



Antihistamine agents and pitolisant might be useful for anorexia nervosa

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ABSTRACT

This hypothesis is that patients with anorexia nervosa (AN) demonstrate derangement in the histamine central nervous system. It might be possible to ameliorate these by careful use of histamine receptor antagonists targeting Histamine 1, 2, or 3 receptors. Histamine 3 receptors are exclusively present in the brain. Pitolisant is the only one agent currently available that targets these receptors. Pitolisant (brand name Wakix) was approved in the European Union, as a treatment for narcolepsy in March 2016.

Hypothesis

This hypothesis is that patients with anorexia nervosa (AN) demonstrate derangement in the histamine central nervous system. It might be possible to ameliorate these by careful use of histamine receptor antagonists targeting Histamine 1, 2, or 3 receptors. Histamine 3 receptors are exclusively present in the brain. Pitolisant is the only agent currently available that targets these receptors. Pitolisant (brand name Wakix) was approved in the European Union, as a treatment for narcolepsy in March 2016. It is not approved in the US, but has been granted “Priority Review” for a new drug application, and is being developed by Harmony Bioscience LLC (Harmony). Harmony’s goal is to obtain FDA approval, and begin marketing pitolisant in the U.S. in 2019. Results of treating 1,094 patients with average duration of treatment 84 days submitted to the European review, showed that pitolisant was generally well tolerated with no serious or life threatening side effects [1]. Nausea, headache, and depression were reported more frequently than in patients who received placebo. This recent development has stimulated a fresh look at the histamine system in many neurobehavioral disorders, including AN. This hypothesis is a call for testing these agents in the activity based anorexia rodent model, and if suggestive, starting small clinical trials in patients. The activity based anorexia paradigm calls for placing the test rodent in a cage with a running wheel, and limiting the food intake slightly. When both conditions are met, some animals (more often adolescent female) will run to excess, and will decrease feeding until she starves, or the experiment is stopped. This replicates many of the features of human AN—excessive activity and self starvation, and has been a model for the disease since the 1980s [2].

Brief review of discovery of central nervous system histamine system

Histamine is a simple amine; the name is derived by combining the amino acid histidine with amine (NH₂ group). It was isolated over one century ago, in 1910 and shown to cause vasodilation and contraction of smooth muscles [3]. By the late 1940s several antihistamines were developed for treatment of itch and allergic responses including anaphylaxis [4,5]. They remain mainstays of treatment today. It was quickly recognized that these antihistamines cause drowsiness, and therefore it was assumed there were histamines in the brain responsible for wakefulness, but it was not until the 1980s that the system was clearly defined.

Two independent groups noted that the sole source of histamine in the rat brain arises from a small area near the hypothalamus located near the third ventricle, made up of approximately 100,000 neurons, known as the tuberomammillary nucleus (TMN) [6,7]. This small nucleus has projections to many areas of the brain and spinal cord. This discovery solved an old problem—at the end of WWI, during the influenza epidemic it was noted that some victims developed extreme lethargy (named encephalitis lethargica) and at post mortem examination their brains showed inflammation in a small area around the posterior hypothalamus [8]. This clinical history and the 1980 mapping studies made it clear that a major role of histaminergic neurons is to maintain wakefulness and arousal. While wakefulness is the most dramatic effect of the histaminergic system, the effects are protean. Being vital for controlling sleep/wake cycles, implies that this system is intimately linked to feeding (as an individual must get food when awake), as well as “motivation”, learning, reproduction, and probably circannual rhythms and hibernation [9]. Because the outputs from the TMN are vast and complex, it is useful to conceptualize the system as an interconnected web, and expect that manipulation of the system can

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lead to unexpected results. A further complication, is the unanswered question whether the histaminergic system consists of functionally distinct subpopulations of neurons. In short, pharmacological histamine stimulation can cause anorexia in a test animal, and under different circumstance can cause increased feeding activity.

Histamine receptors

Currently four distinct G protein-coupled histamine receptors (H1-H4) have been identified [5]. The H1 receptor is expressed on mast cells in the periphery, and is also present in the central nervous system. The H2 receptor is expressed by enterochromaffin cells in the stomach that cause acid production, and is also present in the central nervous system. The H3 receptor is thought to be only expressed in the brain; and the H4 receptor is not expressed in the brain.

H1 receptor antagonists (brand name Benadryl) are not specific for the H1 receptor, often displaying anticholinergic effects. While the CNS effects especially drowsiness are commonly considered annoying “side effects” there have been several efforts to explore these action for therapeutic purposes. Cryptoheptadine (brand name Periactin) causes weight increase and it has been shown to be effective for patients with weight loss due to illness such as cystic fibrosis [10]. A small study found Hydroxyzine (brand name Vistaral) it to be highly effective for treating generalized anxiety [11]. It should be noted that these agent were developed in the 1940s and 1950s, hence not patentable and thus not of interest to pharmacologic companies to develop.

In 1977 cimetidine (brand name Tagamet), a H2 receptor antagonist was developed as a treatment for peptic ulcer disease, followed by ranitidine (brand name Zantac) and famotidine (brand name Pepsid) [12]. They are thought to be poorly absorbed through the blood/brain barrier, but a patient with schizophrenia showed improvement of the negative symptoms of the disease while on famotidine [13]. This ultimately led to a small clinical trial, using high doses, which found famotidine effective in abating the negative symptoms of schizophrenia [14].

The histamine H3R was first identified in the rat brain in 1983 [15], and successfully cloned and functionally expressed by Lovenberg in 1999 [16]. The H3 receptor is an inhibitory autoreceptor meaning that when histamine tone is high, histamine binds to the H3 receptor on TMN neurons causing the neurons to hyperpolarize and hence reducing the activity of these cells. These inhibitory autoreceptors are essentially a built in negative feedback loop. Drugs that interfere with H3 receptor signaling (such as pitolisant) block the inhibitory effect of the H3 receptor and increases brain levels of histamine. The H3 receptor does not only exert negative feedback on histamine; it is also expressed on a variety of neurons, including cells that make dopamine, serotonin, norepinephrine, acetylcholine, GABA, and glutamate. Therefore antagonism of the H3 receptor with pitolisant could cause general increases in levels of serotonin, norepinephrine, dopamine, and possibly other neurotransmitters.

Histamine system, anorexia nervosa and feeding behavior

The self starvation, and frequent hyperactivity of patients with AN are the core symptoms of the disorder. Yet, patients with AN are often very interested in food—preparing it for others, reading cook books, sometimes hoarding it. They do not eat it, or at least not much of it, and become very obsessed with what they are eating. Torrealba et al. have advanced the theory that histamine is crucial for appetitive behavior for food (being awake, seeking it out) but then it acts to decrease consumption [17]. Rats placed on a slightly limited but highly scheduled diet, demonstrated that TMN activation begins one hour before mealtime, and quickly disappear as the animals began to eat [18]. Brown et al. have suggested that histaminergic system is responsible for response to threat. Test animals show anti-nociceptive action in response to histamine, adaptive anorexia, and increased exploratory behavior—

actions that would be necessary to respond to threat [19]. Of note, patients with AN often display an unusually high pain threshold [20]. The hyperactivity of patients with AN can be seen as equivalent to increased exploratory behavior in study animals.

Data presented to the European review, noted that 1.3% patients treated with pitolisant experienced weight increase compared to 0.4% treated with a placebo. In short the effect of H3 receptor inverse agonist in humans seems to encourage weight gain.

Putting these clues together, implies patients from AN show an abnormal histaminergic system—they are active, seek out food, have a high pain threshold, but then ultimately, they fail to eat.

Histamine system, activity based anorexia, learning, and the hippocampus

Rat studies have shown that histaminergic fiber reach the hippocampus, and CA1 pyramidal cells are directly and strongly excited by Histamine 2 receptor activation. This is important because the hippocampus has consistently been shown to be intimately involved in learning, especially spatial learning [21]. Aoki et al., has used the activity based anorexia model to find specific synaptic changes in the CA1 pyramidal cells of the hippocampus [22]. While patients with AN are often good students, there has recently been attention to the subtle learning difficulties they face especially with cognitive flexibility (inability to shift mental strategies), central coherence (preoccupation with details at cost of global processing), and spatial difficulties [23]. Putting these clues together, suggests patients with AN may have deficits in hippocampus function, and these might be strongly influenced by abnormal histamine signaling.

Histamine system, anorexia nervosa, and alcoholism

Soft links have been found between alcohol abuse and the histaminergic system. Rats selected for ethanol preference display elevated brain histamine levels, high turnover, and low H1 and H3 receptor activity. Similarly rats bred for sensitivity to ethanol induced motor impairment (low threshold to intoxication) have much lower brain histamine and higher H1 and H3 receptor activity [24]. Recently, low doses of H3 receptor blockers have been shown to decrease alcohol intake in wild type rats [25]. Unfortunately there is a strong association between AN and subsequent development of alcohol dependence, and this adds greatly to the morbidity of the disorder [26].

Histamine system, anorexia nervosa and sleep/wakefulness

The most dramatic effects of blocking H1 receptors are drowsiness; and pitolisant acting on H3 receptors is wakefulness. Sleep/wake cycles are disturbed in patients with AN, but this is not the most clinically relevant issue. Studies have consistently shown that while acutely underweight, patients sleep less, have frequent awakenings, and have decreased rapid eye movement sleep compared to controls [27].

Histamine system, anorexia nervosa, and Prader Willi

Prader Willi syndrome (PWS) is a complex genetic disease, effecting males and females equally, that is due to loss of function of specific genes on chromosome 15. A cardinal manifestation is that after a period of failure to gain weight in infancy, individuals experience hunger, food obsession, and if not managed with diet and weight control, become obese by adolescence. Thus, in many ways it seems like an opposite syndrome to AN. There are many similarities however. Both patients with PWS and AN are usually obsessed with food. Both patients with AN and PWS struggle with obsessive thoughts, again often centering on food. Both struggle with learning disabilities. Biochemically they both show very elevated ghrelin levels, yet the expected behavior response is different—patients with PWS eat, and those with anorexia restrict eating [28]. The relationship between ghrelin and histaminergic system

is not well understood, but both share food entrainment circadian rhythms. Spearheaded by parents of children with Prader Willi, an open label clinical trial of pitolisant showed improvement in 9/10 children who were treated with the medication. Improvement was seen in daytime sleepiness and cognitive ability [29,30].

Histamine system, anorexia nervosa, and hibernation

Several theories have been proposed that suggest AN is an adaptation to flee famine, as the hyperactivity, self starvation, and seeming lack of concern regarding low body weight would be valuable if the nomadic tribe were searching for a better food supply [31]. It has been suggested that AN, marked by self-starvation, low grade hypothermia, and hyperactivity is a rogue hibernation state that the patient enters if she is physiologically receiving strong signals that food is scarce [32]. Thus, it behooves us to study the hibernation literature, and perhaps clues will emerge that can help patients with AN. The histamine system, intimately tied to circadian rhythm, food entrainment, temperature control, reproduction, is a prime candidate for dictating hibernation cycles. A 2003 study found that histamine H3 receptor, m-RNA increases dramatically in the cortex, caudate nucleus, and putamen during hibernation, accompanied by elevated receptor binding in the cortex, globus pallidus, and substantia nigra; and there was a delay in arousal from hibernation when histamine was infused into the hippocampus of the hibernating ground squirrel [33].

Histamine system in patients with anorexia nervosa and gender dichotomy

In 2009 a small PET scan study compared the binding of H1 receptors in the brains of 12 acutely ill patients with anorexia nervosa to 12 normal females to 11 males [34]. They found, as expected, there was much higher binding in females than males. They also found there was increased binding in patients with AN compared to normal females especially in left lenticular nucleus and the right amygdala. They found, surprisingly there was a weak but present inverse relationship between the degree of anxiety and depression and the amount of H1 binding in patients with AN. Thus in short there are hints of dysregulation in the system, and strong support for a gender difference in histamine tone. Of note, AN is at least twice as common in females than males.

Histamine system, endocannabinoid system, and connection to fat nutrient supply

The role of the cannabinoid system in feeding behavior has been known for years, although the mechanism remains unclear [35]. Oleoylethanolamide (OEO) is a lipid, derived from oleic acid, an 18 carbon monounsaturated fatty acid. Long considered, an “entourage cannabinoid” it is intimately involved with endocannabinoid effects, although it does not act as a “classic cannabinoid” receptor such as amantadine or 2 archidonoylglycerol [36]. In fact, OEO has long been recognized as an anorexia inducing agent [37]. OEO is released from the small intestine and is a fat sensing agent that seems to signal satiety in the central nervous system. A recent study demonstrated that the anorexic effect of OEO is diminished in rats who were manipulated to become histamine deficient (histamine synthesizing enzyme histidine decarboxylase was knocked out) [38]. It is interesting that the endocannabinoid system has been implicated in the activity based anorexia model [39]. Thus OEO might be a clue linking the endocannabinoid system and the histamine system. This study also emphasizes the importance of specifying diet, especially fat content, in studies of feeding behavior. It has been suggested that a high fat ketogenic diet might be helpful for patients with AN, although there have been no clinical trials [40].

Conclusion and suggestion

Manipulation of the histaminergic system, with either older H1 and H2 receptor agents, or the new H3 receptor specific inverse agonist, pitolisant might be helpful for patients with AN to pull themselves out of the metabolic hole that captures them and causes them to live a difficult life of semistarvation. We are not aware of any studies that employed the activity based anorexia model to test this hypothesis. There was one study that found that pyrrolamine (an H1 receptor antagonist that is commercially available; present in Midol) did decrease the locomotor activity of mice during the dark (the awake time for mice), but did not effect the food anticipatory behavior [41].

This hypothesis is a strong recommendation that these studies be conducted, and if promising, clinical trials can be considered for patients with AN.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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