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6. HISTAMINE IN THE CENTRAL NERVOUS SYSTEM

Histamine potentiates neuronal excitation by blocking a calcium-dependent potassium conductance

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Abstract

Histaminergic neurones send their axons to the whole forebrain. The diffuse projection is consistent with a modulatory role of these pathways. In hippocampal slices from rats a mechanism for this modulation is described, on pyramidal neurones of the CA 1 area: Strong excitations induced by intracellular current injection, ionophoretic administration of glutamate or synaptic stimulation normally restrict themselves by the activation of the calcium-dependent potassium current (gK(Ca)). This current causes a long lasting afterhyperpolarization and an accommodation of firing. Their block by histamine and impromidine (reversed by metiamide and cimetidine) leads to a profound potentiation of excitatory signals. It is suggested that HA, through H2 receptors, accelerates the removal of intracellular free Ca^{++} ions.

Introduction

Histaminergic neurones located in the supramammillary area of the mesencephalon send their manyfold dichotomizing axons to the whole forebrain [1, 2]. Ionophoretic administration of HA to neocortical and hippocampal neurones usually causes an H2-receptor mediated depression of firing due to a hyperpolarization which is accompanied by a modest conductance increase [3, 4]. HA is therefore considered as a putative inhibitory transmitter in the cortex. More recently, with bath application on hippocampal slices an excitatory and excitation-potentiating mechanism was detected [5]: HA blocks a calcium-activated potassium conductance (gK(Ca), see [6]), which normally restricts strong excitations. The present report enlarges these findings and demonstrates the block of accommodation by HA.

Methods

Transverse slices from the hippocampi of 39 rats were incubated in a perfusion chamber as previously described [7]. Conventional techniques were used for extra- and intracellular recording and stimulation. Microelectrodes were filled with K-acetate or K-chloride and had resistances between 30 and 100 $M\Omega$. Histamine and related drugs were added to the bathing medium. Excitatory amino acids (glutamate, DLH) were administered by ionophoresis from multibarrel glass pipettes to the apical dendrites of pyramidal cells. Impromidine, cimetidine and metiamide were gifts from SKF.

Results

1. Resting potential and spontaneous firing

Histamine (HA) and impromidine (IMP) at 1 μM usually depolarized CA 1 pyramidal neurones by a few mV (2.5 ± 1.5 SD mV, $n = 16$) and always increased the firing rate even in cells which were not stimulated in any other way. Recordings with K-chloride filled electrodes allowed the observation of spontaneous depolarizing (inverted) synaptic potentials which presumably reflect the firing of inhibitory interneurones. Their firing rate was also enhanced.

2. Afterhyperpolarization (AHP)

The slow afterhyperpolarization after a burst of action potentials or a calcium spike was reduced in a dose-dependent manner by adding HA or impromidine to the perfusion medium at concentrations of 0.1 to 10 μM. Figure 1 illustrates such an experiment in a tetrodotoxin poisoned preparation: although the calcium spike, which reflects an inflow of Ca^{++} into the pyramidal cell is not reduced – it was in fact sometimes increased or doubled – the following slow AHP which reflects the Ca^{++}-activated K^+ outflow is markedly reduced.

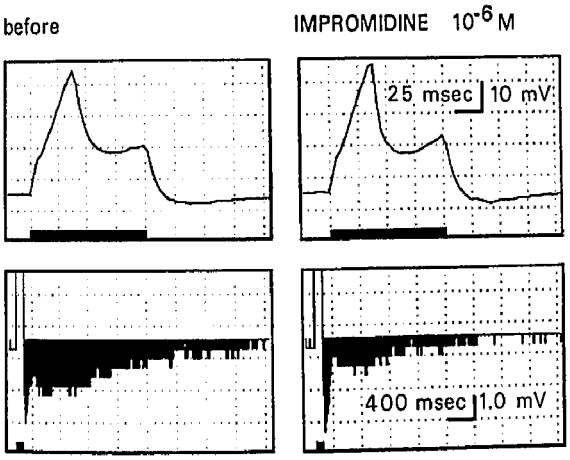

Figure 1
Impromidine blocks the long lasting afterhyperpolarization (AHP) but not the calcium spike. Upper traces: calcium-spike evoked by an intracellular depolarizing current pulse (during the time indicated by black line, 100 msec). Lower traces: The same but at higher gain (×8) and showing a longer time (×8). After the calcium spike (indicated by black square, 100 msec) follows first a short lasting AHP which is unchanged (or enhanced) during impromidine and then the long lasting AHP which is markedly reduced during impromidine. Each trace is an average from 9 sweeps. AHPs are filled in in black.

3. Accommodation

Long depolarizing pulses often show an accommodation of firing which is also caused by (gK(Ca)) [8]. When HA (1–10 μM) was present in the bath this accommodation was abolished

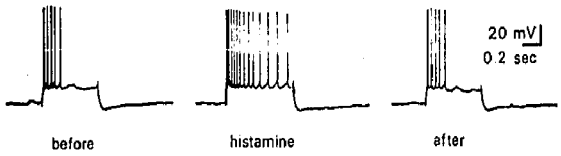

Figure 2
Histamine blocks accommodation of firing. A depolarizing intracellular current pulse (0.5 μA, 600 msec) causes action potential firing only for the first 200 msec. During histamine 1 μM the firing lasts through the whole pulse.

and the firing was only terminated at the end of the depolarizing pulse (Fig. 2).

A prolongation of the firing caused by local ionophoretic administration of excitatory amino acids (glutamic and DL-homocysteic acids) was observed as well in the presence of HA or IMP. The effect of the amino acids was sometimes registered as a negative DC shift [9], which was also potentiated in a dose-dependent way by HA (1–10 μM). Figure 3 illustrates such an experiment.

4. Synaptic transmission

After stimulation of the stratum radiatum a fiber volley (I in Fig. 4) and an excitatory postsynaptic potential, EPSP (E) can be recorded as negative potentials extracellularly [10] in this layer where the apical dendrites of CA 1 pyramidal cells are extended. At the same time, in

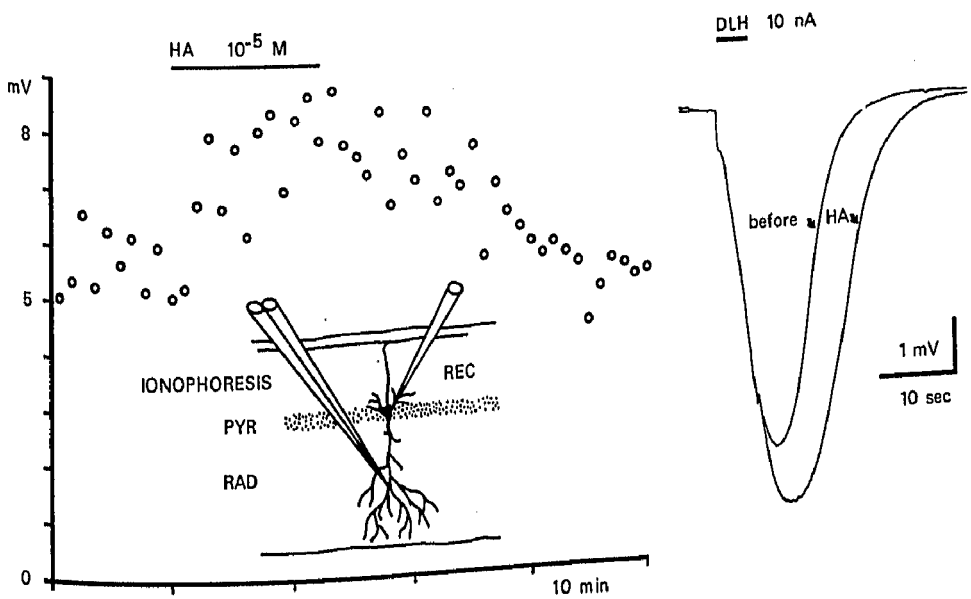

Figure 3
Histamine potentiates the action of an ionophoretically applied excitatory amino acid (DL-homocysteic acid, DLH). The effect of dendritic DLH ionophoresis (see insert) was measured as a negative DC shift (right). This shift reflects the firing of several cells. The diagram shows the size of the shift on the ordinate. Histamine perfusion is indicated above.

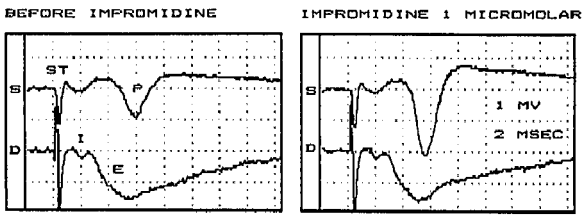

Figure 4
Impromidine enhances population spike. Stimulation (ST) in stratum radiatum, recording in stratum radiatum (D, dendritic) and stratum pyramidale (S, somatic). The input volley (I) and the EPSP (E) are unchanged but the population spike (P) is doubled by 1 μM impromidine. Each trace represents the average of 9 sweeps.

the cell body layer (stratum pyramidale) a positive synaptic potential and a negative population spike (P) are registered. The input fiber volley (I) and the EPSP (E) were unchanged in 7 experiments whilst the postsynaptic population spike (P) was always increased by 0.1 to 10 μM impromidine (46.6 $\pm$ 6.2%, $n = 5$, for 1 μM).

Discussion

All these findings could find their explanation by the block of gK(Ca). In perfusion experiments this action overrides the hyperpolarizing effect seen with locally restricted HA administration [4] and it may well be a better model for the natural effects of HA released from diffusely projecting pathways. Both actions are mediated by H2-receptors, the block of gK(Ca) seems to require occupation of a larger number of receptors.

The long lasting AHPs have an influence on firing rate, as they keep the cells away from firing threshold for up to several seconds after an action potential or particularly a burst of action potentials. This accounts for an increase in firing rate by HA sometimes even in the virtual absence of changes in the resting potential. The accommodation of firing during depolarizations evoked by positive current injection, ionophoretic glutamate administration or natural events appears as a self restriction of excitatory signals through gK(Ca). Release by HA from this restriction leads to a prolongation of action potential firing, a potentiation of the excitation. This effect is bound to be more prominent with strong excitations which are accompanied by a large Ca^{++} ion inflow, and thus increases the signal to noise ratio in neuronal communications. The afferent fiber volleys and the excitatory postsynaptic potentials in CA 1 were not significantly affected by HA but an increase of EPSPs in CA 3 has been reported [11]. The postsynaptic population spike, however, was enhanced and it is conceivable, considering the time course of gK(Ca) [6], that even such a short excitation is potentiated by this mechanism.

The small depolarization by HA and IMP may be due to block of a tonic potassium current which depends on the level of free Ca^{++} ions inside or the Ca^{++} flow into the neurone. In slices bathed in a low Ca^{++} high Mg^{++} solution inward Ca^{++} currents are abolished and AHPs are blocked. Nevertheless, HA and IMP cause a remarkable increase in excitation (firing and bursting) in this situation [12]. This finding is consistent with a potassium current depending on the intracellular Ca^{++} level rather than an actual Ca^{++} inflow. HA could block the potassium channel or regulate the intracellular Ca^{++} level. It is known that HA increases cyclic AMP levels in the hippocampus [13, 14] and reported [8] as well as own preliminary experiments indicate that cyclic AMP and a phosphodiesterase inhibitor (Ro 20-1724) can mimick the electrophysiological H2 effects in hippocampal slices. It may thus be hypothesized that H2 receptor activation leads to a stimulation of adenylate cyclase and subsequently to an increase in Ca^{++} binding proteins (through protein phosphorylation), which would down-regulate the level and increase the speed of removal of Ca^{++} ions at the inside of the neuronal membrane. This mechanism allows histaminergic afferences to regulate cortical responsiveness very effectively.

References

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