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Histamine and Noradrenaline are Blocked by Amitriptyline on Cortical Neurones

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Introduction

Inhibition of histamine (HA) sensitive adenylate cyclase has recently been suggested to be a common biochemical action for a number of structurally diverse antidepressant drugs [1, 2]. The activation of this adenylate cyclase by HA was blocked by metiamide, a histamine H_2-receptor antagonist, but not by α-adrenergic, β-adrenergic or muscarinic cholinergic antagonists.

Evidence is increasing that HA is released as a neurotransmitter from the endings of an ascending pathway in the hypothalamus and the whole telencephalon [3, 4]. Single cells in most regions of the mammalian brain are depressed by microiontophoretic application of HA. This effect is antagonized by metiamide and therefore involves H_2-receptors [4]. If this electrophysiological action depends on activation of adenylate cyclase, antidepressant drugs should be expected to block it. Amitriptyline was chosen to test such a possibility for it is among the most potent inhibitors of HA-sensitive adenylate cyclase and it presents no problems in the iontophoretic application to the immediate environment of single neurones.

Materials and methods

Recordings were obtained from 31 neurones of the sensorimotor cortex (depth 800–1200 μm) of 6 rats (250–300 g) anaesthetized with urethane (i.p. 1.2 mg/kg). Conventional techniques were used for recording and iontophoretic application of histamine dihydrochloride (HA, 0.5 *M*, pH 3.5), noradrenaline hydrochloride (NA, 0.5 *M*, pH 4), amitriptyline hydrochloride (AMI, 0.2 *M*, pH 4.6).

Results

When histamine (HA) was applied alone it had only depressant actions (17 cells) or was ineffective (100 nA, 3 cells). Noradrenaline depressed the firing of 19 cells, excited 1 cell and was ineffective on 3 cells. Leakage from the micropipette or ejecting currents below 5 nA were used to test for antagonism to the amines. Such amounts of AMI did not usually affect the size of the action potentials but led to a very slow depression, taking about 5 min for a 50% reduction in firing rate. AMI blocked the action of NA on 12 out of 15 cells tested, on the other 3 cells a block was not obtained with such low ejecting currents of AMI. The one excitation was not modified by AMI. The depression evoked by iontophoretic HA was blocked on 10 out of 12 cells tested. On 4 further cells excitant actions of HA (4 cells) and NA (1 cell) became apparent under the influence of AMI. A significant potentiation of the effects of the amines was never seen. In two animals an intraperitoneal injection of AMI blocked the NA-evoked depression and reduced or blocked the action of HA (Fig. 1).

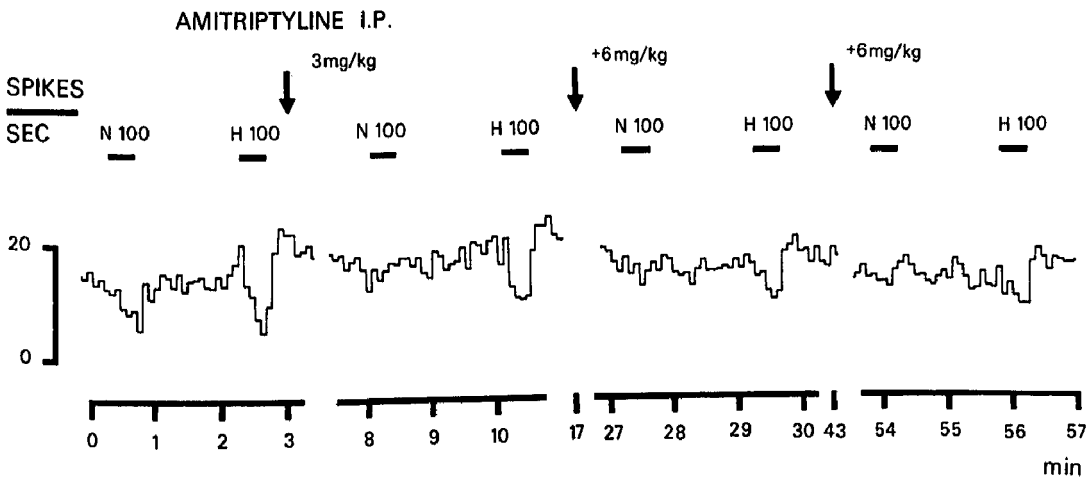

Figure 1
Ratemeter recording showing the blocking action of intraperitoneal amitriptyline (injection at arrows) on depressant effects of iontophoretically applied histamine (H, 100 nA) and noradrenaline (N, 100 nA) on a pyramidal tract neurone from the rat cortex.

Discussion

These findings are in keeping with the actions of amitriptyline on the HA- [1, 2] and the NA- [5] sensitive adenylate cyclase: the depression of cell firing by HA and NA is blocked by the antidepressant drug. The antagonism against HA bears similarities to the action of metiamide, an H_2-receptor blocker. Metiamide, like AMI, sometimes revealed excitant actions of HA [4], an effect which was never observed with H_1-receptor blockers. Further experiments are in progress to investigate the impact of these findings on the mechanism of action of tricyclic antidepressants.

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Central Hypotensive Effects of Imidazole Acetic Acid and Rolipram (ZK 62 711) in Rats

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Abstract

In urethane-anaesthetized rats the administration of imidazole acetic acid (IAA), 34–272 μg per rat intracerebroventricularly (i.c.v.), induced a dose-related fall in blood pressure. Rolipram (ZK 62 711), a potent and selective inhibitor of cyclic AMP phosphodiesterase (cAMP-PDE), also lowered the blood pressure in a dose-dependent manner when administered at the doses of 1–64 μg per rat i.c.v. A subhypotensive dose of rolipram (0.25 μg per rat i.c.v.) did not change the hypotensive effect of IAA. Pretreatment of the rats with metiamide, 1.1 mg per rat i.c.v., shifted the dose-response curve for IAA significantly to the right. The present results make it unlikely that the central hypotensive effect of IAA could be due to the stimulation of cAMP-PDE by this agent. Central histamine H_2-receptors may be involved in the hypotensive effect of IAA.

Introduction

Imidazole acetic acid (IAA) is formed from histidine in the rat brain [1], either as a metabolite of histamine or as a transamination product of histidine [2]. Intracerebroventricular administration of IAA lowers the blood pressure in cats [3]. It has been suggested that the central hypotensive effect of IAA might be due to a fall in the cerebral level of cyclic AMP since IAA is known to stimulate cyclic AMP phosphodiesterase (cAMP-PDE) [3]. The aim of the present work was to study the effect of IAA on blood pressure in rats. An attempt was made to elucidate the mechanism of action of IAA.

Materials and methods

Male Sprague-Dawley rats (250–300 g) were anaesthetized with urethane (1.5 g/kg i.p.). The rectal temperature was kept at 37 ± 0.5°C with the help of a heating lamp. The trachea was cannulated with a polyethylene tube and the rats were allowed to breathe spontaneously. The mean blood pressure was measured directly from the left femoral artery by means of a pressure transducer (Harvard apparatus 377). The rats were placed in a stereotaxic instrument and an injection needle introduced into the lateral cerebral ventricle. A polyethylene catheter, filled with the solution to be infused, was attached to the needle. The solution was allowed to flow slowly by means of hydrostatic pressure. Each drug dose was infused in a volume of 20 μl during 1–2 min. The maximal hypotensive effect of each IAA dose was seen within 10–20 min. Therefore, in order to obtain a cumulative dose-response curve, IAA was administered at 20-min intervals. For the same reason the interval between rolipram administrations was 20 min. The control animals received the same volumes of appropriate solvents. At the end of each experiment, methylene blue was injected and the position of the needle in the cerebral ventricle was ascertained.

IAA (Sigma Chemical Co., St. Louis) was dissolved in 0.9% (w/v) NaCl (saline). Metiamide (kindly donated by Smith, Kline and French Laboratories Ltd., Hertfordshire) was dissolved in 0.1 *N* HCl, and the pH was adjusted to 6 with 0.1 *N* NaOH. Rolipram (kindly supplied by Schering AG, Berlin) was dissolved in 96% ethyl alcohol and diluted with saline.

Student's *t*-test was used in the statistical analysis of the results.

Results and discussion

The administration of IAA intracerebroventricularly (i.c.v.) at the doses of 34–272 μg per rat induced a dose-related fall in blood pressure (Fig. 1). If this effect would be due to the stimulation of cAMP-PDE [3] it should be antagonized by inhibitors of cAMP-PDE. Rolipram (ZK 62 711) is a potent and selective inhibitor of cAMP-PDE, and it increases the intracellular level of cyclic AMP but not that of cyclic GMP in the brain [4]. Pretreatment of the rats with rolipram at the dose of 0.25 μg per rat i.c.v., which itself did