Neuroscience Letters, 22 (1981) 75–78

HISTAMINE HYPERPOLARIZES HIPPOCAMPAL NEURONES IN VITRO

H.L. HAAS

Neurophysiology Laboratory, Neurochirurgische Universitätsklinik Zürich, CH-8091 Zürich (Switzerland)

(Received November 6th, 1980; Revised version received November 20th, 1980; Accepted November 20th, 1980)

The postsynaptic effect of histamine and impromidine, an H_2-receptor agonist on CA1 pyramidal and dentate granule cells in the hippocampal slice of the rat is a hyperpolarization. Depolarizations are indirectly mediated. It is suggested that the hyperpolarization is generated by a conductance increase to potassium ions in the dendrites.

Convincing evidence for a role of histamine (HA) in synaptic transmission has been provided in the central nervous system of *Aplysia* [3, 9]. In the mammalian brain much circumstantial and suggestive evidence for such a function comes from biochemical and pharmacological experiments [7]. The hippocampus receives histamine-synthesizing fibres through both major inputs, the fornix and the perforant path [2]. The majority of central neurones are depressed by iontophoretically applied HA, an effect which is mediated by H_2-receptors; in the hypothalamus, however, excitant effects are frequently observed [6].

I have now investigated the effects of HA on membrane properties of principal neurones (CA1 pyramidal and dentate granule cells) in the hippocampal slice of the rat because this preparation offered unique advantages for such a study on identified neurones, which are good candidates for being innervated by histaminergic fibres. Intracellular recordings were obtained from 78 CA1 pyramidal and 54 dentate granule cells in slices obtained from 42 rats and kept in a perfusion chamber [5] and similar results were found on both cell types. Conventional methods were used for recording and current injection. Microelectrodes were filled with potassium acetate (2 M) or potassium chloride (3 M). Monopolar stimulation of stratum radiatum, the alveus, or the perforant path fibres was through a micropipette (0.2 msec, 30–150 μA).

HA and impromidine, an H_2-receptor agonist [4], were applied locally by pressure ejection into the slice (10^{-4} M) or as microdrops on the surface (10^{-4} M, approx. 1–10 nl) or by iontophoresis (0.2 M) from micropipettes separate from the recording electrode.

Microdrops often produced a depolarization, but also mechanical artifacts and apparent changes in electrode resistance and capacity. These depolarizations were blocked or replaced by hyperpolarizations when the cells were synaptically isolated by reducing calcium (Ca) ions (0.2 mM) and (or) adding magnesium (Mg) ions (4 or 8 mM) to the perfusion fluid (6 of 8 cells). Iontophoresis and pressure ejection or local diffusion from a pipette orifice, however, usually produced a hyperpolarization of up to 9 mV, which was sometimes (in 25% of the affected cells) accompanied by a conductance increase of up to 30%. Table I gives detailed information and a typical example is illustrated in Fig. 1. These hyperpolarizations were not blocked in Ca-deficient and Mg-enriched medium but were usually enhanced under such conditions. Hyperpolarizations were also observed in highly polarized cells and exceeded the equilibrium potential for the recurrent IPSPs evoked by synaptic or antidromic activation, which was usually found between -70 and -75 mV. This IPSP is believed to be largely mediated by a chloride conductance [1]. Furthermore, hyperpolarizations were also produced by HA and impromidine when the IPSP had been inverted to a depolarizing potential by intracellular injection of chloride ions. During hyperpolarizations the cell excitability to injected depolarizing pulses and spontaneous activity, if present, were always reduced. Depolarizations were usually accompanied by an increased excitability, but in two cases by a reduced excitability and firing frequency. With drop application, and sometimes also with pressure ejection and iontophoresis, EPSPs evoked by Schaeffer collateral stimulation were reduced for up to 30 min.

These results suggest that HA hyperpolarizes CA1 pyramidal and dentate granule cells by an action on the postsynaptic membrane, and that this is possibly due to a potassium conductance increase in the dendrites. Chloride ion movements are unlikely to play a significant role. The depolarizations were probably indirect actions as they were absent in Ca-deficient, Mg-enriched medium. Such indirect

TABLE I

EFFECTS OF HISTAMINE AND IMPROMIDINE ON THE MEMBRANE POTENTIAL OF HIPPOCAMPAL NEURONES

The numbers of CA1 pyramidal and dentate granule cells are given.

	Hyperpolarization		Depolarization		No effect	
	Pyr.	Gran.	Pyr.	Gran.	Pyr.	Gran.
Histamine						
Iontophoresis or pressure	28	19	2	1	18	12
Microdrop	4	4	9	6	2	3
Impromidine						
Iontophoresis or pressure	5	6	2	1	6	4

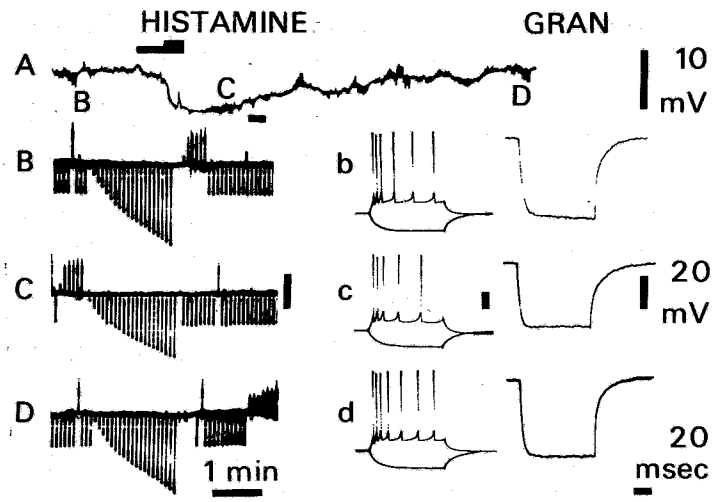

Fig. 1. Intracellular recording from a dentate granule cell. A: membrane potential (68 mV) replayed from magnetic tape with increased speed so that fast voltage deflections are not visible. Histamine was applied by pressure ejection from a micropipette in the dendritic region about 250 μm from the soma layer. The black bar above the trace indicates 20 and 50 mm Hg ejection pressure. B, C and D: expanded traces taken before, during and after histamine action as indicated in A. Voltage deflections are produced by constant current injection of $\pm$ 0.5 nA or -0.1 to -2.0 nA and $+0.1$ to $+0.5$ nA. b, c and d: such deflections at an even more expanded time base ($\pm$ 0.5 nA and -2.0 nA).

effects, which have recently been described [8], must in fact be expected with a drop application spreading on the whole slice surface and, to a lesser extent, with the more locally restricted methods of administration too. They could be occurring through other cells or through synaptic endings and varicosities. The observation that hyperpolarizations were actually enhanced in synaptic isolation suggests that a population of surrounding principal cells which are hyperpolarized will tend to depolarize their neighbours by way of reduced recurrent inhibition and thus mask the hyperpolarization. The occurrence of depolarizations with reduced firing is consistent with the idea of a dendritic inhibition and a somatic disinhibition. An action of HA on the dendrites would also explain the relatively small or absent change in conductance measured at the soma membrane. The observation that many cells were unaffected by local administration of HA and impromidine might be explained by a relative sparsity or local restriction of HA receptors on the dendritic tree.

This work was supported by the Swiss National Science Foundation (3396-78). Impromidine was a gift from Dr. C.R. Ganellin, SKF.

1 Allen, G.I., Eccles, J.C., Nicoll, R.A., Oshima, T. and Rubia, F.J., The ionic mechanisms concerned in generating the i.p.s.ps of hippocampal pyramidal cells, Proc. roy. Soc. B, 198 (1977) 363–384.

2 Barbin, G., Garbarg, M., Schwartz, J.C. and Storm-Mathisen, J., Histamine synthesizing afferents to the hippocampal region, J. Neurochem., 26 (1976) 259–263.

3 Carpenter, D.O. and Gaubatz, G.L., H_1 and H_2 histamine receptors on *Aplysia* neurones, Nature (Lond.), 254 (1975) 343–344.

4 Durant, G.J., Duncan, W.A.M., Ganellin, C.R., Parsons, M.E., Blakemore, R.C. and Rasmussen, A.C., Impromidine is a very potent and specific agonist for histamine H_2 receptors, Nature (Lond.), 276 (1978) 403–405.

5 Haas, H.L., Schaerer, B. and Vosmansky, M., A simple perfusion chamber for the study of nervous tissue slices in vitro, J. neurosci. Meth., 1 (1979) 323–325.

6 Haas, H.L. and Wolf, P., Central actions of histamine: microelectrophoretic studies, Brain Res., 122 (1977) 269–279.

7 Schwartz, J.C., Histaminergic mechanisms in brain, Ann. Rev. Pharmacol. (Kbh.), 17 (1977) 325–339.

8 Segal, M., Histamine produces a Ca^{2+}-sensitive depolarization of hippocampal pyramidal cells in vitro, Neurosci. Lett., 19 (1980) 67–71.

9 Weinreich, D., Synaptic responses mediated by identified histamine-containing neurones, Nature (Lond.), 267 (1977) 854–856.