

GASTROENTEROLOGY AND HISTAMINE'S FUNCTIONS IN THE BODY.

F. BATMANGHELIDJ, M.D.

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A*bstract:* The widening gap between the advancement of science and understanding of microphysiology and its incorporation into medical practice can be to the long-term disadvantage of the patient. Particularly when pursuit of sub-specialities can further delay filtration of advancements in other fields of research, that can shed light for a better understanding of some disease conditions confronted within the practice of a particular sub-speciality. This gap becomes more and more apparent in the field of gastroenterology, an arbitrarily divided branch of medical practice that falls between the disciplines of endocrinology, clinical and chemical pathology and food and water metabolism controlled by a very complex group of organs, catering to the needs of the total body. If we were now able to push aside the inherited bias in favor of any one particular line of treatment and look at gastroenterology from the direction of its involvement in the total body metabolism, and of water in particular, may be a more patient serving and much more effective approach to clinical medicine will emerge.

Key Words: Histamine, Dyspepsia, Water, Peptic

Ulcer

We can begin by accepting the fact that, next to oxygen water is the single most important substance for the survival of the body, and that some of its functions and mechanism of regulations are as follows. Water, in its free form, is involved in hydrolysis of fat and protein in normal metabolism of food and in gluconeogenesis and in the breakdown of stored energy. Water intake regulates the intracellular fluid volume, and sodium intake regulates the extracellular fluid volume (1). Water is a most efficient physiological diuretic (2). Its intake by the body decreases because of a failing thirst sensation (3,4,5) to the point that the ratio of the extracellular fluid volume to intracellular fluid volume changes from an approximate figure of 0.8 to over 1.1 from age twenty to age seventy (6).

When all the tightly coupled protein and enzyme functions in the cell (7) have a greater efficiency of function in solutions of lesser viscosity (8), including cation pumps and adenylate cyclase activation in the cell membrane (9,10,11); when in effect, ATP synthesis and the energy for cation exchange is brought about by the energy of hydration at the selectivity filter of the cation pump (12,13,14); not only the cation transport is water dependent but, the axonal transport of neurotransmission systems is also dependent on the

microstream flow of low viscosity regions around the microtubules in the length of the axons(15,16). Although the thirst sensation seems to fail, does this mean that the efficiency of protein and enzyme functions are less water dependent? Hardly so, it would not seem sound to think that nature in us is oblivious to this disparity of need to the availability of free water in the body.

Histamine is a neurotransmitter (17,18,19), it is an osmoregulator (20) that is involved in water intake of the body (21,22,23,24,25,26,27), with a regional representation in the upper part of the intestinal tract (28). Histamine strongly acts as an antidiuretic hormone releasing factor (29), when ADH in turn promotes water preservation of the body, as well as, by the creation of "shower head" cluster perforations in the cell membrane, that permit the single file entry of only one molecule of water at a time into the cell (30), it promotes a more efficient entry of water into the cells sensitive to its stimulation. Among the tissues, other than the kidney, sensitive to ADH function is the brain, when the blood brain barrier capillaries develop a modified permeability rate to water, at the same time as, the brain itself consolidates its learned memory under the influence of ADH (31). If chronic dehydration should impair the function of cation exchange through the loss of the role of free water in pump protein activation, histamine, through H₁ receptor stimulation, liberates the intracellular calcium ions from their stores activating calcium-dependent potassium channels in the cell membrane, with an oscillatory pattern of activity (32); and since the exchange of other cations, including the hydrogen ion, is regulated by the move-

ment of potassium across the membrane (33,34), histamine must be considered to be a regulator of volume homeostasis and the pH buffering system in activated cells, which possess receptors for its stimulation.

Histamine also activates the renin-angiotensin system (35). The renin-angiotensin system is another pathway for the stimulation of the dipsogenic receptors of the subfornical organ in the brain (1,36). Histamine is directly involved in modulation of lymphocyte biology, membrane receptor activation, its functions and signal transduction. H₁ or H₂ activation can produce different behavioral response in the white cell population, that seem to have nonrandom distribution of histamine receptors on the particular lymphocyte subpopulation (37).

DISCUSSION

Recent thrust in histamine research is revealing a far greater useful functional role in the body for this neurotransmitter that also demonstrates autacoid activity. Its functions as a neurotransmitter seems to involve it in the dipsogenic pathways for water intake and osmoregulation of the body. Its ADH releasing role, in an effort to preserve the body water content, as well as, by initiating the dipsogenic effect of angiotensin II, subsequent to plasma renin activation, allocates it a primary position as the regulator (rationing mechanism) of the body free water reserves. By activation of calcium-dependent potassium channels in the cell membranes, histamine may be responsible for the cation exchange at the intracel-

lular membranes, as well as the plasma membrane, a function attributed to free water itself. The immediate concern in body water disturbance would be the renal function, its body pH regulation, and hydrogen ion excretion which depends on urine volume flow. In chronic dehydration (3,4,5,6) and the consequential decreased urine production, body pH regulation can become a problem, unless the concomitant action of histamine on the parietal cell and its excessive hydrogen ion production is to be buffered by food (or commercial antacids), is considered to be also a part of the body pH buffering system. Thus, the stomach may be also acting as a closed-loop pH exchanger when the free flow exchange in the kidney is not efficient, because of cellular dehydration of the body. Since the capillaries of the stomach possess both H₁ and H₂ receptors (38), a physiologic histaminergic drive for water intake of the body, as well as parietal cell activation will undoubtedly produce a physiological inflammatory state in the mucosa of the stomach and the duodenum. By this simple logic and from the fact that between the initial nonspecific dyspepsia (39) and ulcer crater formation, there is a lapse of time, the early dyspepsia would become an important signal (40), that could also be a signal of the total body pH malregulation (a consequence of inadequate water intake by the body), not to be ignored because an ulcer crater is not seen. This nonspecific, nonerosive, (41) early stage (40) physiologic mucosal states of the stomach and the duodenum may benefit from the recognition of the role of histamine as a neurotransmitter involved in the primary drive for water intake of the body. In view of the multifunctional role of histamine in the body, long term

manipulation of histamine receptors may not be in the best interest of the patient. Histamine granule containing vesicles are stabilized in solutions of low viscosity (42); the rat mesenteric mast cells become depleted when water is injected into the peritoneum, and become replaced after four to six weeks (20); the mast cell in the amphibians does not contain histamine granules (27). Accordingly, it may be in the best interest of the patient to begin to satisfy the natural physiological drive of histaminergic neurotransmission for water in dyspeptic conditions before exposing the patient to the short or long term side effects of receptor blocking agents superimposed on dehydration. The long-term welfare of the patients, whose histaminergic drive for water intake becomes symptom producing, places a responsibility on the physician to become acquainted with the intricate role of histamine in the body, before advocating the use of histamine blockers. Particularly as peptic ulcer disease, in its fully blown crater producing stage, seems to be a part of a heterogeneous group of disorders that have the ulcer crater in common (43); that some of those conditions could have possibly benefited from a more efficient body water regulation if the initial symptom producing cell dehydration had been properly recognized and naturally treated to the benefit of the total body of the patient; also mindful of the fact that bleeding and complications of peptic ulcer disease, even with the copious use of H₂ blocking agents has not decreased (44,45).

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