COMPARATIVE SENSITIVITY OF HIPPOCAMPAL NEURONS IN SURVIVING SECTIONS TO CORTICOSTEROIDS AND ANGIOTENSIN II

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The attention of neurophysiologists and neuropharmacologists studying neurochemical mechanisms of single unit activity in the CNS has recently been drawn increasingly not only to the classical neurotransmitters, but also to oligopeptides and hormones such as substance P, angiotensin II, somatostatin, ACTH, hydrocortisone, dexamethasone, etc. Interest in these substances increased after it had been shown that oligopeptides and hormones can exert a definite influence on single neurons in different regions of the mammalian and invertebrate CNS [1, 3, 6, 7, 9, 11]. However, many problems connected with the mechanism of action of these biologically active compounds on cells of the brain and spinal cord still remain unexplained and disputed. One of the main factors making the results obtained difficult to interpret is that all previous investigations were conducted on the whole brain, and under those conditions it is impossible to differentiate between the direct action of peptides and hormones on nerve cells and effects due to the action of these substances on the microcapillaries and neighboring structures of the brain.

It was accordingly decided to study the effect of angiotensin II and corticosteroids on hippocampal neurons in surviving sections. A most important advantage of this model is that it eliminates the effect of test substances on microvessels and on other brain regions. This model also enables the recording microelectrode to be introduced into particular zones of a test structure under visual control with great accuracy.

EXPERIMENTAL METHOD

CBA mice were decapitated and a transverse section through the hippocampus, 200-400 μ thick, was cut after craniotomy [4]. The section was placed in a special continuous-flow chamber equipped with a heater. The temperature of the perfusion fluid, which was either Earle's or Sims' solution, was maintained at 36-37°C. The temperature of the fluid was monitored by a TPÉM-1 electrothermometer.

Unit activity was recorded intracellularly by glass microelectrodes filled with 2.5 M potassium citrate.

From a special micropipette $2 \cdot 10^{-2}$ or $2 \cdot 10^{-3}$ M angiotensin II, 0.5M hydrocortisone hemisuccinate, and a 0.1 M solution of the sodium salt of dexamethasone-21-phosphate was injected into the perfusion fluid.

EXPERIMENTAL RESULTS

In the course of the experiments activity of 27 hippocampal neurons in area CA_3 was recorded.

The results showed that, by contrast with neurons of the subfornical organ, anterior and lateral hypothalamus, visual and somatosensory cortex, and supraoptic neurosecretory cells which, as several workers have found [5, 8, 9, 12-15], changed the character of their spontaneous activity clearly in response to angiotensin II, none of the 23 hippocampal neurons

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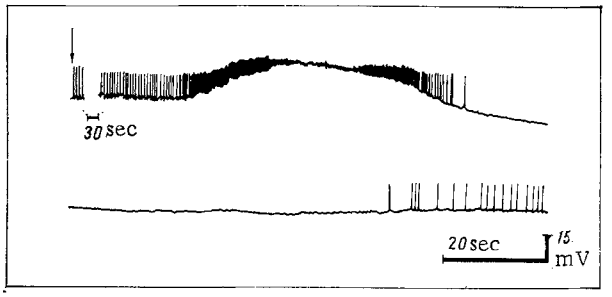

Fig. 1. Response of hippocampal neuron in surviving section (area CA_3) to injection of hydrocortisone hemisuccinate solution into perfusion chamber. Beginning of injection of drug indicated by arrow. Duration of injection 30 sec.

recorded in the present experiments responded to this peptide, despite the fact that sufficiently concentrated solutions ($2 \cdot 10^{-2}$ and $2 \cdot 10^{-3}$ M) were used.

The action of hydrocortisone was studied on 22 hippocampal neurons. These experiments showed that the overwhelming majority (18 of 22) of the recorded cells responded clearly and uniquely to injection of this corticosteroid into the flow of perfusion fluid. The unique character of the action of hydrocortosone on hippocampal cells was expressed primarily by the fact that in most cells, after a relatively short (2-5 sec) latent period, a marked increase in the frequency of the spike discharges was observed to develop against the background of distinct depolarization. Characteristically, if the dose of hydrocortisone injected was increased, a depolarization block develops, varying in duration from 15 sec to several minutes, after which the initial level of spike discharge frequency was restored. In one case, immediately after the depolarization block, prolonged (up to 1 min) after-hyperpolarization developed (Fig. 1). In two hippocampal neurons a definite decrease in the following frequency of spike discharges was observed against the background of marked hyperpolarization in response to injection of hydrocortisone.

Injection of dexamethasone into the fluid bathing the section induced a considerable increase in spike discharge frequency in all 10 hippocampal neurons studied, followed by the development of a prolonged (over 5 min) depolarization block; in four cases the original rhythm of the cell discharges was not restored. An increase in the spike discharge frequency in response to injection of dexamethasone began after a shorter latent period (1-2 sec) than after injection of hydrocortisone.

The results show that hippocampal cells are highly sensitive to steroid hormones. These results agree with data in the literature indicating selective [7, 11, 14] accumulation of corticosteroids in the hippocampus when injected intraperitoneally. On the basis of these facts it has been suggested that the hippocampus is one of the main targets for these biologically active preparations. The results of the present experiments also confirm the view, expressed by many workers [2, 9, 10, 14], that steroid hormones can play the role either of neuromodulators or of neuromediators in hippocampel neurons and, consequently, that specific receptors for these biologically active compounds may exist on postsynaptic membranes in the hippocampus.

The present experiments thus showed that, first, hippocampal neurons are highly sensitive to corticosteroid hormones and, second, that surviving brain sections are a convenient and promising model for the study of neurochemical mechanisms of action of various biologically active and pharmacological preparations.

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NEUROPHYSIOLOGICAL AND PHARMACOLOGICAL EVIDENCE OF SELF-REGULATION IN THE NIGROSTRIATAL SYSTEM

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Electrical stimulation of the substantia nigra in cats evokes stereotyped behavior which, as analysis has shown, is linked with potentiation of nigrostriatal dopaminergic transmission. In the course of a study of nigral stereotypy it was found that this condition can decline progressively during repeated electrical stimulation of the nucleus. This phenomenon is of fundamental importance and requires more detailed study, for it probably lies at the basis of processes determining the cardinal features of activity of the nigrostriatal system as a whole. The facts described below are evidence that the cause of the rapid decline in nigral stereotypy could be activation of presynaptic dopamine autoreceptors on nigral axons.

EXPERIMENTAL METHOD

Experiments were carried out on 14 cats of both sexes weighing 2-3.5 kg. Under pentobarbital anesthesia bipolar nichrome electrodes (diameter 0.2 mm) were inserted into the substantia nigra on both sides, and also into adjacent structures of the midbrain. The source of current was a square pulse generator. The experiments were begun 4-7 days after the operation. The cats were kept in a chamber measuring 60 × 60 × 60 cm. The animals' behavior was evaluated before, during, and after stimulation of the brain by visual, photographic, and cyclographic methods [3]. The EEG in the sensomotor cortex was recorded in two cats by the usual method. The substances for testing were injected intraperitoneally in physiological saline. After the end of the experiments the brain was fixed and the position of the electrodes determined in frontal sections and compared with coordinates of the atlas [11].

EXPERIMENTAL RESULTS

Weak unilateral stimulation of the compact part of the substantia nigra triggered a set of motor automatism in the cats, in the form of rhythmic rotations of the head from side to side and up and down, with intervals of sniffing and periodic motionlessness. During sufficiently prolonged (1-1.5 min) or stronger (by 0.5-1 V) stimulation of the nucleus this state persisted for several minutes even after the current had been switched off. This type of nigral after-stereotypy was a sufficiently specific response, for it did not arise from the extranigral formations of the midbrain or even from the reticular zone of the substantia nigra, as was shown previously it was dopaminergic in nature and, therefore, it was used as the main test object in the present investigation. A considerable external similarity between this behavioral change and amphetamine-induced stereotypy must also be emphasized.

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