

CORRESPONDENCE

The water regulatory role of histamine in the body seems to have eluded even the journalist and immunology pundits. As a result, conclusions to some research findings are so grossly neglecting of the natural processes developed around the water metabolism of the body that claims and disclaimers become subjects of heated controversy. One such example is the publication of an article, "Human basophil degranulation triggered by very dilute antiserum against IgE." by Drs. Davenas and Benveniste et al. - *Nature*, 30 June 1988, and the subsequent invalidation of the published article, again - by *Nature*, July 28, 1988. The error in evaluation of the findings and its publication would not have taken place if the water regulatory role of histamine had been understood and taken seriously. *Nature* had already published an article (*Daniel Goldstein and Jose Halprin, "Mast cell histamine and cell dehydration thirst," Nature, 19 May 1977, PP. 250-252*) on the effect of water in degranulation of mast cell histamine. This same comment to Professor Lazar generated an angry response from Dr. Benveniste, to which a reply became necessary. The points in the letter are pertinent to the subject of this volume, and for that reason it is being published here. It is hoped that the scientific content of the letter will be the subject of attention and not the media exposed irritations of the past discussions on this topic.

16 November 1989

Dear Dr. Benveniste,

The prime purpose of the letter to Professor Lazar was the introduction of new ideas on the subject of AIDS, about which we have put out a special issue. We thought your National Research Institute would be happy to receive added information on AIDS.

As for the comments about Dr. Davenas' experiment, I did appreciate that the solution used was saline based, the word "water" was used to indicate that the solvent you have used is by itself capable of degranulating the histamine from mast cells. I did not wish to go into other details on the subject, thinking that the use of the word "water" will act as a thought provoking trigger mechanism for experienced researchers, most particularly for those who handle histamine containing cells. It should become obvious, when water and ion regulation across the cell membrane have different mechanisms, and water by itself is capable of altering the histamine content of mast cells, a conclusion that it is the IgE antiserum imprint and not the osmoregulatory properties of histamine itself, be it in the mast cell or the basophil (that is demonstrating a hitherto unknown property) will need quite a number of other supportive experiments to make the conclusion to the article possible.

What makes you think that the basophil is not a tissue type mast cell? Blood is a tissue; the basophil and the mast cell (tissue or mucosal) manufacture histamine and they arise from the same bone marrow stem cell origin. If your criterion for this inattention is the size and shape, tissue mast cell and the mucosal mast cell are also different in that respect. The fact that histamine is a neurotransmitter amine that is involved in the osmoregulation of the environment of cells, by its presence in the basophil, as well as the mast cell that arise from the same bone marrow stem cell, dictates that the basophil should be anticipated to have the same osmoregulatory properties that have been demonstrated in the mast cell. In short, it is the natural property of histamine that dictates a role and function for the cells that manufacture it, i.e. the basophil must have osmoregulatory properties like the mast cell.

It seems that the best reported results of Dr.

Davenas were produced when the preparations were left over night in the cold (this detail came out of the report by the observers from Nature). A very important issue in osmoregulation of the cell membrane is the differential between water permeation through the membrane, normally, at the rate of 10^{-3} cm. per sec. - as opposed to 10^{-12} for the main cations. In addition, at a transition temperature of 26-28* C the cholesterol regulation of water permeability through the membrane changes, it becomes more permeable to water below the transition temperature. Cation exchange in the process of osmoregulation is dependent on the efficiency of the various pumps. The efficiency of these pumps is determined by the rate of the conformational change that the pump protein is capable of undergoing.

The frequency of conformational change of these pump proteins is temperature dependent; as an example, at 5 degrees centigrade, the aromatic amino acids within proteins are estimated to have almost no rotational freedom, whereas at 43 degrees centigrade they have a rotational freedom with a correlation time of 0.14 nano-seconds, or even less. It may seem to you that your saline solution is well selected for the experiment in question (although even that is questionable) but, is the cell membrane capable of efficient osmoregulation of the composition of the various cations within the design of the experiment? Could you be sure that the cytosol is not fractionally gaining water through the membrane diffusion when the coupled transport of water by the cation exchange is not effectively carried out, when the rotational property of the pump proteins may be affected by the lower temperature of medium, in the very experiments that seem to have worked?

The amphibian mast cells do not contain histamine. With increased availability of water, histamine granules are normally stabilized

within the vesicles and eventually recycled. How can you be sure that the altered staining properties of the basophils, left over night in a cold solution of saline, is the result of degranulation and not the result of the intracellular metabolism of histamine granules, among other functions, for the calcium-dependent cation exchange at the mitochondrial or other intracellular membranes?

You see Dr. Benveniste, before you could establish a role for the effect of antiserum against IgE that has been removed from the solution that subsequently contains the basophils, your experiments have to allow for the above "water-dependent" physiological situations that can possibly duplicate the results that IgE would produce if it was present itself - even if the experiments are well and unquestionably controlled, and even if they could be duplicated every time.

I have no idea why some clinicians and scientists involved in histamine research still insist on blocking the action of histamine, instead of satisfying it with the increased water intake it demands; such a paradigm change will mean simplification of medical treatment procedures and the exposure of sophistries that have completely confused the practice of medicine. I hope, by making some effort toward further exposure of the paradigm change yourself, you will demonstrate that, like me, you do not knowingly tolerate the continued sophistication of the very basis of science in medicine - the confused inattention to the signals and the demands of the neurotransmitter systems that regulate the water metabolism of the body.

Sincerely,

F. Batmanghelidj, M.D.©

Copy to Professor P. Lazar,

Dr. J. Maddox,

Dr. E. Davenas.