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Histamine may act through cyclic AMP on hippocampal neurones

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Abstract

Bath applied histamine and 8-bromo-cyclic AMP and intracellularly injected cyclic AMP block-long-lasting after-hyperpolarizations and the accommodation of firing in CA1 pyramidal cells recorded in rat hippocampal slices. This action is due to reduction of a calcium-activated potassium conductance (gK(Ca)) and leads to potentiation of excitatory signals including epileptiform discharges. The effects are further potentiated and prolonged by a phosphodiesterase inhibitor (Ro 20-1724).

Introduction

Highly localized ionophoretic administration of histamine usually causes a hyperpolarization and suppression of firing in most brain regions including the hippocampus [1, 2]. However, bath application of this amine slightly depolarizes hippocampal pyramidal cells and blocks their accommodation of firing and the long-lasting afterhyperpolarizations (AHPs) attributed to a calcium-activated potassium conductance (gK(Ca)) [3, 4]. This effect is also seen with noradrenaline (beta-receptor) and cyclic AMP [3–5]. Histamine (H2) and noradrenaline (beta) but not the other amines present in projections to the hippocampus stimulate an adenylate cyclase in hippocampal slices [6–8].

Methods

Slices prepared from the hippocampi of 23 rats were incubated in a perfusion chamber. Microelectrodes were filled with 1 *M* NaCl for extracellular and 2 *M* KCl or CsCl for intracellular recording. Some pipettes contained 10 m*M* cyclic AMP and 2 *M* KCl. Histamine and 8-bromo-cyclic AMP were added to the perfusion medium, which contained also tetrodotoxin in some experiments.

Results

The blocking effect of histamine on gK(Ca)-mediated AHPs was confirmed in all 19 cells tested in this investigation. It is illustrated here on a spontaneously 'epileptic' slice exhibiting paroxysmal depolarization shifts followed by an AHP. This AHP is blocked and the burst firing prolonged in the presence of histamine (Fig. 1). Histamine and 8-bromo-cyclic AMP always increased the frequency of epileptiform bursts, but had often little effect on their duration. On five cells, 8-bromo-cyclic AMP was applied at 100 μM before or after the histamine effect was seen. In each case, including one in the presence of TTX, a similar block of accommodation and

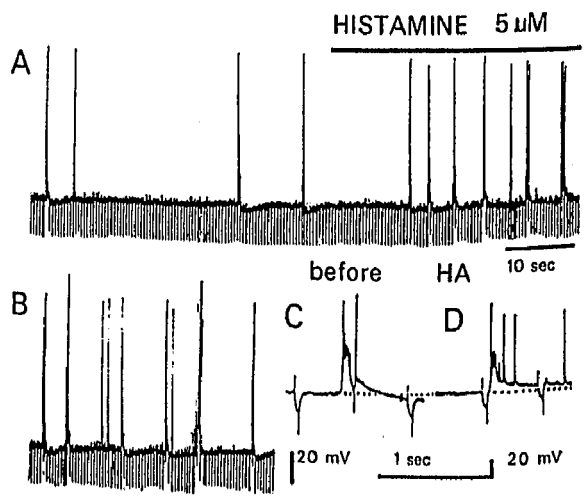

Figure 1

Intracellular recording (KCl) from a CA 1 pyramidal cell in a spontaneously epileptic slice from the rat hippocampus. Upstrokes are paroxysmal depolarizations followed by an afterhyperpolarization (AHP). No. 2 in A and nos. 3, 4, 7 in B are single action potentials. When histamine is perfused during the time indicated by the bar above the trace in A, AHPs disappear whilst the bursts are accelerated and prolonged. B illustrates partial recovery after 20 min. C, D: Oscilloscope photographs of paroxysmal depolarizations before and during histamine action.

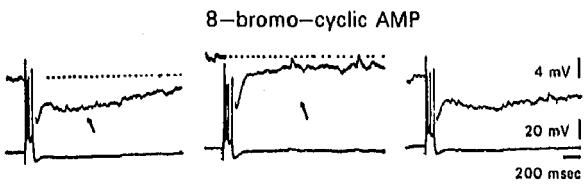

Figure 2
Oscilloscope pictures at two different gains of intracellular records before (left), during and 20 min after (right) perfusion with 100 μM 8-bromo-cyclic AMP. While the early AHP after a burst of spikes is unaffected, the late AHP (arrows) is markedly reduced. Spikes are only visible in the low gain records (lower traces). Histamine had the same effect on this cell at 1 μM.

afterhyperpolarization was observed (Fig. 2). Although CA1 pyramidal cells normally showed some variation in their AHPs and accommodation of firing, these phenomena were always present. However, in 6 cells recorded with cyclic AMP-containing pipettes, accommodation and late AHPs were blocked within a few minutes after impalement. Such an action could be explained by a reduction of the calcium inflow itself and thus a secondary reduction of gK(Ca). However, in the presence of TTX and with intracellular Cs loading through the CsCl-filled microelectrodes, when overshooting calcium spikes can be observed, these were not reduced by histamine and 8-bromo-cyclic AMP. Rather, they were increased in amplitude, width and number.

Although a potentiation and prolongation of the intracellularly recorded histamine effect by Ro 20-1724 (100 μM) was noted in one of 3 experiments, another paradigm was used to quantify the phosphodiesterase inhibitor effect. The population spike in CA 1 after stimulation of the stratum radiatum is regularly enhanced by histamine [4, 9]. A concentration of 5 μM caused an increase of 35.6 $\pm$ 10.5 (SD)% ($n = 7$) in normal conditions but an increase of 87.4 $\pm$ 48.6 (SD)% ($n = 7$) in the presence of 100 μM Ro 20-1724. The Wilcoxon-signed ranks test showed a significance of this difference on the $P < 0.05$ level. The histamine effect outlasted the perfusion considerably longer in the presence of Ro 20-1724 than without (*ca.* 30 min v. *ca.* 10 min in completely submerged slices).

Discussion

Histamine and noradrenaline stimulate cyclic AMP accumulation in hippocampal slices of the rat and block long-lasting AHPs and accommodation of firing. Both effects of the amines are mediated by H2- and beta-receptors respectively. The other amines present in hippocampal afferent fibers which have contrary actions to histamine and noradrenaline [3] are also ineffective in stimulating cyclic AMP accumulation. Intracellularly-administered cyclic AMP or extracellularly-applied 8-bromo-cyclic AMP mimicked the action of histamine and, furthermore, a phosphodiesterase inhibitor, Ro 20-1724, potentiated and prolonged the histamine (H2) effect on population spikes. These results are consistent with the possibility that the excitation potentiating effect of histamine in the hippocampus is mediated by cyclic AMP. The described effects are due to the reduction of a calcium-dependent potassium conductance. This gK(Ca) can be regulated by a change in the intracellular calcium level and in particular by changes in the dynamics of calcium sequestration, which may in turn (through phosphorylation of calcium-binding proteins?) be under the control of cyclic AMP.

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