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Review

The role of histamine on cognition

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ABSTRACT

Histamine was intensively studied at the beginning of the 20th century because of its important role in allergic and inflammation processes. In those days it was very difficult that researchers could envisage another impacting function for the imidazolamine in the living systems. Once the imidazolamine was found located in neuron compartment in the brain, increasing evidence supported many regulatory functions including its possible role in memory and learning. The specific participation of histamine in cognitive functions followed a slow and unclear pathway because the many different experimental learning models, pharmacologic approaches, systemic and localized applications of the histamine active compounds into the brain used by researchers showed facilitating or inhibitory effects on learning, generating an active issue that has extended up to present time. In this review, all these aspects are analyzed and discussed considering the many intracellular different mechanisms discovered for histamine, the specific histamine receptors and the compartmentalizing proprieties of the brain that might explain the apparent inconsistent effects of the imidazolamine in learning. In addition, a hypothetical physiologic role for histamine in memory is proposed under the standard theories of learning in experimental animals and humans.

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Contents

1. Introduction

The biological role for histamine has experienced a long and increasing recognition, since the molecule was originally isolated from the mould ergot in 1910 by Sir Henry Dale and his colleagues at the Wellcome Laboratories. In spite that at the beginning, histamine called the attention of many researchers for its relation to allergic reactions and inflammation, and later near the end of the 20th century for its possible role in the central nervous system, still traditional pharmacologists refer to histamine as an "autacoids", natural molecules in search of a biological function [12]. It was difficult to be accepted by them that the imidazolamine could have a physiological role in the brain. Description that histamine was contained into neuron compartments, and that there was only one site in the central nervous system where histamine is synthesized, was strong evidence establishing the biological role of histamine in the

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brain [51,63,58]. Histamine-producing neurons are located at the posterior hypothalamus in the tuberomammillary nucleus of the brain [17].

2. The tuberomammillary nucleus as a general integrating neural center

Histaminergic neuron cells are about 30 μm in diameter and appear organized into three main cell clusters in the hypothalamic tuberomammillary nucleus [28,51,63]. Each of these cell clusters is composed of a rather small number of cells; about 600 neurons for the medial tuberomammillary subgroup; 1500 neurons for the ventral tuberomammillary subgroup, and about 100 cells for the diffuse tuberomammillary subgroup [17]. At first sight the relative modest number of neurons for each of the tuberomammillary regions appears contrasting to the many physiological functions attributed to histamine in the brain [17,54,35]. However, a simple mathematical analysis can show that the amount of histaminergic neurons might be enough to fulfill many of the biological functions where histamine participates. Lets assume that any of the neurons in the tuberomammillary nucleus can exist in only two states: conducting an electric signal at a frequency f_1 or at a frequency f_2 where $f_2 \neq f_1$, and each frequency controls one function. This assumption is based on what it is known about the electric proprieties of the tuberomammillary neuron which appears to be of the type *pacemaker* [35]. Thus, when one neuron is active there will be only two functions ("f_1", one signal, and "f_2", other signal). If two neurons act in combination in order to form an elemental two-cells net, four functions could be codified. Three neurons at the same time could codify eight functions, and if 300 neurons are taken into combination, about 2×10^{90} different functions could be performed. This is simply because the combined activation of neurons acting in "f_1–f_2" fashion follows an exponential function of the type $Y = 2^X$, where Y = number of functions (or commands) and X = number of neurons involved.

In spite of the existence of the three main histaminergic neuronal regions in the tuberomammillary nucleus suggesting specific functional specialization, it is thought that because of projection patterns of fibers to different parts of the brain are similar and considerably overlap, all regions can function as a unity [62]. Nevertheless, from a functional point of view, discrete modulating neuron units controlling different functions are predictable, and the histaminergic clusters of the tuberomammillary nucleus should not be homogeneous. Hypothalamic histaminergic neurons send axons practically the entire brain, including the spinal cord [51,63]. This innervation occurs by two ascending and one descending pathways [50], thus many important brain structures such as the septum, olfactory bulb, thalamus, hippocampus, amygdala, forebrain structures, brain stem and spinal cord are innervated [17]. It is possible to visualize that the hypothalamic tuberomammillary nucleus might represent a complex multicompartment neural unit modulating general coping behaviour, since the physiological actions of histamine involve arousal, homeostatic mechanisms, cognition, motivation, pain perception and stress which sustain this behavioural mechanisms [54,17,15,57,39].

3. Histamine receptors

Now it is clear that the histamine effects on biological systems are mediated by the specific activation of four receptor types; H_1-, H_2-, H_3- and H_4-receptors [17,35,52]. The molecular activation of the membrane receptors produces various biological responses because receptors are coupled to several G-protein mediators such as $G_{q/11}$, G_s and $G_{i/o}$ which are linked to several intermediate complex effector systems such as phospholipase C, phospholipase A, and adenylyl cyclase [35,17]. The various cascade intermediate molecules which are activated by the intermediate complex effectors give an amazing spectrum of responses which can activate or inhibit the neuron's functions [60,64,36,17]. Perhaps, this is one of the reasons why many times it has been reported opposing actions for histamine in some brain functions. The pharmacology and molecular proprieties for the different histamine receptors have been reviewed in extensive details by other authors [35,17,52].

4. Histamine and learning

The first evidence that histamine might be involved in the complex processes of learning and memory came from the basic experiments performed by de Almeida and Izquierdo [21,22], whom in a step-down inhibitory avoidance task model found that the combination of cimetidine and promethazine blocked the facilitation of the step-down inhibitory avoidance behaviour induced by the intracerebroventricular injection of histamine. In spite that the intracerebroventricular route of administration for the imidazolamine and its antagonists represents a very wide spectrum for possible histamine targets in the brain, and the side effects at central level of cimetidine and promethazine, including sedation, incoordination, blurred vision, anticholinergic actions, and confusional effects can distort the putative brain action of histamine, this evidence suggested that during learning histamine has a facilitatory action on consolidation of the task. Since it was necessary the injection of both H_1- and H_2-histamine receptor antagonists in order to block the assumed histamine effect on memory, it was apparent that both histamine receptors were mediating the consolidation of the task [21]. Nevertheless, this conclusion was based on the prolonged time the animals stand in the step-down during testing. Recently, it was found that the imidazolamine locally applied into the baso-lateral amygdala and the nucleus accumbens decreased exploration and increased emotionality in a conflictive environment (Alvarez and Banzan, unpublished results, Fig. 1). Thus, the prolonged permanency in the platform of the step-down inhibitory avoidance task may not necessarily be related to an increased efficiency of memory but to an increased resistance to step-down due to an increased emotionality. Nevertheless, the role of histamine on learning gained additional support because of evidence of some other authors working with a variant of the step-down avoidance response model [42,44]. In this model the task consisted to avoid an electric shock delivered to the feet of the animals in a dark room after an sliding door was opened, guiding the rat to a safe lighten room. The oral administration of classical H_1-histamine receptors inhibited the active avoidance response by prolonging the latency to escape of animals [42], and similar results were found when the histamine receptors antagonists were administered by intracerebroventricular route [44]. In addition, the administration of α-fluoromethylhistidine, an inhibitor of the histamine synthesis enzyme, either by systemic or intracerebroventricular injection prolonged the response latency of the active avoidance response in rats [43]. Unfortunately, α-fluoromethylhistidine is a compound that binds irreversibly to the histamine synthesis enzyme, and the only possible site where this inhibitor can act is at the level of the posterior hypothalamus, the only brain region where neurons can synthesize histamine. Thus, the reduction of histamine brain levels affects many important neural histamine centers controlling several homeostatic functions that can interfere indirectly with the learning process, weakening the idea about a direct histamine action on cognitive functions. In spite of this, the role of histamine on learning gained additional support with the description that histamine locally applied into the ventral hippocampus of rats was able to interfere the evocation of an active avoidance response to an ultrasonic tone [1]. In this model, the task consisted

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