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Biological Benefits of Helicobacter Pylori and the Intelligence of Juxta-mucosal Ammonia

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Abstract This review aims at throwing simple light on a huge biological symphony of cure and poison which is being played in great vital harmony by the wonderful ammonia produced by the bacterium ***Helicobacter pylori*** close to the gut mucosa and nitric oxide (NO) liberated by the micro-capillary endothelium. ***H. pylori*** colonized the stomach since an immemorial time, it is leading in the stomach the behavior of natural bacteria. It has got a long history of minor harm inside the stomach before development of the antibiotic strategy against it, it has got huge natural talents of survival within the strong gastric acid, its recurrence in the stomach is un-avoidable and in addition it has got highly protective vital benefits. ***H. pylori*** is hugely biologic, it protects the gastric wall via its juxta-mucosal ammonia from its acid if it goes in excess, it protects from the harmful sequels of absence of the acid during absence of food due to scattering of the ammonia at its immediate vicinity while searching remnants of food in gastric lumen, its constant residual gastric ammonia maintains the integrity of gastro-esophageal sphincter protecting against acid reflux disorders, it is mostly responsible for formation of the protective thick viscous gastric mucus layer via its juxta-gut mucosal ammonia and NO liberated due to the effect of shear stress of ammonia, its residual ammonia helps to maintain the integrity of intestinal motility protecting from delay of intestinal contents and it helps to support the bowel motion functions via helping formation of the soft colonic mucus that helps to make the motion easy while maintaining the colonic contractions helps to shape/form the bowel contents and wrap it with the soft mucus. In addition, residual colonic ammonia produced due to the natural existence of ***H. pylori*** is responsible to maintain a normal physiologic liberation of pelvic NO and hence it participates in maintaining the integrity of the natural physiological desire and sense of libido that allows a person normal sex drive response and satisfactory sexual performance during ultimate situations. Residual colonic ***H. pylori***-produced ammonia participates to maintain a normal physiological level of systemic ammonia that helps to ensure the micro-capillary endothelial-induced NO liberation via the effect of shear stress and therefore it could be healthy for many vital organs and functions in the body. Normal levels of systemic ammonia was demonstrated healthy towards the symptoms and onset of Alzheimer disease. In conclusion, ***H. pylori*** accordingly is biologic and not pathologic or it is not essentially pathologic by its own but it is forced to any pathologic attitude related to it due to misbehavior in food habits or the antibiotic aggression towards it. A highly vital series of physiological benefits are being played by the natural existence of ***H. pylori***, its juxta-mucosal ammonia and the NO liberation produced due to shear stress effect of ammonia; when these parameters exceed its natural limits then a cure turns into a poison.

Keywords Ammonia, Helicobacter pylori, Nitric oxide

1. Introduction

Helicobacter pylori colonized the stomach since an immemorial time; as if both the gastric wall and the bacterium used to live together in peace harmless to each other [1-3]. More than 160 years before in 1852, it was reported that ammonia exists in the stomach. In 1930s, it was reported that the ammonia demonstrated in the stomach is due to the effect of a urease enzyme. In 1960s, it was confirmed that urease activity in the stomach is not a property of the stomach wall but it is of a bacterial origin. Early in 1980s, it was clearly emphasized that the ammonia detected in the stomach is not toxic but it is even beneficial [4]. In 1985, ***H. pylori*** was re-discovered or as claimed by two Australian physicians; "I got it, a bacterium surviving in the stomach". They accused it for causing gastritis, gastric ulcers and cancer; therefore, they started their antibiotic violence against this bacterium in 1986. Accordingly, a world's medical attitude was established against ***H. pylori*** and that its eradication should be a necessary attempt due to a suggestion of its close relation to acid peptic disease, gastric carcinoma and lymphoma [1-3]. Thereafter, a lot of scientific inconvenience among researchers and

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investigators was expressed during medical meetings and conferences about the story claimed by the two Australian doctors about ***H. pylori***. [2]

The last three decades have shown prevalence of abnormal-behavior ***H. pylori*** strains and the rising figures of many medical challenges related to these strains. Therefore; the last three decades demonstrated re-discovery or the claim of discovery of ***H. pylori***, the antibiotic aggression towards it, the prevalence of its abnormal-behavior strains instead of getting rid of it and the flare up of a lot of medical challenges related to these ***H. pylori*** strains [1, 3]. A medical assessment that does not correlate between these well established four observational findings is definitely not employing a clinical sense.

Existence of ***H. pylori*** in the stomach is life-long unless eradicated but recurrence of ***H. pylori*** in the stomach is un-avoidable [5-7]. In children, existence of ***H. pylori*** starts trans-familial early during childhood and the ***H. pylori*** strain is often identical with that of parents. Interestingly, children maintain the same strain genotype even after moving to a different environment [8]. Frequent elimination/migration of ***H. pylori*** in children is probably common due to the frequent use of antibiotic for different reasons; yet, trans-familial recurrence in children is still hardly avoidable [7, 8].

H. pylori resides and colonizes under the layer of mucus overlying gastric mucosa. Although gastric acid plays an important role in the protection against many enteric organisms and ***H. pylori*** can be readily killed by a brief exposure to diluted hydrochloric acid solutions; survival of the bacterium inside the stomach is achieved through various defense mechanisms. The organism's intense urease activity produces ammonia from organic urea of gastric juice in such amounts that can buffer the pH of gastric acid. The gastric mucus layer is relatively thick, alkaline and viscous allowing for ***H. pylori*** pH gradients from approximately pH 2 close to the gastric lumen until pH 7.4 immediately adjacent to the mucosa. The high motility of ***H. pylori*** via its flagellates even in the very viscous mucus allows the organism to swim freely and migrate to reach the most favorable pH gradient. Elaboration of ammonia from endogenous urea that buffers gastric acid reaching the immediate vicinity of the bacterium constitutes an essential mechanism for survival of ***H. pylori*** in its strongly acidic gastric habitat [9-13].

H. pylori in the stomach is leading the behavior of natural bacteria such as its existence since an immemorial time, its huge biological talents of survival inside the strongly acidic gastric lumen atmosphere, the extremely long history with minor harm before the antibiotic violence towards it, its recurrence in the stomach is absolutely un-avoidable and its documented biologic protective benefits [1-3].

AIM: This review aims at throwing simple flash of light on a huge biological symphony of cure and poison played in great vital harmony by the intelligent juxta-mucosal production of ammonia of the bacterium ***H. pylori*** and the smart nitric oxide (NO) liberation by the micro-capillary endothelium.

2. Review

A normal-behavior ***H. pylori*** never exists inside the gastric lumen during presence of food, it remains settling under the gastric mucus layer until travel of food from the stomach and drop of the gastric acid to a residual level where the bacterium can pick up its nutrition from remnants of food within the gastric lumen in a blink like momentum protected with a shield of ammonia around its immediate vicinity before it returns back to its natural secure habitat under the gastric mucus layer leaving behind it scattered traces of ammonia in the gastric lumen. This scattered ammonia excites the gastric wall to secrete the acid preventing in this way absence of the protective role of the gastric acid during absence of food and helping in turn to guard against low acidity-related complications at the cardiac end of the stomach such as carcinoma and accumulation of pathogens [1-3, 14].

Accordingly, ***H. pylori*** plays without real intention of its own two opposed vital biological functions; it protects the gastric wall from its acid if it goes in excess via buffering any acidity reaching its immediate vicinity. ***H. pylori*** is rather 20 times sensitive to acidity than the gastric wall [1, 3, 14]; as if the bacterium has been created in this place in order to protect the gastric wall from the acid through protecting itself. ***H. pylori*** without intention also protects the gastric wall from sequels of absence of the acid during absence of food as gastric acid is a major defense against bacteria and pathogens [1, 3]; ***H. pylori*** as all living structures will seek its nutrition and via a natural instinct it picks up its food from the gastric lumen when the acid drops to a residual level protected by a shield of ammonia, exactly the same as the automatic behavior of a person hurrying up to his car when the heavy rain slows down to slight drops protected by a rain coat. The residual ammonia scattered in the lumen before ***H. pylori*** returns to its shelter excites the secretion of the gastric acid to buffer this scattered ammonia protecting in turn from absence of the acid during absence of food.

H. pylori via doing this double opposed function of protecting the gastric wall from its acid if it goes in excess and protecting from absence of the acid during absence of food is providing an integral value for the gastro-esophageal function. This double function of ***H. pylori*** leads to a continuous buffering process between ammonia and the acid round the clock ensuring accordingly a constant residual ammonia in the gastric lumen all the time, day and night. Ammonia is a smooth muscle tonic; therefore, this residual gastric ammonia helps to maintain the integrity of the gastro-esophageal tone protecting in this way from incidents of acid reflux whether a person is eating or not, lying flat or upright and awake or asleep [1, 3, 14]. These facts conform with the observational studies which have proposed a protective role of ***H. pylori*** against the development of gastro-esophageal reflux disease and suggested that ***H. pylori*** eradication treatment may increase the incidence of reflux symptoms. It was observed that prevalence of ***H.***

pylori has been decreasing in developed countries while the prevalence of gastro-esophageal reflux disease and esophageal adenocarcinoma have been increasing since 1930s [15-18]. Antibiotics force ***H. pylori*** to migrate from the stomach with consequent loss of its protective gastro-esophageal function; prevalence of the esophageal acid reflux disease has been demonstrated after development of the anti-***H. pylori*** antibiotic strategies and hence stop fighting ***H. pylori*** with antibiotics has been recommended [19].

Ammonium ion was demonstrated to increase the tone of rat portal vein and it was suggested that ammonium compounds increase vascular tone by causing influx of extracellular calcium through the voltage-dependent calcium channel and intracellular alkalinisation [20]. Accordingly, the residual ammonia of gastric ***H. pylori*** strains that could travel down the intestine to reach the colon or the ammonia of the minor ***H. pylori*** strains migrating to the colon in physiological amounts and conditions could lead to an increased micro-vascular tone constituting a shear stress; stimulating in turn endothelial-induced NO liberation in response to the effect of this shear stress [21]. NO is a highly diffusible short-lived free radical gas permeating bio-membranes with a wide range of brilliant physiological functions [22]. NO has important beneficial implications for cardiovascular, immune and gastrointestinal functions [23]. In the gut, NO serves several physiological functions such as regulation of mucosal blood flow, intestinal mobility and mucus thickness [23, 24].

It was observed that whenever ***H. pylori*** exists, mucus is always there or wherever there is mucus, ***H. pylori*** exists and whenever ***H. pylori*** exits in high percentage mucus around is thick and viscous while when it exists in minor percentage mucus is thin and soft [2, 3, 25]. Whether ***H. pylori*** loves the mucus or the mucus loves it or either ***H. pylori*** is attracted to the mucus or the mucus is stimulated by it, it might be correct that both of them are having affinity towards each other. It was emphasized that ***H. pylori*** was behind the secret of the silence of the silent maxillary sinus syndrome and it could be a direct reason to produce the mucus or it is a factor behind the profuse accumulation of thick viscous mucus due to NO liberation by the shear stress effect of its ammonia until the sinus cavity is obliterated in silence. That is probably not due to any true pathologic attitude of the bacterium but it is actually its natural need of having the sinus and the mucus stimulated by its ammonia as a secondary shelter for the purpose of hiding from the antibiotic aggression towards it [26].

As juxta-mucosal ammonia of ***H. pylori*** stimulates endothelial-derived NO liberation via shear stress effect [19, 21], and as NO functions in regulating intestinal motility and mucus thickening [23, 24]; accordingly, ***H. pylori*** is supporting the integral biological functions of the gut either through a direct irritant effect of its ammonia elaborated close to the mucosa or through NO liberated due to the effect of shear stress of ammonia. The thick viscous gastric mucus layer that constitutes the main natural protection of stomach wall from gastric acid could be related to the high existence of ***H. pylori*** in the immediate proximity of gastric mucosa. Simply, as much as ***H. pylori*** could be the reason for the profuse production of mucus without any pathologic attitude except using the maxillary sinus and mucus as a secondary shelter until obliteration and collapse of the sinus occurs in silence [26], major existence of ***H. pylori*** in the stomach which constitutes its commonest and main natural habitat could be in the same way responsible without any physiologic protective intention towards the gastric wall for the development of the protective thick and viscous gastric mucus layer which acts as a shield for the bacterium itself and for the gastric wall in turn from the aggressive gastric acid. In the other way, the minor existence of ***H. pylori*** in the colon in natural conditions or the minor amounts of ammonia that travels down the intestine to reach the colon in residual levels could be responsible for the thin soft colonic mucus that lubricates the formed motion contents so as to make the motion easy; if it is thick mucus, it would render passage of motion hard and difficult. Ammonia or NO through supporting the integrity of intestinal motility and movement of intestinal contents it could help therefore to prevent delay of intestinal contents and allow shaping/formation of colonic motion contents together with wrapping it with a soft lubricant mucus.

Major migration of ***H. pylori*** strains to the colon that occurs mainly due to the influence of antibiotic abuse will cause accumulation of profuse toxic amounts of ammonia leading to pelvic congestion. Pelvic congestion is a major reason that badly affects erectile function and sexual desire in both males and females [3, 27]. In addition, profuse toxic amounts of ammonia, via the effect of shear stress could predispose to local NO toxicity sequels or undesirable effects of NO towards these sexual functions. These facts are supported by the suggestion that NO generated by gut bacteria in the immediate vicinity of gut mucosa may exert either beneficial effects or at higher levels interfere with mucosal functions [23]. Meanwhile, the residual ammonia of gastric ***H. pylori*** strains that travels down the intestine to reach the colon or the ammonia of the minor ***H. pylori*** strains migrating to the colon in minor figures or existence could lead to an increased arterial pelvic inflow or the residual colonic ammonia of ***H. pylori*** through the influence of shear stress will lead to liberation of NO in physiological levels with consequent micro-vascular dilatation in the pelvic area helping to maintain the integrity of the natural desire, sexual sensations and erectile function in turn [21, 28]. Accordingly, physiological levels of pelvic ammonia and NO could participate in maintaining the integrity of the natural physiological desire and sense of libido that allows a person normal sex drive responses and satisfactory sexual performance during ultimate situations.

Residual ***H. pylori***-produced ammonia contributes to maintain the normal level of systemic ammonia which is healthy to the brain via the endothelial-derived NO liberation due to the shear stress effect while accumulation of profuse amounts of colonic ammonia is toxic to the brain and

unhealthy to the onset and symptoms of Alzheimer disease [29].

3. Discussion

It is worthy to clarify some misconceptions and sequels of misbehavior towards ***H. pylori*** in order to show how a cure could turn into a poison when it exceeds the limits of natural existence. ***H. pylori*** is not pathologic by its own but it is forced for any pathologic attitude related to it due to misbehavior in food habits or the antibiotic violence against it. ***H. pylori*** resides and colonizes under the thick gastric mucus layer which allows the bacterium pH gradients from 2 close to gastric lumen to pH 7.4 adjacent to the mucosa, accordingly the bacterium is surviving in a neutral atmosphere and it can readily buffer any further acidity reaching its immediate vicinity [1]. Repeated misbehavior in food habits with over satiety and over filling of the stomach leading to stretching of the stomach wall and thinning up of the gastric mucus layer will cause excess acidity to reach the bacterium forcing it to get embedded within the mucosal folds, a behavior which is unrecognized and intolerable to the gastric mucosa. The mucosa reacts to this unusual behavior of ***H. pylori*** by pushing the bacterium with lymphocytic infiltration leading to lymphocytic gastritis that could end by atrophic gastritis and gastric ulcers. Lymphocytic infiltration could aggregate into a mass to form a gastric lymphoma while gastric carcinoma could arise from transformation of the lymphoma or from the edges of chronic gastric ulcers. All these pathologies are limited to the stomach and were in minor incidence among only a range of some filthy people, not even all of them [1, 5, 6, 30]. Accordingly; gastritis, gastric ulcer, lymphoma and gastric carcinoma are not essentially caused by a natural behavior of ***H. pylori*** of its own.

In addition, migration of ***H. pylori*** from the stomach under the influence of antibiotics would render it a foreign structure to the tissues as ***H. pylori*** is only recognized by the stomach wall tissues. Hence, this could lead to an inflammatory reactions, local tissue pathology or an auto-immunity. Migration of ***H. pylori*** to the colon will lead to accumulation of ammonia in profuse toxic amounts leading to biologic toxic stress with development of various adverse toxic disorders and sequels in the body such as toxic myocarditis and cadrdiomyopathy, toxic nephritis, toxic thyroiditis and toxic pancreatitis with consequent stress diabetes. Accumulation of excess amounts of ammonia in the colon could be smooth muscle spastic leading to multiple colonic spasms and a high rectal spasm causing a colonic re-absorptive error with consequent retention of fluids and salts in the body, this error could be a direct reason for the development of a challenging hypertensive illness [2, 3, 14, 31, 32].

Residual pelvic ammonia and physiological levels of colonic NO improves erectile functions and sexual desire while major migration of ***H. pylori*** to the colon under the influence of antibiotics would lead to pelvic congestion and unhealthy sequences to the desire and erectile function [27, 28]. In the same way, normal levels of systemic ammonia are healthy to the cerebral micro-circulation and towards the onset of Alzheimer while accumulation of profuse amounts of colonic ammonia will lead to elevated levels of systemic ammonia which is toxic to the brain [29].

Furthermore, it appears that ***H. pylori*** is a natural bacterium as evidenced by the scientific facts of its existence since an immemorial time, having huge biological talents for survival inside the strongly acidic gastric lumen, its un-avoidable recurrence in the stomach and its highly biologic benefits towards the human body [1-3]. A logic thinking might wonder; so long ***H. pylori*** can survive in the colon, hence what forces a weak bacterium that can not tolerate dilute weak acids to choose by its own this suicidal attempt close to the aggressive gastric acid unless it is obliged for a natural function there!! As long as ***H. pylori*** can reside in the oral cavity, why it does not decide to enjoy fun and company with millions of bacteria in the mouth!!

Is ***H. pylori*** eradication necessary and possible or un-necessary because it is impossible!! Is ***H. pylori*** antibiotic eradication therapy effective or in-effective!! Obviously, it is not possible and eradication therapy is of no value as proved by the fact that ***H. pylori*** recurrence in the stomach is un-avoidable. It seems that ***H. pylori*** is not even eradicated from the stomach but forced to migrate where complications start to take place as proved by the scientific evidences of its appearance in new secondary shelters with development of new pathologic sequels. More-over, antibiotics are even seldom effective against extra-gastric ***H. pylori*** strains [1, 3, 33]. These suggestions are supported by the finding that pseudo-membranous toxic colitis and toxic mega-colon have developed after eradication of ***H. pylori*** from the stomach by antibiotic therapy [34, 35]; complications related to ***H. pylori*** were of minor incidence and limited to the stomach while after the anti-***H. pylori*** antibiotics medical challenges flared up and exceeded limits of the stomach [1-3, 14, 26, 31, 32, 36]. Migration of ***H. pylori*** from the stomach will force it to become a poison itself by inducing auto-immunity and a source of poison by producing profuse toxic amounts of ammonia for a reason or no reason, un-opposed or buffered by any acidity outside the stomach [1, 3].

A lot of controversy has been shown as concerns the efficacy of ***H. pylori*** antibiotic eradication therapies. The efficacy of ***H. pylori*** eradication treatment for non-ulcer dyspepsia is also controversial, different randomized controlled trails have given conflicting results. Overall, ***H. pylori*** eradication treatment for non-ulcer dyspepsia had no significant effect on quality of life compared with placebo. ***H. pylori*** eradication for non-ulcer dyspepsia symptoms was found more costly if compared to antacid treatment. However, it has been of small but statistically significant benefit for dyspepsia symptoms of non-ulcer patients; patients receiving eradication treatment would benefit by an average of an extra 0.56 months free from dyspepsia per year than those given antacid. Further studies comparing between

H. pylori treatment and eradication for non-ulcer dyspepsia showed improvement of dyspeptic symptoms after treatment or eradication with little differences between them [14].

In a comparison of the efficacy of natural measures for ***H. pylori*** eradication Vs antibiotics, it was shown that natural measures were superior to antibiotic eradication therapies. It was found also that the definitive eradication of ***H. pylori*** from the colon is by employing the natural senna leaves extract purge [14, 37].

4. Summary

In summary, ***H. pylori*** is highly biologic and protective to the human body functions either directly or through stimulation of NO liberation while its juxta-mucosal ammonia in turn is extensively intelligent helping integral mucosal properties and functions of the gut such as 1. ***H. pylori*** protects the gastric wall from its acid if it goes in excess via the buffering effect of ammonia at its immediate vicinity, 2. It protects the gastric wall from flare up of pathogens and carcinoma at its cardiac end via preventing absence of the acid during absence of food, 3. It helps to maintain the integrity of gastro-esophageal tone protecting against acid reflux disease, 4. It is the stimulus for gastric wall to secrete its thick viscous mucus layer which constitutes the main natural guard for the stomach wall from its aggressive acid, 5. It maintains the integrity of intestinal motility and moves of its contents preventing intestinal delay, 6. It participates in formation of the thin soft colonic mucus for lubrication of motion, 7. It maintains the colonic motility which is responsible for the formation of the bowel motion contents and surrounding the formed contents with a thin layer of lubricant mucus, 8. It helps to maintain the integrity of the natural desire and sexual sensations that is in favor of the usual response to sexual drives, satisfactory erectile function and sexual performance during ultimate situations and 9. Normal physiological levels of ammonia of ***H. pylori*** contributes for the physiological levels of systemic ammonia and NO in turn which is integral for the cerebral micro-capillary circulation and is therefore healthy for the onset and symptoms of Alzheimer disease. As if in this way "the nature protects the nature" or the natural bacterial microbiota of the gut protects the human body natural physiology.

All these biological protective values, namely the gastric protective benefits, the integral supportive elements for the bowel functions and the vital contributions to maintain the integrity of sexual desire and cerebral circulation are just examples for the huge biological benefits that could be achieved due to the natural existence and structure of ***H. pylori***. As this natural existence could include maintaining a constant level of residual ammonia in the gut, contribution to maintain a constant level of systemic serum ammonia and in turn normal physiological levels of NO liberation through the effect of shear stress, hence this natural existence of ***H. pylori*** could be healthy and integral for the welfare of many vital structures and functions in the body.

5. Conclusions

A huge biological symphony of cure and poison is being played in great vital harmony by the intelligent production of ammonia of the bacterium ***H. pylori*** and the smart NO liberation by the micro-capillary endothelium due to the shear stress effect of ammonia. Therefore; should we fight and kill or save ***H. pylori***!! It seems that we should save ***H. pylori*** as it is not pathologic or is not pathologic by its own but it is forced to any pathologic attitude related to it. More-over, it is a bacterium with many natural behaviors which are hugely biologic and protective towards the human body while its juxta-mucosal ammonia is highly intelligent and supportive at least for the integral physiological functions of the gut. It can be said accordingly that "the nature protects the nature" or the natural bacterial microbiota of the gut protects the human body natural physiology.

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