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Histamine: action on single hypothalamic neurones

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For a long time histamine has been considered to be a transmitter candidate in the central nervous system[7]. Recent detailed studies on regional and subcellular localization, turnover and release have boosted the evidence for such a role of histamine in the mammalian brain. In all species investigated by far the highest levels are found in the hypothalamus and it is evident that a major portion of brain histamine is localized in nerve terminals. Moreover a very rapid rate of turnover accelerated by stress and the release of endogenous histamine by potassium induced depolarization from slices of rat hypothalamus have been demonstrated[17].

In a number of studies histamine or metabolites have been applied microelectrophoretically on single neurones in various parts of the central nervous system in anaesthetized[3,4,6,9,14–16] or decerebrate unanaesthetized[2,8,14] animals. No action or weak depression was found in the spinal cord[4,14], cuneate nucleus[6], medullary reticular formation[2,8], lateral geniculate body[3] of the cat nor in the cerebellum of the rat[16]. In the cortex, however, depression by small amounts and both excitation and depression by larger amounts of histamine were described by Phillis *et al.*[15]. None of the microelectrophoretic studies in the hypothalamus have hitherto included histamine[1,5,10–12].

In the present preliminary investigation histamine was applied to unidentified neurones in the hypothalami of 9 rats anaesthetized with i.p. sodium pentobarbitone (40 mg/kg) or a mixture of urethane and sodium pentobarbitone (400 and 50 mg/kg respectively). These initial doses were supplemented by sodium pentobarbitone i.p. as required. Three- or 5-barrel micropipettes and conventional microelectrophoretic techniques were used. In 7 experiments the hypothalamus was approached stereotactically from the dorsal surface of the brain using a David Kopf device and the atlas of Pellegrino and Cushman[13]. After successful recordings the microelectrodes were advanced until the tip reached the ventral surface of the brain. The distance of recording sites from both the dorsal and the ventral surface was measured. Subsequently the electrode was broken and the tip left in the tissue in order to allow recovery of the electrode tracks after fixation. In addition in one experiment the location of dye

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marks ejected from the micropipette (pontamine sky blue 6BX, G.T. Gurr Ltd., London, 2% in 0.5 *M* sodium acetate) confirmed the recording sites in the hypothalamus. In two rats a transpharyngeal approach was used[5].

The action of histamine was examined on cells firing spontaneously (51 cells) or fired by microelectrophoretically applied glutamate (4 cells). The effect of at least one of the following substances was always also assessed on these cells: monosodium-L-glutamate (Koch–Light, 0.5 *M*, pH 8), acetylcholine bromide (BDH, 0.5 *M*) and imidazoleacetic acid hydrochloride (Calbiochem, 0.5 *M*, pH 3–4). Histamine dihydrochloride (Calbiochem, 0.5 *M*, pH 3–4) ejected with currents of 10–100 nA excited the majority of cells (46 of 55), a few cells being depressed (4) or unaffected (5). Almost every cell was excited by glutamate whereas acetylcholine excited more than half of the neurones tested (18 of 30) the remainder being depressed (4) or unaffected (8). Imidazoleacetic acid had a depressant effect on 3 and no effect on 2 cells. Cells were considered to be 'unaffected' if their firing rate was not altered by a substance ejected from the micropipette by at least 100 nA. As judged from the ejecting currents used, the time course and strength of the excitatory action of histamine was comparable to that of ACh being usually slower in onset and weaker than glutamate. On 5 cells, however, histamine was found to be more potent than ACh and/or glutamate.

Fig. 1 shows typical examples of the actions of histamine, acetylcholine and glutamate on 3 hypothalamic neurones. In A the action of histamine was slower and weaker than that of ACh whereas cell B was very sensitive to histamine but insensitive to ACh. The response to histamine shown in B consisted of 3 large bursts of spikes. Generally, cells that responded with a high frequency of firing to relatively small amounts of histamine tended to do so by firing in bursts. There was no obvious correlation between the sensitivities of cells to histamine and ACh. Atropine (10 m*M*

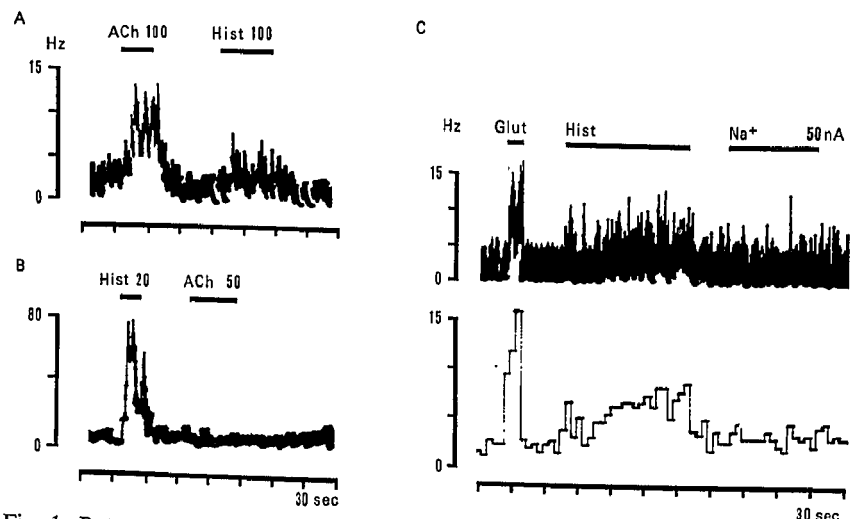

Fig. 1. Ratemeter recordings showing the effects of histamine (Hist), acetylcholine (ACh) and glutamate (Glut) on 3 spontaneously firing hypothalamic neurones. Lower trace in C shows a digital counter output. Microelectrophoretic administration of substances is indicated by bars above tracings. Ejecting currents are given in nA (10^{-9}A). In C all substances were ejected by 50 nA. Ordinates, firing frequency; abscissae, time.

in 165 m*M* NaCl), microelectrophoretically applied by currents of less than 10 nA antagonized reversibly the action of ACh but not that of histamine on 2 cells. On 4 more cells tested however, a selective action of atropine could not be demonstrated. Mepyramine maleate (May and Baker, 0.1 *M*, pH 3–4) applied by currents up to 30 nA antagonized the action of histamine and ACh as well as the spontaneous firing on 3 cells, indicating a non-specific type of action. This effect was also observed by Phillis *et al.*[15] on cortical neurones. With the same electrodes used for recording in the hypothalamus, 29 cells in the overlying structures were tested for their sensitivity to histamine. On 14 of these cells histamine had a weak depressant action, 5 cells were unaffected and 10 cells were excited. Eight of the 10 excited cells were found in the cortex cerebri and in the ventral parts of the thalamus. In one experiment some comparatively strong excitatory actions of histamine were observed on cells within the central grey of the midbrain.

Thus in contrast to other brain areas investigated the majority of neurones in the hypothalamus of the rat is excited by locally applied histamine. This result is of particular interest in the context of the biochemical findings suggesting the presence of histaminergic nerve terminals in this structure[17]. Further detailed investigation including the study of identified neurones is likely to reveal more about the physiological function of histamine in the mammalian hypothalamus.

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