The Role of Vitamins B_3 and C in the Treatment of Histadelia

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Suicidal depression, obsessive-compulsive rumination, mental fogginess, disperceptions, and hyperactivity (overarousal) characterize the psychiatric manifestations of histadelia, a type of schizophrenia.[1] The non-psychiatric clinical features of histadelia include: increased salivation, elevated metabolic rate, allergic symptoms, frequent headaches, diminished pain threshold, heightened sexual responsiveness (a greater ability to achieve orgasm), and strong cravings for sugar.[2,3] Increased basophils (greater than 50 cells/mm^3) and elevated blood histamine levels (greater than 70 ng/ml) confirm the diagnosis of histadelia.[4]

The goal of orthomolecular treatment for this disorder is to restore blood histamine levels to normal. This can be achieved through dietary modifications (low protein and high fruit/vegetable diet), a combination of various nutrients (calcium, methionine, zinc, and manganese), and sometimes the drug phenytoin (Dilantin).[5] A low protein diet reduces the amount of ingested L-histidine, which is a precursor to histamine. Calcium helps mobilize bodily stores of histamine, and also might increase histamine catabolism. Methionine lowers blood histamine by reacting with histamine to form N-methylhistamine, an inert methylated ring structure. Zinc and manganese replenish possible deficiencies, and phenytoin negates the compulsive behaviors and depression.

It has been proposed that the histadelic patient does not respond "to the classical meganutrient (B_3, vitamin C) therapy."[6] This lack of response is confusing considering that thousands of schizophrenic patients have benefited from taking megadoses of vitamins B_3 and C.[7] If 20% of all schizophrenics are thought to have histadelia,[8] it is possible that favorable therapeutic responses to vitamins B_3 and C have occurred among many histadelic patients. The therapeutic potential of vitamins B_3 and C in the treatment of histadelia is clear given the biochemical functions of these vitamins.

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Vitamin B_3 and Histamine

Both forms of vitamin B_3, nicotinic acid (niacin) and nicotinamide (niacinamide), are necessary to counteract the clinical problems associated with high blood histamine. When histamine levels are in excess, the enzyme nicotinamide-adenosine dinucleotidase (NADase) catalyzes the removal of a nicotinamide moiety from nicotinamide-adenosine dinucleotide (NAD) and irreversibly replaces it with a molecule of histamine.[9] The net effect of excess histamine would be increased production of histamine-adenosine dinucleotide (HAD), an inert compound devoid of the energetic properties of NAD. Other conditions with an associated NAD deficiency include alcoholism, drug addiction, violent behaviors, and schizophrenia.[10]

Using niacin to treat histadelia might seem contradictory considering it will augment the release of histamine from basophils and tissue mast cells.[11] However, there is evidence that the niacin flush is mediated by the release of prostaglandin D2 (PGD2) from dermal macrophages and not from degranulation of basophil and tissue mast cells.[12,13] Further, Hoffer suggested that daily intake of niacin gradually lowers total body histamine by chronically depleting storage levels.[11] Niacin has a complicated mechanism of action that modulates

histamine release, lowers total blood histamine, and increases the production of PGD2.

The amide form of vitamin B_3 (nicotinamide or niacinamide) does not directly promote the degranulation of histamine containing cells, deplete tissue stores, or increase PGD2 release. Nicotinamide might function primarily by reducing the histaminergic response to antigenic stimulation. Various investigators have shown that certain foods, especially wheat and milk, can trigger schizophrenic-like symptoms in susceptible people.[14-17] Specific protein fractions, derived from wheat and milk, might be responsible for the schizophrenic-like effects.[18] Chronic release of histamine, in response to certain foods, might be a potential mechanism by which behavior is severely affected.[19] Nicotinamide has been shown in vivo (guinea pigs) to reduce anaphylactic reactions mediated by antigen inhalation. Antigen-antibody induced histamine release can therefore be suppressed by nicotinamide.[9] Nicotinamide also has been demonstrated to prevent degranulation of mouse peritoneal mast cells after exposure to compound 40/80, a specific antigen mixture composed of aluminum hydroxide and egg albumin.[9] Bekier and Maslinski hypothesized that nicotinamide might exert its antihistaminic actions in vivo (guinea pigs) by inhibiting the enzyme phosphodiesterase (PDE). Inhibition of PDE would increase cyclic adenosine-3', 5'-monophosphate (cAMP) and therefore, relax smooth muscles.[20] Further, in vivo (guinea pigs)[9] and in vitro (chopped guinea pig lung)[21] studies demonstrated that nicotinamide inhibits the enzyme NADase. Inhibition of NADase enzyme activity reduces HAD formation, an energetically inert molecule possibly implicated in the development of schizophrenia. The actions that vitamin B_3 has upon histamine metabolism are summarized in Table 1 (below).

Histadelia is a clinical syndrome metabolically driven by elevated histamine levels and perhaps provoked by chronic food sensitivities in susceptible people. The following hypotheses might be proposed: (1) chronic use of nicotinic acid depletes tissue stores of histamine and lowers total blood histamine, (2) nicotinamide attenuates histamine release in response to antigen-antibody interactions, inhibits mast cell degranulation, relaxes smooth muscles and prevents the formation of excess of HAD and (3) both forms of vitamin B_3 might be essential in correcting the central defect of this disorder - the NAD deficiency induced by the excess activity of NADase.

Vitamin C and Histamine

The exact biochemical mechanism underlying low plasma ascorbate levels and high blood histamine remains to be eluci-

Table 1. Biochemical interactions between vitamin B_3 and histamine.

Substance	Evidence	Lowers Blood Histamine
Nicotinic Acid	anectdotal (humans)	depletes storage sites with chronic use
Nicotinamide	in vivo (guinea pigs)	reduces antigen-mediated anaphylactic reactions and inhibits both PDE and NADase
	in vitro	reduces histamine degranulation in response to antigen and inhibits NADase
Nicotinic acid and Nicotinamide	theoretical	inhibits NADase

dated. However, in vitro studies have shown that the activity of enzyme histidine decarboxylase (HDC) increases in a medium deficient in ascorbic acid.[22] HDC is the enzyme that converts L-histidine to histamine.[23] Another in vitro study demonstrated that ascorbic acid increases histamine degradation by promoting the formation of a mono-oxygenated form of N-acetylhistamine (NAH).[24] NAH is one of the byproducts of histamine catabolism, and is produced by the action of N-acetylhistamine deacetylase, the rate-limiting enzyme in its synthesis.[23] Further, it has been suggested that excess histamine binds the copper site of monoamine oxidase (MAO). The function of histamine-bound MAO accelerates the oxidation of ascorbate instead of eliminating dopamine and other monoamines.[25] This hypothesis would support the link between reduced vitamin C levels and schizophrenia, as well as the high dopamine levels potentially linked to this disorder.

Vitamin C also has been shown to lower blood histamine and indirectly augment neutrophil chemotaxis in healthy human subjects.[26] Johnston et al demonstrated an association between low plasma ascorbate levels and elevated blood histamine in humans.[27] Suboticanec et al. determined that schizophrenic patients have lower fasting plasma ascorbate levels compared to controls, despite adequate dietary intake of ascorbic acid.[28,29] Further, schizophrenic patients (in contrast to control subjects) exhibited a greater reduction in the urinary excretion of vitamin C when measured 6-hours after an oral loading dose of ascorbic acid.[28,30] These findings suggest that schizophrenia might be characterized by impaired ascorbic acid metabolism that might lead to increased blood histamine levels. Optimal doses of ascorbic acid might be necessary to combat the ill effects of histadelia. Table 2 (below) summarizes the ways in which vitamin C lowers blood histamine.

Histamine and Schizophrenia

The histadelic-type of schizophrenia is marked by disordered histamine metabolism. Kobayashi and Freeman demonstrated that higher amounts of conjugated imidazole acetic acid appear in the urine of schizophrenics.[31] Imidazole acetic acid is a breakdown product of histamine catabolism.[21] Heleniak and O'Desky hypothesize that defects in the histaminergic system play a primary role in the etiology of schizophrenia.[32] It has been suggested that histamine functions as a mast cell stabilizer, acting in a paracrine fashion to down regulate its own release.[33] In the histadelic

Table 2. Biochemical interactions between vitamin C and histamine.

Substance	Evidence	Lowers Blood Histamine
Vitamin C	in vitro	likely inhibits HDC through correcting deficiency of ascorbic acid, and increases histamine catabolism
	in vivo (humans)	correcting deficiency lowers blood histamine through an unknown mechanism of action

patient there is probably a defect in the negative feedback circuit that inhibits histamine release and/or there might be a problem with the catabolism of histamine. Future case reports and studies should help to clarify the exact defect responsible for the excess histamine.

Genetic studies have been inconclusive. Orange et al found an increased incidence for the H2R649G allele (histamine type-2 receptor gene; H2 receptor gene) in schizophrenics compared to normal subjects.[34] However, a follow-up study found no increased allelic variations in the H2 receptor gene amongst schizophrenic patients when compared to controls.[35] A clinical research review of the H2 receptor antagonist drug, Famotidine, demonstrated that it is helpful in the management of schizophrenic symptoms. This suggests that Famotidine does bind H2 receptors and should be considered as an alternative when the usual antipsychotic agents have not been successful.[36] Another study failed to demonstrate unique polymorphisms in the histamine N-methyltransferase (HNMT) gene of schizophrenic patients.[37] All of the above findings imply that abnormal histamine metabolism is linked to schizophrenia; however, no current genetic evidence clearly establishes this link.

Conclusion

Optimal (megadose) amounts of vitamins B_3 and C might be necessary treatments to correct the impaired histamine metabolism of the histadelic patient. The therapeutic use of these vitamins for histadelia contradicts the "preferred" treatment for this disorder as described by the late Carl C. Pfeiffer.[5] In vivo and in vitro studies demonstrate that both of these nutrients can normalize blood histamine levels by influencing various biochemical functions. To date, it is not yet established that the histadelic patient is genetically predisposed to defects in the histaminergic system. The current evidence does suggest, however, that disordered histamine metabolism plays a central role in this specific type of schizophrenia.

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