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MECHANISM OF FORMATION OF THE INTEGRAL HYPOTHALAMIC RESPONSE DURING PSYCHOEMOTIONAL OVERSTRAIN

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KEY WORDS: psychoemotional overstrain; hypothalamus; integral response

Psychoemotional overstrain is an important factor in the development of many pathological processes. Investigations have shown that the mechanism of realization of psychoemotional overstrain (PEO) is triggered in the hypothalamus by nervous impulses arriving from the cerebral cortex, reticular formation, and limbic system [1-3], which may have either an excitatory or an inhibitory action. However, there is as yet no single concept which can explain the general response of the hypothalamic region to various kinds of PEO (the stress reaction). It was accordingly decided to analyze changes in hypothalamic structure and function in rats exposed to various kinds of PEO, differing in intensity and duration.

EXPERIMENTAL METHOD

Experiments were carried out on 63 noninbred male albino rats initially weighing 180-220 g. The animals were divided into 4 groups. Group 1 (control) comprised 12 intact animals. The 18 rats of group 2 were repeatedly immobilized for 3-4 h at a time. Emotional stress was induced in the 10 rats of group 3 by subjecting them to hypokinesia by artificially restricting their movements by keeping them in especially made cages. The rats of groups 1-3 were killed under superficial ether anesthesia on the 1st, 7th, 20th, 30th, 45th, and 60th days of the experiment. The rats (15) of group 4 were intermittently starved. The animals were isolated in separate cages and given nothing but water for 5-7 days, after which they were put back on a normal diet. These animals were thus subjected to starvation 1, 2, 3, 4, and 5 times and killed after 7, 20, 30, 45, and 60 days of the experiment. The rat's brain was fixed in Bouin's fluid, and after hardening the hypothalamic region was embedded in paraffin wax. From a single block of hypothalamus 600-800 serial frontal sections were cut and stained by Missl's method. Some of the material was fixed in a 4% solution of paraform ("Fluka," Switzerland), made up in 0.1 M cacodylate buffer, followed by postfixation in buffered 1% osmium tetroxide solution and embedded in resins. Ultrathin sections were studied in EVM-100LM and PEM-100 electron microscopes. Negatives were standardized under magnification of 6000 and 15,000 times. A wide range of morphometric methods of investigation was used: the volume of the nuclei of the neurons, the internuclear distance, bulk density and specific surface area of the neurons, and their number per unit volume were determined. The degree of damage to the neurons was studied by counting the unchanged nerve cells, those with slight and severe changes, and those absent altogether. Some of the material was studied on a "Microvideomat-2" microscope ("Opton," Germany) with a microcomputer (USA), using the "Stereo-1" program. The numerical results were analyzed by computer. The hypothalamic region of the rats was investigated in accordance with the classification suggested by Szentagothai and co-workers [2]: the suprachiasmatic nucleus (SCH), supraoptic nucleus (SO), paraventricular nucleus, parvocellular part and magnocellular part (PV, not distinguished in Figs. 2 and 3), ventromedial nucleus (VM), dorsomedial

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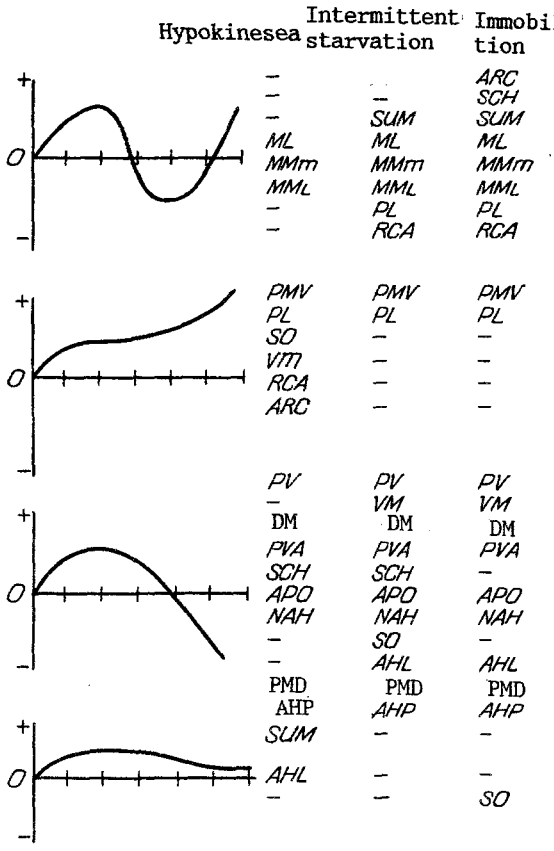

Fig. 1. Dynamics of functional activity of hypothalamic neurons of rats with various types of PEO. Initial level (O); increased (+) and decreased (–) functional activity.

nucleus (DM), arcuate nucleus (ARC), dorsal premammillary nucleus (PMD), ventral premammillary nucleus (PMV), lateral mammillary nucleus (ML), medial part of medial mammillary nucleus (MMm), lateral part of medial mammillary nucleus (MML), prelateral mammillary nucleus (PL), posterior hypothalamic region (AHP), anterior hypothalamic field (NAH), retrochiasmal area (RCA), supramammillary nucleus (SUM), lateral hypothalamic area (AHL), periventricular area (PVA).

EXPERIMENTAL RESULTS

During immobilization hypokinesia at the beginning of the experiment (days 1-7) the study of the animals revealed reduction of the elementary granules of secretion, hypertrophy of the mitochondria, and devastation of the synapses in most neurons of the paraventricular nucleus and in some neuronal assemblies of the supraoptic and dorsomedial nuclei. Changes in the morphometric parameters of the neurons compared with the control group were not significant. Very slight hypertrophy of neurons and hypertrophy and hyperplasia of ultrastructures were observed in the "receptor" and "trophic" zones of the hypothalamus. A sharp increase in functional activity took place in neurons of the premammillary and mammillary nuclei, as shown by a marked increase in volume of the nuclei of the nerve cells, an increase In their specific surface area and bulk density, a decrease in the internuclear distances, and hyperplasia of ultrastructures. On the 20th-30th days of immobilization hypokinesia signs of dystrophy were observed, namely, swelling of dendrites and axons, lysis and fragmentation of mitochondria, acute swelling of neurons and vacuolation of their cytoplasm, ectopia of the nucleus and nucleolus in the neurosecretory cells of the paraventricular nucleus (in both magnocellular and parvocellular parts), and in individual neuronal assemblies of the supraoptic and dorsomedial nuclei, the anterior hypothalamic field and the lateral area. Functional activity of the neurons was mainly increased in the "trophic" and "receptor" zones of the hypothalamus (ventromedial and arcuate nuclei, most neuronal assemblies of the anterior hypothalamic area) and also in the premammillary and

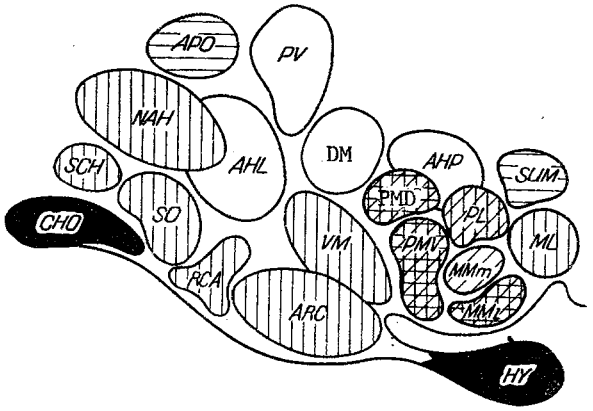

Fig. 2

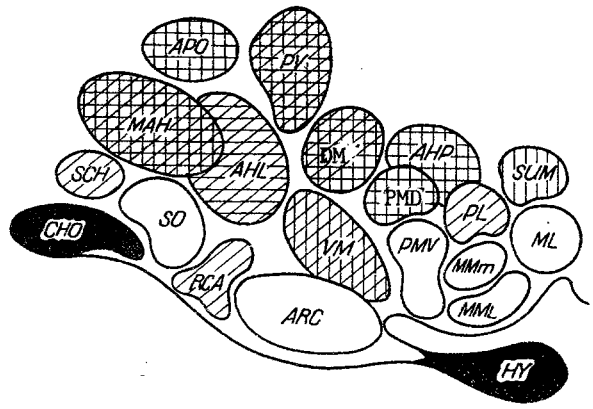

Fig. 3

Fig. 2. Location of zones with greatest functional activity of hypothalamic neurons in rats with various kinds of PEO. Zones with greatest functional activity of neurons are shaded. Here and in Fig. 3: horizontal shading – hypokinesia; vertical – intermittent starvation; oblique – immobilization.

Fig. 3. Location of zones with greatest severity of damage to hypothalamic neurons in rats with various kinds of PEO. Zones with severest damage to neurons are shaded.

mammillary nuclei. With continuing exposure to the stress factor (the 45th day of immobilization hypokinesia) signs of dystrophy were found mainly in the paraventricular nucleus (55% severity of the damage) and also in the dorsomedial (65%) and suprachiasmatic (45%) nuclei. Most neuronal assembles of the premammillary and mammillary nuclei, supraoptic nucleus, arcuate nucleus, and retrochiasmal area were characterized by increased functional activity, although a very few neurons had vacuolated cytoplasm and a deformed nucleus.

In the final stage of the experiment (60th day) damage to the neurons amounted to 100% in the paraventricular nucleus, 95% in the dorsomedial and 84% in the supramammillary nuclei, 95% in the anterior and posterior hypothalamic areas, and 50% in the suprachiasmatic nucleus. Very little damage to neurons (from 15 to 20%) was found in the arcuate, supraoptic, and mammillary nuclei; only in the ventral premammillary nucleus were solitary neurons found to be in a state of acute swelling.

The time course of structural and functional changes in neurons of the hypothalamic region of ratfi subjected to intermittent starvation was about the same as in rats with the first two types of stress, but the degree of damage to the neurons was less severe and dystrophic changes were found in the 30th-45th days.

A number of general conclusions can be drawn from the morphological data. First, neuronal functional activity in different hypothalamic nuclear formations is a multiphase, asynchronous process (Fig. 1). Second, zones with maximal functional activity (Fig. 2) and zones in which dystrophic changes become predominant in a situation of increasing PEO (Fig. 3) can be distinguished in the hypothalamus.

Morphometric analysis of functional activity of neurons together with the study of the rapidity of development of dystrophic changes as a function of the duration and severity of PEO suggest the sequential activation of different hormonal lines. It can be tentatively suggested that the mechanism of formation of the hypothalamic reaction under the strong influence of the stress factor differs from that which operates during exposure to a moderate or chronic influence.

The results also are evidence that the hypothalamus does not possess any marked adaptive mobility, for PEO induces dystrophic changes (or even necrotic) in neuronal assemblies of the paraventricular nucleus relatively quickly; this leads to a disturbance of rhythms of hypothalamic secretion, and subsequently to a disturbance of the coordinated functioning of hypothalamic structures and of the entire neuroendocrine system.

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EFFECT OF ESTROGENS ON NEURONAL DEVELOPMENT IN NUCLEI OF THE TRACTUS SOLITARIUS TRANSPLANTED INTO THE ANTERIOR CHAMBER OF THE EYE IN RATS

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KEY WORDS: estrogens; sexual differentiation; nucleus of tractus solitarius

Evidence has been obtained of sex differences in the morphology and fraction of brain regions involved in the regulation of sexual behavior and cyclic gonadotropin secretion [4]. The manifestation of these differences depends on the action of sex hormones on the developing brain in the early stages of individual development. Androgens, which undergo aromatization in the brain into estrogens, stimulate growth of neurons and their processes during this period in sex-dependent brain structures, and they also modulate synaptogenesis [1, 2 5, 7, 8].

Evidence has been obtained to show that one of the nonhypothalamic structures involved in the mechanisms regulating cyclic secretion of gonadotropic hormones is the nucleus of the tractus solitarius (NTS) in the medulla [3]. It can accordingly be postulated that the neurons of these nuclei also serve as the target for estrogens, which will exert a neurotropic action on their development. This hypothesis has been tested on a model of a nerve tissue graft cultured in an immunoprivileged region of the recipient animal, namely the anterior chamber of the eye.

EXPERIMENTAL METHOD

Experiments were carried out on 40 mature, preliminarily ovariectomized female Wistar rats. Animals of the experimental group 1 week before transplantation were anesthetized with ether and a silastic capsule ("Dow Corning Corp.," USA) 3 cm long, filled with crystalline estradiol-17β (USSR) was implanted subcutaneously. The authors are grateful to Dr. Y. Arai (Japan) for providing the silastic capsules and to Dr. Biol. Sci. K. K. Pivnitskii for providing the estradiol, synthesized by himself. A capsule not containing the hormone was implanted in animals of the control group. Tissue samples containing NTS were removed under control of a stereoscopic microscope from the corresponding region of section of the lower brain stem in 20-day embryos. By means of a glass needle the extirpated tissue was injected through an

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