CAN FUNCTIONS OF HISTAMINE IN THE BODY OFFER EXPLANATION FOR SOME OF THE PROBLEMS SEEN IN GASTROENTEROLOGY?

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Abstract: Although Campylobacte Pylori is being considered to be ivolved in the production of gastritis, duodenitis and ulcer formation, it is possible that this organism is a part of the normal bacterial flora of the intestinal tract, that can benefit from the histidine and nascent histamine formation and turn-over in the stomach, when the histaminergic neuronal system is activated for water intake of the body. Since histidine and nascent histamine are important for rapidly growing cells of living matter, C. Pylori may be demonstrating this natural response to the enriched environment suited to its growth to the transformed level of becoming a local irritant; if the pain and the local irritation is indeed caused by the bacillus and not considered to be a physiological inflammatory signal of thirst, caused by histaminergic neuronal system activity. Therefore, increased water intake to satisfy the natural drive of the histaminergic neuronal system is recommended before any other medical treatment procedures.

Key Words: Histamine, Histidine, Serotonin, Renin-Angiotensin, Water, Campylobacter, Peptic Ulcer, Gastritis, Duodenitis, Dyspepsia, Pain, Thirst.

The different stages of gastritis, duodenitis and ulcer formation are currently being associated with Campylobacter Pylori, with a further descriptive association between the function of a corkscrew and the method of tissue penetration of the curved bacillus. Since the reports from Camp Ylobacter of Colorado (1, 2) give the indication that the pendulum is being forced to swing in favor of one causative factor, namely the curved bacillus being responsible for the different inflammatory states of the local mucosa of the stomach and the duodenum, it seems that a strong question is being raised against a hard and fast division of gastritis and duodenitis and their respective ulceration stages, up to now considered different pathological entities. Although the report does not favor a decisive treatment procedure targeted at the bacillus in these conditions, the latter apparent conclusion that one causative factor may be responsible for the local pathology in these regions could prove to be more of a bonus than it seems at first; once it is determined whether it is the bacillus that causes the local inflammatory process, or it is the physiological inflammatory process of the region served by diffusion of histamine from the histaminergic neurotransmission system that causes this bacillus spices to grow beyond their function as a component of the local bacterial flora.

Histamine is now being recognized to be a neurotransmitter (3,4). Because L-amino acid decarboxylase and the specific L-histidine decarboxylase are found in very high activity in catecholaminergic and serotonergic neurones, histamine is now classified as a neurotransmitter, also possessing a specific neuronal system of its own, particularly in the duodenal region (3,5,6). As a neurotransmission system, apart from the H_1 and H_2 receptors, it is reported to have an auto-inhibitory H_3 receptor sub-class, shown to inhibit histamine release and synthesis. In vitro experiments have shown the inhibitory action of H_3 receptors to be concentration dependent with a maximal feedback inhibition of up to 60% (7, 8).

The histaminergic neuronal system has been shown to be involved in the regulation of water intake of the rat as its primary central action in the different parts of the hypothalamus (9, 10). Histamine is also involved in induction of drinking by food intake (11), and drinking elicited by insulin in the rat (12); there is also a preabsorptive, pregastric, vagally mediated histaminergic component of drinking elicited by eating in the rat (13, 14). Goldstein and associates report evidence suggesting that the mast cell is an osmolar receptor and that histamine participates in the afferent link of the drinking behavior elicited by hypertonic saline in rats (15). They further report qualitative and quantitative changes in mesenteric mast cell population of rats exposed to acute cell dehydration and water deprivation, with concomitant change in vascular permeability (16). Apart for its central action in induction of water intake histamine is also involved in regulation of water intake through induction of the renin-angiotensin system peripherally, also affecting change in plasma levels of Na^+ and K^+ (17).

The parietal cell uses vast quantities of water from the circulation (18), it requires water in order to operate the H^+-K^+ ATPase pump (19). It seems that when this normal physiology is not efficient histamine takes over, since the capillary circulation of the stomach has H_2 as well as H_1 receptors to maintain circulation (20) and maintain not only the local circulation but, it seems also to be involved in maintenance of cation transport efficiency (21) by being responsible for the post receptor energy release for this function (22).

The serotonergic neuronal system seems also to be involved in the system for water intake of the body (15, 36), as well as regulation of acid production in the stomach, volume flow, and mucus production, with a threshold of action for inhibition of the acid producing effect of histamine (23, 24). It has been shown that serotonin inhibits the action of histamine within a particular osmolar concentration range of the perfusion medium in the experiment performed by Holstein and Cerberg, indicating that there must be a mechanism of osmoregulation involving both histamine and serotonin (23). The renin-angiotensin system is involved in water regulation of the body (25). It seems that this system, other than being activated in the renal tissue, has a second central nervous system site of production (26). This system is indirectly activated by histamine (17) but, it is activated by the direct action of 5-Ht. (15).

On the basis of the exposed localization of histaminergic neuronal system identified in the serotonergic system as well as its independent representation in the upper intestinal tracts and its involvement in water regulation of the body, it would be logical to assume that its greatest functional activity is represented in the region of the stomach and the duodenum, where fluid intake and food are sampled and where its independent network of nerve tissue have been identified. Its excess activity would mean enlargement and varicosity of its nerve terminals in the region where the nascent histamine could diffuse, a possible site of breakdown of tissue and release of over produced histamine, causing further inflammation of the immediate surroundings. This could be a possible explanation for the recurrence of ulcers in the same region, where the nerve terminals are present and active.

Nascent histamine and histidine are also very extensively involved in the process of growth in the living tissue (38, 39,40). Histidine is considered to be an essential amino acid for growth in children, and also in adults, because of limitation in its rate of production in the body (27). Through its combined H_1-H_2 effect and mobilization of calcium-calmodulin, activation of protein kinase C (7) and production of voltage gradient, by its action on Na^+-K^+ ATPase pump (44), histamine is thought to be involved in production of (similar to, if not the same as Phospholamban - 37) protein, acting as a "local" growth hormone, that enhances phosphorylation of proteins, involved in growth of tissue (21). The action of histamine through calcium release (44) may be responsible for activation of membrane proteases that can proteolyze protein kinase C to protein kinase M, a growth promoting kinase independent of calcium activation (45). Tada and associates report that Phospholamban phosphorylation by Ca^{2+}-calmodulin-protein kinase C could also take place in a Ca^{2+} dependent and cAMP independent manner (37); an understandable physiological function for the gastrointestinal tract and its vast need for continuous enzyme production and its very rapid tissue turn-over. Histamine-forming activity of histidine decarboxylase in rapidly growing tissues (38), in plants (39) and animals is increased significantly (28, 40). Bacteria too have a need for histidine (27) and, possibly, histamine for growth, if the process of growth is considered to depend on mobilization of calcium, as well as production of a voltage gradient (29,44). Taking these points into consideration, it seems that the mucosa of the pyloric region of the stomach and the duodenum's greater unbalanced activity of its histaminergic system, to the point of ulceration, would be an ideal culture medium for an opportunistic organism responsive to the optimum growth promoting possibilities made available to it. Campylobacter spices of bacteria may be benefiting from the ideal environmental factors produced, when all the time the body of the host is instituting an over-ride to the histaminergic neurotransmission mechanism to increase its water intake.

Whilst procedures are being investigated to treat the bacterial infection, using bismuth salts or antibiotics, ironically, the best treatment procedure may be the act of giving in to the logic of nature in the host, by satisfying the natural drive of histamine for water, namely, increasing the patients' water intake (30, 31, 21). It is possible that increase in water intake will decrease the microviscosity within the bilayer membrane of the cells involved in the feedback inhibition of H_3 receptors; a proposed possible mechanism for inhibition of over-production and activation of the interlocking feedback mechanisms for neurotransmission and hormonal systems that institute function within the bilayer membrane of their respective target cells (21). There is a mechanism for its resecretion into the stomach when water is taken by mouth, with its optimum return after a half hour (32); this may be an effective "backwash" mechanism for mucus in the stomach, since sodium salt produced in the buffer zone of the mucus layer, by a process of "charge shielding"of the monovalent cations will compromise the consistency and effectiveness of mucus as a protective barrier (33). Heavy metal cations with greater than one valency, iron inparticular, will increase the elasticity and resilience of mucus (33) (may be the wisdom of nature for gastric bleeding, when reabsorption of water content of blood poured into the intestinal tract becomes necessary). The protective function of mucus lining the stomach may be enhanced by the intake of bismuth salts used in treatment of Campylobacter "infection".

An oral water load produces a volume dependent sustained secretion of the intestinal hormone motilin (34) yet, according to Bryant et al., enterochromaffin cells containing motilin granules of density 1.20 stain for motilin as well as for serotonin, indicating that serotonin and motilin granules of density 1.20 are the same EC2 granules (35). Since serotonin has been shown to inhibit the action of histamine for production of acid (23, 24), as well as increase mucus production, water, by stimulating secretion of motilin, should be considered the ideal inhibitor of excess histaminergic activity, altering the local growth promoting properties of greater histidine and histamine turnover that the Campylobacter could benefit from; as well as being a mucus barrier activator in the stomach, with an outward direction of flow of resecreted water, washing the bacteria and salt away from the mucosal lining of the stomach.

Added to all these advantages, it is possible that serotonin, released by intake of water, will stabilize the calcium current by forcing calcium and potassium ions into the over activated cells (41) (perhaps the growing bacteria too). Increase in the intracellular calcium concentration will inhibit the Ca^{2+}-dependent ATPase activity, when the concentration of Ca^{2+} in the cell reaches 10^{-4} M. ATP hydrolysis absolutely depends on Ca^{2+} concentrations between 10^{-8} and 10^{-5} M.(37, 50). This interaction of the cell calcium regulation by serotonin and histamine could be the natural logic to the way mast cells collect 5-Ht. and at the time of degranulation both histamine and 5-Ht. are release at the same time (16).

CONCLUSION

It seems that nature has ordained histamine, serotonin, and the renin-angiotensin system activated by them, to regulate water intake of the body, even in the innermost part of each cell. It also seems that the time has come to consider this need of the body for regulation and maintenance of the "milieu interieur" to be of primary importance and thus the primary concern of these agents. The natural drive of these agents for water should be fully satisfied, before evaluation of any other treatment procedure with respect to these agents is considered, particularly in the discipline of gastroenterology. Because histamine has a strong vasopressin releasing effect in the body (46). Vasopressin seems to be responsible for water regulation through the membrane of the cells that have receptors for is action. A review by Finkelstein indicates that vasopressin has the ability of forming a "shower head" effect in the membrane, with a cluster of perforations of about 2 Anstrong units at the inner leaf of the membrane, allowing the single file passage of only one water molecule at a time through the perforations (47). Microviscosity alterations in the axoplasm of nerve cells may directly influence the two way transport in the neuronal tissues of the body, since a hydrodynamic, microtubule directed microstream flow seems to be a major component of the transport system in nerve tissue (48,49). Consequently, continued pain signal producing dehydration could be far more damaging to the body than has been recognized up to now (21), also mindful of the fact that bleeding and surgery for the complications of peptic ulcer disease, even with liberal use of H_2 blocking agents, has not decreased (42, 43).

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