antral gastric mucosa in mice. *Significantly different from infected mice ($P < 0.03$).

explain the positive effect of rebamipide in inflammatory bowel diseases.[26]

In an experimental model with C57 Black mice infected with *H. felis*, rebamipide contributed to the normalization of gastric permeability to macromolecules after eradication of the bacteria. The gastric antral permeability to horseradish peroxidase measured in an Ussing chamber was significantly increased in the presence of *H. felis*-associated inflammation in mice. After bacterial eradication, in mice only treated with antibiotics, no significant reduction in gastric permeability to horseradish peroxidase was observed, relative to infected nontreated mice. However, mice which after eradication received rebamipide (30 μg / day) for 4 weeks had a significantly lower permeability to horseradish peroxidase in the antrum than infected placebo-treated mice (Figure 5).[45] These results suggest that rebamipide facilitates the restoration of normal permeability to macromolecules. The mechanisms of this action are not known. At least two pharmacological features of rebamipide could play a role: hydroxyl radical-scavenging activity and inhibition of lipid peroxydation. Infection with *H. felis*, like infection with *H. pylori*, is often accompanied by an activation of neutrophils and by the production of oxygen free-radicals, which are believed to be responsible for the damage on the gastric mucosa which is found in the presence of bacteria. Rebamipide has been shown to remove the oxygen radicals induced by *H. pylori*-activated neutrophils,[46] and also to reduce the adherence of *H. pylori* extract-elicited neutrophils to the endothelial cells.[47] The inhibition of neutrophil activity and the elimination of free radicals by rebamipide may be involved in its beneficial effect on gastric permeability. The increase in gastric permeability is a complex phenomenon initiated by the bacteria, but subsequently maintained by the inflammatory process that takes place in the mucosa. When the bacteria disappear, the inflammatory process should also disappear, but it is possible that dietary antigens have a role in prolonging this vicious circle. Rebamipide, by inhibiting neutrophil activity and/or eliminating free radicals, would then have a beneficial effect on gastric permeability which in

turn may contribute to inhibition of the recruitment of polynuclear cells (PMN). Indeed, in this experimental study, the PMN were present in only 2 of 11 (18%) mice treated after eradication with rebamipide vs. 4 out of 9 mice (44%) of those treated with placebo.

INTERFERENCE OF REBAMIPIDE WITH THE MUCOSAL IMMUNE HOST RESPONSE TO DIETARY ANTIGENS?

One could hypothesize that in *H. pylori*-infected subjects, the increase in the absorption of antigens across the digestive epithelial barrier by *H. pylori*[20, 21] could lead to a sustained increased load of food proteins in the digestive mucosa and induce, in susceptible individuals, food protein sensitization and favour food allergy. Indeed, an association between *H. pylori* infection and the development of food allergy has already been suggested in both children[48] and adults.[49] Rebamipide could provide protection against allergic sensitization to foreign antigens by normalizing macromolecular transport across the gastric mucosa. In order to study this hypothesis, a systemic immune response to dietary antigens was studied in C3H/He mice infected with *H. felis* using two approaches: the study of oral tolerance and the study of oral sensitization. Oral tolerance is defined as a systemic unresponsiveness, i.e. the lack of production of specific antibodies to the systemically delivered antigen, induced by the prior feeding of the same antigen. Abolition of oral tolerance can be considered as a promotion of sensitization. We were able to show that infection with *H. felis* inhibited the development of oral tolerance to ovalbumin (OVA) in mice by the measurement of significantly higher serum specific anti-OVA IgE titres in animals tolerized to OVA and infected with *H. felis* than in OVA-tolerized but noninfected animals. Treatment with rebamipide, which was administered to mice together with the tolerization protocol, abolished the inhibitory effect of *H. felis* on oral tolerance since in infected mice treated with rebamipide, the anti-OVA IgE titres were similar to those observed in OVA-tolerized noninfected mice (Figure 6). Similarly, in a sensitization study to orally administered hen egg lysosyme (HEL), rebamipide inhibited the development of sensitization to HEL, shown by lower specific IgE and IgG titres in mice sensitized to HEL and treated with rebamipide relative to HEL-sensitized and placebo-treated mice (Figure 7)

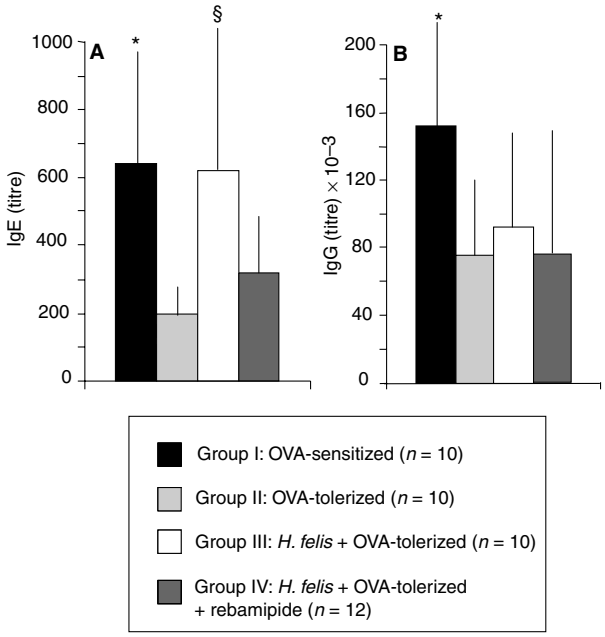

Figure 6. Specific anti-OVA serum IgE (A) and IgG (B) titres (mean ± s.d.). OVA-sensitized mice present significantly higher IgE and IgG titres than OVA-tolerized mice or mice treated with rebamipide. *H. felis*-infected OVA-tolerized mice present significantly higher IgE titres than OVA-tolerized mice, reflecting the abrogation of oral tolerance by *H. felis*. *Significantly different from groups 2 ($P < 0.03$) and 4 ($P < 0.04$). §Significantly different from groups 2 ($P < 0.01$) and 4 ($P < 0.05$).

(Matysiak-Budnik *et al. Infect Immun* 2003, in press). This study demonstrates the protective effect of rebamipide with respect to the maintenance of oral tolerance, and the tendency of this compound to inhibit the development of allergic sensitization to an orally administered dietary antigen. This effect of rebamipide could be partly explained by its beneficial action on the intestinal epithelial barrier function, as was previously described, i.e. the reinforcement of the epithelial barrier integrity and normalization of protein transport across the gastric mucosa. Both phenomena may have contributed to the inhibition of the immune response to orally administered antigens in infected animals, although other mechanisms could also play a role. Rebamipide could attenuate the immune response to orally administered antigens, i.e. antigen-specific IgE and IgG production, by inhibiting the secretion of different cytokines directly or indirectly implicated in antibody production. Indeed, rebamipide has been shown to inhibit the secretion of IL-1β, IL-8, IL-10, IFNγ and TNFα by *H. pylori*-stimulated human

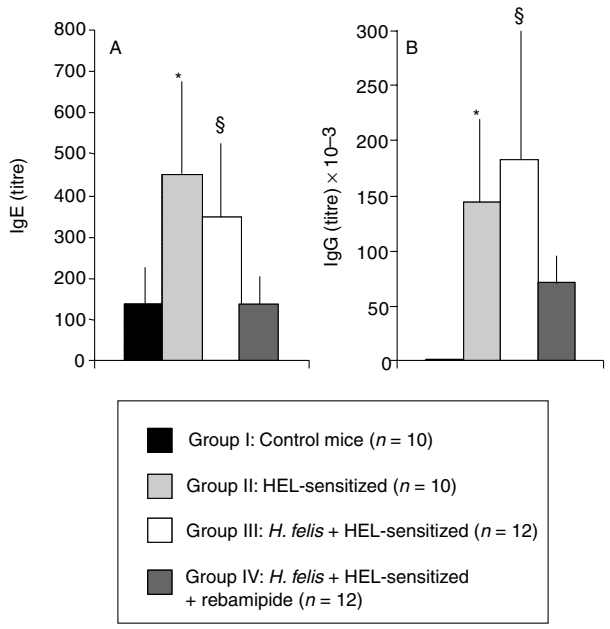

Figure 7. Specific anti-HEL serum IgE (A) and IgG (B) titres (mean ± s.d. of 1/titre) in mice. For IgE panel: *significantly different from groups I ($P < 0.004$) and IV ($P < 0.002$); §significantly different from groups I ($P < 0.04$) and IV ($P < 0.04$). IgG panel: significantly different from group 1: *($P < 0.03$), §($P < 0.004$).

peripheral blood mononuclear cells,[29] or of IL-8 by gastric epithelial cells.[50] This inhibition, as well as the anti-inflammatory properties of rebamipide, could be related to its known capacity to nonspecifically block the NFκB pathway.[51, 52] The down-regulation of pro-inflammatory cytokine production may also interfere with antigen presentation by decreasing the expression of co-stimulatory molecules on APC.

CONCLUSION

Rebamipide shows protective properties with respect to the digestive epithelial barrier both *in vitro and in vivo*, and a capacity to diminish allergic sensitization and to promote oral tolerance to dietary antigens in mice. These properties can explain its beneficial effect in the treatment of gastritis, and may suggest its potential usefulness in the prevention and/or the treatment of food allergy and inflammatory bowel diseases, since an excessive antigenic stimulation of the mucosal immune system is likely to play a role in the pathogenesis of these diseases.

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