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Histidine and Humans Disease

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Abstract

Background: Histidine is an important amino acid with important properties that enable it to play a vital part in many activities in the human body, such as proton buffering, metal ion chelation, scavenging of reactive oxygen and nitrogen species, erythropoiesis and the histaminergic system. This review presents the impact of histidine level fluctuation on the body function, the physiological role and metabolic pathway of histidine in various parts of the human's body. Also, we investigated that histamine production by Histidine decarboxylase gene and there is relationship between histidine food intake and level of Histamine in blood, which resulting in the obesity, anemia and other nutrition issues. In addition, a neurotransmitter is included oin histamine that is widely distributed throughout the human brain; its deficiency could cause problems in the nervous system. This study revealed that deficiency of histidine contributed to mental problems like Parkinson's disease (PD), schizophrenia (SCZ), kidney and prion disease as well. As a result, histidine is important to keep human body healthy, and it is also found that hisidine is used as a suitable drug for people who have schizophrenia. This review revealed that the correlation between histamine and asthma is still not well understood. So, this review will open way for researchers to focuses on this aspect.

Keywords: Histidine, Histamine, physiological role, Parkinson's disease and human disease

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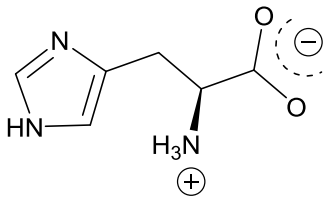
Introduction

One important alpha amino acid is histidine which consisting of imidazole as a functional group, essentially plays a role in the synthesis of different proteins. Albrecht Kossel, a German surgeon, was the first who isolate histidine in 1896[1].



Histidine

Figure (1): Histidine chemical structure

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The conjugate acid (protonated form) of the imidazole side chain of Histidine has a pKa of around 6.0 (Figure 1). This means that slight changes in pH will change its average charge at physiological pH values. The Henderson-Hasselbalch equation describes how the imidazole ring is mainly protonated below pH 6:

pH = pKa - log ([acid]/[salt])

Protonated imidazole ring structure includes two NH bonds. When protonated, a positive charge appears in nitrogen atoms. The positive charge is localized evenly through all nitrogen atoms and can be expressed by two distinct resonance structures. At all pH levels, histidine's imidazole ring is aromatic. It has six pi electrons, two from a nitrogen ion pair and four from two double bonds; the positive charge complicated the pi-stacking interactions[1]. UV data shows that in shorter wave length can absorb like amino acids, but it absorbs more wave length than other amino acids. Imidazole compounds and its derivatives have antioxidant and anti-inflammatory. L-efficacy histidine's in protecting inflamed tissue because imidazole ring in histidine has ability to absorb oxygen radical which produced during acute inflammatory responses by cells [2].

Histidine and Histamine

Histamine and carnosine biosynthesis based on histidine, increased level of histidine in the blood is a sign of inborn defects in histidine biosynthesis, such as histidinemia and maple syrup urine disease. Rheumatoid arthritis patients are associated with low blood histamine and low serum histidine[3]. The amalgamation of histamine start with the decarboxylation of L-histidine via the enzyme histidine decarboxylase (HDC) as shown in Figure (2), and its properties of the amine then distributes by receptors of activating histamine (HR1, HR2, HR3, and HR4) on different cells in the body[4]. Two important proteins histamine N-methyltransferase (HNMT) and diamine oxidase damage histamine and allowing it to be removed from the body[5].

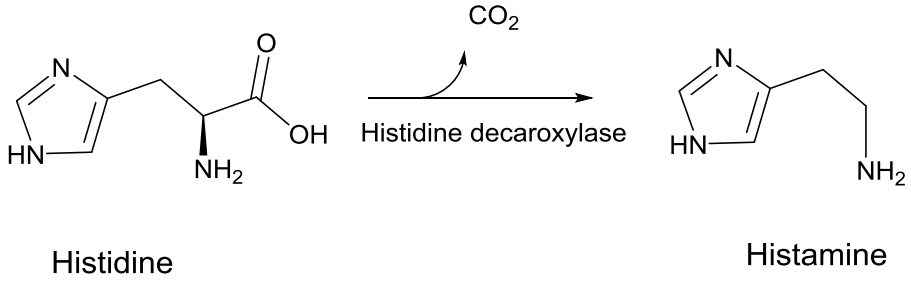

Figure (2): Biosynthesis of histamine by histidine decaroxylase

Histidine and Asthma

A chronic inflammatory condition is called asthma, which is marked by hyper responsiveness of the airways, airflow obstruction, and variable reversibility in response to environmental stimuli. According to survey by National Asthma Surveillance and the Centers for Disease Control and Prevention, asthma prevalence showed that rose in number of patient about (25.7 million)

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every ten years. In general, in developed nations asthma is considered one of the most common chronic childhood diseases; the national Health interview survey demonstrated that more than 7.1 million children were detected with asthma[6], pathophysiology of asthma is a complicated disorder that has not well understood [7].

Asthma with allergen hypersensitivity is well known as allergic asthma. Histamine is one type of biogenic amine that is assumed to play an important factor in the increase of allergic asthma in humans lungs. Bronchospasm and airway obstruction occur when histamine receptors are activated. It was found that there is a correlation between plasma histamine levels with asthma severity[8]. Another study found that use antihistamines in children who considered high-risk to avoid the symptoms of asthma. Histamine is involved in the pathogenesis of asthma as well as the therapeutic response to asthma treatments, especially in allergic asthma[9].

Histidine, Nutrition and Obesity

A main risk factor for a variation of metabolic complications and long-term diseases, including insulin resistance, metabolic syndrome,[9,10] type 2 diabetes, hypertension, cardiovascular disease, and some cancers are caused by obesity. Nutritional factors are affecting treatment, growth, and inhibition of overweight and chronic diseases like hyperlipidemia, diabetes mellitus, and cardiovascular diseases [12]. If a person's body mass index (BMI) is greater than 30, the person is called obese:

$$\textbf{BMI = weight (Kgm) /length (m)}^2$$

Histidine, considered as a specific amino acid to health of human body, is available in red meat and fish. Protein-energy degenerative aggravation and oxidative pressure in persistent kidney infection patients is affected by lower plasma concentration of histidine[6]. Histidine supplementation could minimize body weight and inflammation and oxidative stress in female obese rat models which was confirmed by animal studies. Although animal and in vitro research have shown the important functions of dietary histidine in energy intake management, it is still uncertain if chronic dietary histidine exposure in obese individuals is associated with insulin resistance, inflammation, or oxidative stress. Dietary histidine's contribution is still under investigation[13].

Histidine as antioxidant and anti-inflammatory

L-histidine, is identified as antioxidant due to reducing the fluid accumulating in the intestine, which could protect the tissue of the intestine from S.typhimurium caused damage[14].D-histidine has an inactive protective effect. The L-Histidine efficacy in defending injured intestinal tissue due to the ability of imidazole ring in scavenging reactive oxygen species, which are produced by the intestine cells during the acute response to inflammation. Anti-inflammatory medicines include an L-histidine-like structure might be beneficial in protecting damaged mucosal tissues, regardless of the microbial etiology[15], this drugs act as the hydroxyl radical and singlet oxygen hunter,[16] then protect LDL cholesterol against oxidation[17]. Insulin resistance (IR)

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is the most common symptom of type 2 Diabetes and heart attack. Inflammation and oxidative stress are well-known contributors to the frequency and severity of IR. Aggravation and oxidative pressure are known to assume a focal part in the event and hostility of IR[6]. In this manner, clinicians and general wellbeing specialists have gbeen inspired by the quest for parts from food sources that have action against irritation and oxidative-stress[18]. Furthermore, a previous study revealed that obese women had lower serum histidine levels than healthy women, which was linked to oxidative stress and irritation[19]. In addition, other studies found that histidine levels were lower in young tall adults and patients with type 2 diabetes, and that it increased insulin sensitivity[18]. Histidine may reduce the levels of cytokines like interlukin (IL-6), tumor necrosis factor (TNF-α), and C - reactive protein (CRP) in animal models of liver and lung damage caused by diabetes or acute inflammation[19]. In another vitro study, histidine reduced hydrogen peroxide (H2O2), TNF, and IL-8 secretion in intestinal epithelial cells[20].

Histidine and chronic kidney disease (CKD)

Patients of chronic kidney disease have Low plasma histidine concentrations which related to protein-energy wasting, infection, oxidative stress, and increased mortality [6, 21].

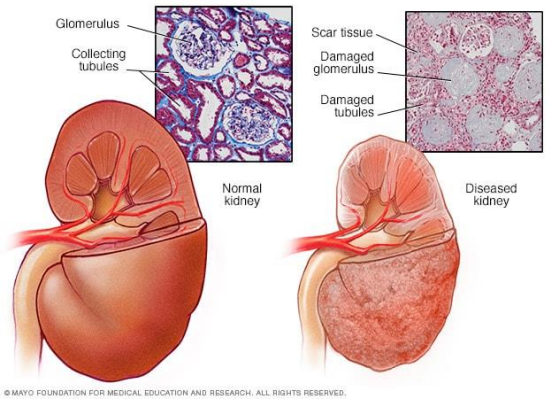

Figure (3): an illustration of the healthy kidney & diseased kidney

Histidine deficiency might cause health concerns in patients have chronic kidney disease (CKD) since it is an antioxidant and anti-inflammatory factor. An irregular sequence of plasma amino acids (AAs) may be found in patients of chronic kidney disease (CKD) with high plasma concentrations of certain non-important (NEAAs) and low concentrations of the majority of essential amino acids (EAAs) [22] Figure(3). Histidine has been classified as a dietary EAA for babies while selected for adult humans, usually as a NEAA[23]. Bergström *et al*. found that histidine is essential for uremia patients and that histidine enhances net nitrogen production in CKD patients[6]. Furthermore, histidine is recognized as a scavenger for the hydroxyl and singlet oxygen radical and has been shown to protect LDL cholesterol from oxidation[24][25].

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Histidine and Mental Disease

Chronic central nervous system diseases including Parkinson's disease (PD) and schizophrenia (SCZ) are unknown causes, but their pathogenesis is similar. As a result of the impairment of histamine N-methyltransferase (HNMT), Histamine degradation was slowed. Several neurotransmitters are dysregulated, like histamine, which was linked to PD and SCZ[26]. In fact, significant evidence links the dopamine metabolism route of PD and SCZ, and the principle medication for PD and SCZ are depend on the dopamine pathway[27]. Histamine can damage dopaminergic neurons specifically, resulting in increased inflammation, which is a diagnostic of Parkinson's disease pathogenesis[28]. According to a previous study has been shown that a low blood Histamine leading to schizophrenia, with high copper. So, histidine seems to be a suitable drug for all patients with low levels of histamine[29]. Furthermore, SCZ patients had 2.6-fold higher Histamine levels in their cerebral fluid than healthy persons, indicating unusually rapid Histamine recycling[30].

Histidine and Prion Diseases

Prions are misfolded proteins that have been linked to a number of fatal neurodegenerative diseases in both animals and humans[23]. The reasons for converting normal protein to misfolded protein are unknown; it's thought that the irregular 3-D structure has infectious properties[31]. In humans, prions have been postulated to be similar to Creutzfeldt-Jakob disease. Commonly, prion diseases influence the system of the brain or other neural tissues in mammals[32]. In compared to other infectious agents identified like fungi, viruses, bacteria, and parasites the hypothesized idea of a protein as an infectious agent stands[33]. It has been shown that Creutzfeldt–Jakob disease may need agent-specific nucleic acids to spread infection[34]. Prion aggregates are persistent, grow in affected tissue, and are linked to cell death and injury. Due to their structural integrity, prions are resistant to denaturation by chemical and physical agents, making disposal and containment of these particles impossible. The structure of prion differs slightly according on the species[35]. PrPC has two structural domains: a folded globular C-terminal domain that is mainly helical, and a glycine-rich N-terminal domain with an octapeptide repeat region (OR) [30]. In specific, the OR district produce the histidine-rich copper-binding complex has been shown to have high reduction potential for the couple Cu(II)/Cu(I) and to create a stable the lower-covalent Cu(I) state, which may lead reactions involving reactive oxygen species (ROS)-mediated events, such as β-cleavage[33,34].

Background of histamine

Histamine was discovered by Henry and colleagues[3]. The first evidence of histamine in the brain was discovered by John J. Abel when he extracted histamine from the pituitary gland. A few decades later, it was discovered that lesions of the lateral hypothalamic region reduced the activity of the histamine-producing enzyme L-histidine decarboxylase, confirming histamine's function as a transmitter. Another decade passed before techniques were developed to clearly reveal that the restriction of histaminergic neurons in human's brain in

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tuberomammillary core of the back nerve center, there were like other amines, histaminergic neurons have cell bodies, from which they transmit projections to almost all areas of the focused sensory system[6]Figure (4). Approximately 4000 histamine neurons are involved in the rat, while around 64,000 histamine neurons are found in brain of human[38].

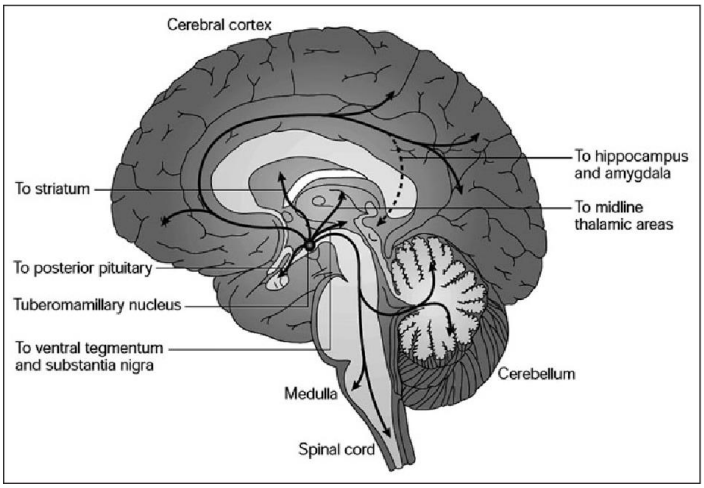

Figure (5): Histaminergic neurons in the brain[38**]**

A neurotransmitter is included of histamine that is widely distributed throughout the human brain, neurons nucleus supplies histaminergic fibers to almost all parts of the human brain[36,37].

Histamine functions

Histamine is an organic nitrogenous molecule that regulates specific immunological responses and works in the brain as a neurotransmitter, uterus and spinal cord, as well as monitoring physiological activity in the stomach. Histamine acts as a central mediator of itch and it has a key role in the inflammatory response. Histamine is released by basophils and mast cells in adjacent connective tissues during an immune response to pathogens[38]. The amount of neurons in the human brain that generate histamine is approximated to 64,000. In the brain, histamine regulates sleep–wake cycles, stress response, appetite, and memory as a neurotransmitter. Histaminergic nervous system is responsible for the pathophysiological of numerous neuropsychiatric disorders, according to extensive research[41]. Histamine plays an essential role as a neurotransmitter in the central nervous system, in addition to mediating allergic reactions, gastric acid secretion, and inflammation in the periphery. Histaminergic neurons in the tuberomammillary nucleus of the posterior hypothalamus transmit projections to practically every area of the brain. Many brain functions, like arousal and pituitary regulation, are influenced by the central histamine system. Both a loss-of-function mutation (EC4.1.1.22) and a key enzyme for histamine production have been related to Tourette's syndrome in the Histidine decarboxylase gene. Cognitive impairment is attributed to pathological changes in histamine neurons.

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Histamine, schizophrenia and Parkinson's disease

The findings from Positron Emission Tomography technique demonstrated that the histamine potential was reduced in patients with depression and schizophrenia (SCZ), also showed that histaminergic nervous system dysfunction can be a contributing factor in a variety of neurological conditions, and that a rise in brain histamine levels may be a result of this dysfunction[41].

In neurological and psychological disorders, changes in the histaminergic pathway have been discovered, indicating that histamine could have therapeutic potential. People with Alzheimer's disease have reduced histamine levels in their brains, while patients with Parkinson's disease and schizophrenic patients have abnormally high histamine levels.

A neuron disorder with symptoms that include motor and non-motor symptoms is called Parkinson's disease. A neurotransmitter deficit exists in the extrapyramidal pathway in Parkinson's disease, with a minimal level of dopamine and GABA and an excess of acetylcholine and glutamate. Serotonin adenosine, dynorphin and P substance are categorized as classical neurotransmitters, which are also involved in the disease pathogenesis. 1% of the people older than 60 years affects by Parkinson’s disease (PD) and men more often than women. In addition, other classical neurotransmitters like acetylcholine, glutamate and GABA also influence the pathophysiology of the disease[38]. A progressive loss of pigmented neurons in the substantia nigra is attributed to Parkinson’s disease (PD) which results in deficiency of dopamine in the striatum and other brain regions. However, PD has also an effect on many other neurotransmitter systems[42]. There is some indication for the contribution of the histaminergic system in PD. Histamine in blood levels increased in PD patients, as is the cerebrospinal fluid concentration and improvement of motor function in some patients[13]. Although the activity of the histamine-synthesizing enzyme, histidine decarboxylase, is reduced in multiple system atrophy (MSA), it remains unaffected in Parkinson's disease (PD), indicating that histaminergic neurons do not degenerate in PD. MSA is a parkinsonian syndrome that shares clinical characteristics with Parkinson's disease and can create diagnostic problems. The pathology in MSA is distinct and not as common as that seen in PD. Despite of the support for the changed PD histaminergic system, there have been no findings on brain histamine concentrations in people with Parkinson's disease, as the most frequent form of dementia. Alzheimer's disease affects 5.5 million individuals in the United States and more than 35 million people globally. Pathological abnormalities seen in Alzheimer's disease symptoms including synaptic damage, dendrite retraction, neuronal cell injury, inflammation, astrocyte activation, BBB death, and the amyloid peptide accumulation [42] within neurons and plaques in the hippocampus and cerebral cortex[43].

Conclusions

Histidine has an important core boundary role in human bodies that is sensitively effectible to many diseases that occur in presence or absence. Also, high or low concentration could result in serious problem. Healthy nutrition that contains a favorable amount of histidine by keeping enough

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amount of histidine. This review shows that increased levels of histidine in the blood is a sign of inborn defects in Histidine biosynthesis, such as Histidinemia and maple syrup urine disease. Also, there is a correlation between plasma histamine levels with asthma severity .It is still uncertain if chronic dietary Histidine exposure in obese individuals is associated with insulin resistance, inflammation, or oxidative stress. There are two types of histidine including L-histidine and D-histidine, Anti-inflammatory drugs including L-histidin due to the ability of the imidazole ring in scavenging reactivel oxygen species, which are produced by intestinal cells during the acute response of inflammation. This review indicated that obese women had lower serum histidine levels than healthy women, which was linked to oxidative stress and irritation. The patients with chronic kidney disease (CKD) might explain to the deficiency of histidine. In addition, histamine plays an essential role as a neurotransmitter in the central nervous system and its deficiency could cause problem in nervous system. It was found that Histidine is seemed to be suitable medications for all patients have schizophrenia.

Recommendations

Future study will focus on the using histidine as a drug and study side effect of these drugs on patients.

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Ethical clearance: This manuscript never submit to another journal.

Conflict of interest: Nill

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الهستدين والامراض البشرية

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الملخص

خلفية الدراسة: الهيستيدين هو حمض أميني مهم له خصائص فريدة تمكنه من لعب دور حيوي في العديد من الأنشطة في جسم الإنسان ، مثل التخزين المؤقت للبروتونات ، والتناسق مع أيونات المعادن ، وطرد الجذورالحرة كالأوكسجين ، وأنواع النيتروجين ، وتكوين الكريات الحمر ، وله دور في دورة نظام الهيستامين. في هذه المقاله بينت تأثير زيادة أو نقص مستويات الهيستيدين على الجسم الوظيفي والدور الفسيولوجي والمسار الأيضي للهستيدين في أجزاء مختلفة من جسم الإنسان.كذلك بحثت الدراسه في العلاقة بين كميه الهيستيدين الداخله للجسم ومستوى الهيستامين في الدم وتعتبر السمنة وفقر الدم وقضايا التغذية الأخرى بالاضافه الى ذلك يعتبر الهيستامين الناقل العصبي للايعازات الى مختلف اجزاء الدماغ واي نقص يسبب خلل في الانظمة العصبية.بالاضافة الى ذلك كشفت هذه الدراسه أن نقص الهيستدين ساهم في مشاكل عقلية مثل مرض باركنسون (PD) وانفصام الشخصية (SCZ) وأمراض الكلى والبريون. بالنتيجه يعد الهيستدين مهمًا للحفاظ على صحة جسم الإنسان ، كما وجد أن الهيستدين يستخدم دواءًا مناسبًا للأشخاص الذين يعانون من مرض انفصام الشخصية. كشفت هذه المقاله أن العلاقة بين الهستامين والربو لا تزال غير مفهومة جيدًا.لذلك نحتاج الى المزيد من التركز في هذا الجانب.

الكلمات المفتاحية: الهيستدين، الهستامين، الدور الفسيولوجي، مرض الزهايمر، الامراض البشرية

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