# ROLE OF THE PITUITARY–ADRENAL SYSTEM IN THE MECHANISMS REGULATING VASCULAR PERMEABILITY DURING STRESS

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The state of permeability of the microvessels was determined by the "vascular labeling" method in hypophysectomized and adrenalectomized rats during stress induced by immobilization. Animals undergoing mock operations served as the control. Hypophysectomy or adrenalectomy was shown to disturb the permeability of the mesenteric vessels. The disturbances of vascular permeability in hypophysectomized and adrenalectomized rats during immobilization were more marked than in animals undergoing the mock operation. Hypophysectomy and adrenalectomy led to degranulation of the mast cells in the earlier stages of immobilization.

KEY WORDS: vascular permeability; mast cells; immobilization stress; hypophysectomy; adrenalectomy.

The writers showed previously that permeability of the microvessels is disturbed in stress due to immobilization and that histamine and serotonin of the mast cells and also the kinin system participate in the mechanisms of these disturbances [2, 3]. The object of the present investigation was to study the role of the pituitary–adrenal system in the mechanisms regulating vascular permeability in immobilization stress. Experimental and clinical investigations have shown that ACTH and corticosteroids reduce vascular permeability [1]. Adrenalectomy under experimental conditions increases vascular permeability [4]. The normalizing action of glucocorticoids on increased vascular permeability is associated with stabilization of the lysosomal membranes [7, 11].

Since the mast cells play an active part in the regulation of the microcirculation and of vascular permeability, it was decided also to study the morphological and functional state of these cells in hypophysectomized and adrenalectomized animals under conditions of stress. Several workers have shown that hypophysectomy or adrenalectomy does not affect the number or degree of degranulation of the mast cells [9]. However, adrenalectomy is known to prevent the increase in number and degranulation of the mast cells caused by ACTH [8, 10].

## EXPERIMENTAL METHOD

Experiments were carried out on 83 rats. Hypophysectomy was performed by the transauricular method [6] on Wistar rats. The completeness of hypophysectomy was verified by the absence of increase in weight of the animals after the operation, and also by investigations of the pituitary region of the rats at autopsy. Adrenalectomy was performed transdorsally. The rats were used in the experiments 14 days after hypophysectomy and 7 days after adrenalectomy. The hypophysectomized animals were given 5% glucose solution and the adrenalectomized animals 1% sodium chloride solution after the operation instead of water. Rats undergoing mock operations served as the control.

The animals were immobilized lying on their back. Disturbances of vascular permeability were determined in preparations of the mesentery by the "vascular labeling" method with subsequent quantitative assessment by the method suggested by the writers previously [2]. The state of the mast cells was judged in preparations of the mesentery stained with toluidine blue. The results were subjected to statistical analysis [5].

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TABLE 1. Effect of Hypophysectomy on Permeability of Microvessels and on Mast Cells of Immobilized Rats

| Number and description of series of experiments, number of animals | Number of mesenteric "windows," % of number examined | | | Number of rats with different degrees of labeling, % of total number of rats in experiment | | | | | Mean number of mast cells per field of vision (magnification 135×) | Percentage of degranulated mast cells |
|---|---|---|---|---|---|---|---|---|---|---|
| | unlabeled | 1-10 labeled vessels | more than 10 labeled vessels | 0 | I | II | III | IV | | |
| 1. Hypophysectomy (5) | 92 | 8 | 0 | 40 | 60 | 60 | 0 | 0 | 27,6±0,75 | 0,12±0,09 |
| 2. Mock hypophysectomy | No labeling | | | | | | | | 26,4±1,09 | 0,09±0,01 |
| 3. Hypophysectomy + immobilization for 1 h (5) | 64 | 34 | 2 | 20 | 80 | 80 | 80 | 0 | 24,7±1,07 | 0,27±0,07 |
| 4. Mock hypophysectomy + immobilization for 1 h (5) | 84 | 16 | 0 | 40 | 60 | 60 | 20 | 0 | 23,3±1,3 | 0,17±0,03 |
| 5. Hypophysectomy + immobilization for 3 h | 76 | 26 | 0 | 20 | 80 | 80 | 40 | 0 | 24,7±0,73 | 0,27±0,06 |
| 6. Mock hypophysectomy + immobilization for 3 h (5) | 88 | 12 | 0 | 60 | 40 | 40 | 20 | 0 | 23,6±1,16 | 0,17±0,01* |

*$P_{5-6}<0,001$.

TABLE 2. Effect of Adrenalectomy of Permeability of Microvessels and on Mast Cells of Immobilized Rats

| Number and description of series of experiments, number of animals | Number of mesenteric "windows," % of number examined | | | Percentage of degranulated mast cells | | | | | Mean number of mast cells per field of vision (magnification 135×) | Percentage of degranulated mast cells |
|---|---|---|---|---|---|---|---|---|---|---|
| | unlabeled | 1-10 labeled vessels | more than 10 labeled vessels | 0 | I | II | III | IV | | |
| 1. Adrenalectomy (6) | 93 | 7 | 0 | 50 | 50 | 17 | 0 | 0 | 27,3±1,2 | 0,13±0,02 |
| 2. Mock adrenalectomy (5) | No labeling | | | | | | | | 26,8±1,4 | 0,1±0,01 |
| 3. Adrenalectomy + immobilization for 1 h (12) | 53 | 37 | 10 | 0 | 100 | 100 | 66 | 0 | 28±1,0 | 0,25±0,09 |
| 4. Mock adrenalectomy + immobilization for 1 h (10) | 84 | 16 | 0 | 20 | 80 | 80 | 0 | 0 | 27,4±1,6 | 0,36±0,05 |
| 5. Adrenalectomy + immobilization for 3 h (11) | 56 | 28 | 16 | 0 | 100 | 100 | 54 | 0 | 24,6±0,08 | 0,3±0,05* |
| 6. Mock adrenalectomy + immobilization for 3 h (10) | 67 | 23 | 10 | 20 | 80 | 80 | 50 | 0 | 24,2±1,1 | 0,61±0,08† |

*$P_{1-5} < 0.01$.

†$P_{2-6} < 0.001$; $P_{4-6} < 0.02$; $P_{5-6} < 0.001$.

## EXPERIMENTAL RESULTS

After the operations of hypophysectomy or adrenalectomy the mesenteric microvessels became permeable to particles of colloidal carbon (Tables 1 and 2). After immobilization of the hypophysectomized rats for 1 or 3 h their vascular permeability was disturbed; the extent and intensity of the lesions were greater than in animals undergoing the mock operations (Fig. 1a, b; Table 1). Unlike in intact rats exposed to immobilization [3], the disturbances of vascular permeability in the hypophysectomized animals were more severe after immobilization for 1 h than for 3 h. The number of mast cells and the degree of their degranulation in hypophysectomized rats before and after immobilization were virtually indistinguishable from these indices in the control. Only in the hypophysectomized animals immobilized for 3 h was degranulation of the mast cells observed to a statistically

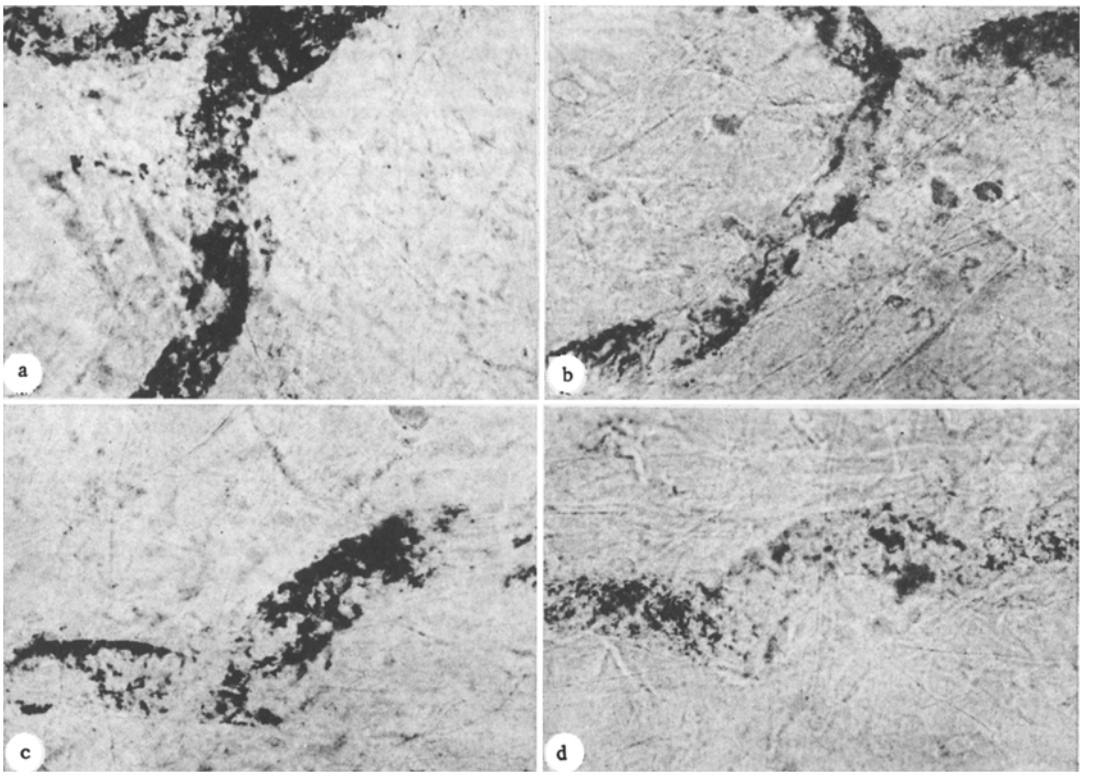


Fig. 1. Deposition of particles of colloidal carbon at sites of disturbed permeability of mesenteric venules (magnification 50 × 2.5): a) in hypophysectomized rat; b) in rat after mock hypophysectomy; c) in adrenalectomized rat; d) in rat after mock adrenalectomy and immobilization for 1 h.

significant degree compared with the degranulation of these cells in rats undergoing the mock operations (Table 1).

In the adrenalectomized animals immobilization caused more profound disturbances of vascular permeability than in rats undergoing mock adrenalectomy (Fig. 1c, d; Table 2) but did not affect the number of mast cells. However, immobilization for 3 h caused an increase of degranulation in the adrenalectomized animals compared with unimmobilized rats, and the operation of adrenalectomy, as the results of this series of experiments showed, reduced degranulation of the mast cells. These last results agree with data in the literature [8, 10].

Comparison of the state of permeability of the microvessels after immobilization of intact animals [3] and of the rats undergoing the mock operations showed that the depth and extent of the disturbances of permeability were greater in the latter.

It can thus be concluded from the results described above that pituitary and adrenal hormones participate in the regulation of vascular permeability. In intact animals these hormones prevent the development of disturbances of vascular permeability, and under conditions of stress may have a normalizing action. Hypophysectomy and adrenalectomy evidently promote degranulation of the mast cells at earlier stages of immobilization (3 h) than in immobilized intact animals, in which they appear after 6-9 h.

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# COMPARISON OF CONTRALATERAL AND IPSILATERAL ROTATORY RESPONSES TO ELECTRICAL STIMULATION OF THE CAUDATE NUCLEUS IN CATS

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High-frequency stimulation of the caudate nucleus evoked two types of rotatory movements of the head and trunk in freely moving cats: in the contralateral and ipsilateral directions. Contralateral rotations (CR) were evoked from a wider area, mainly from the dorso-medio-central zones of the head of the nucleus. Conversely, ipsilateral rotations were evoked from the ventrolateral zone, they more often contained a tonic component, their amplitude was greater, and their senstivity to L-dopa and chlorpromazine was less. Unilateral injury to the region evoking CR led to ipsilateral asymmetry of posture. When this asymmetry disappeared, injection of L-dopa or apomorphine easily evoked circular movements in the same direction. Removal of zones acting as the source of ipsilateral responses gave the opposite result.

KEY WORDS: caudate nucleus; L-dopa; apomorphine.

According to some workers [6, 9, 10] the striatum may be the primary source of extrapyramidal disorders of the torsion dystonia type. However, attempts to treat such diseases by drugs both potentiating (neuroleptics) and weakening (dopaminomimetics) striatal activity have not given unequivocal results [2, 3, 8], possibly because of the existence of functionally different zones in the caudate nucleus, with different roles in the genesis of rotatory movements and with different sensitivity to the action of drugs.

Electrical stimulation of the caudate nucleus and injection of dopamine into the nucleus in fact evoked two types of rotatory movements. They may be either contralateral or ipsilateral in direction [1, 4, 5].

The object of this investigation was to compare the two responses evoked in cats by stimulation and injury of the caudate nucleus.

## EXPERIMENTAL METHOD

Experiments were carried on 34 freely moving cats of both sexes weighing 2-3.6 kg. In the experiments of series I (18 animals) rotatory responses were evoked by electrical stimulation (square pulses, frequency 30 Hz, duration 0.5 msec, duration of stimulation 10 sec) of different zones of the head of the caudate nucleus through previously implanted bipolar nichrome electrodes (thickness of tip 0.1 mm, distance between electrodes 0.5-1 mm). In the experiments of series II (16 cats) electrolytic destruction (dc, 2-4 mA, 3-5 applications for 20 sec each time, at intervals of 1 min, nichrome electrodes 0.3 mm thick) of a definite zone of one of the nuclei was carried out. Rotatory movements in a circle were evoked in these animals by means of dopaminomimetics – apomorphine (1-5 mg/kg) and L-dopa (50 and 100 mg/kg) – injected intraperitoneally 20-30 min before the investigation began. The speed and number of the movements were recorded after 30 min.

In some experiments with electrical stimulation of the caudate nucleus, after control determination of the thresholds of the rotatory responses the animals were given an injection of L-dopa (50 and 100 mg/kg) or chlorpromazine (1 and 5 mg/kg).

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