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SEX DIFFERENCES IN REACTIVITY OF CONSCIOUS AND ANESTHETIZED RATS TO SURGICAL STRESS

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UDC 613.863-02:617-089]-055.1/.2-092.9-07

KEY WORDS: sex differences; stress reactivity; corticosterone; anesthesia

It was shown previously that the amplitude of the hormonal response and the speed of response in female rats during emotional stress are significantly higher than in males [1, 2]. This correlates with the higher level of emotional excitability in females in situations of acute [6, 15] and chronic [14] stress. Negative emotional states formed during exposure to unfavorable influences, which are the most rapid and integral method of situation evaluation [3], are known to constitute the first stage of systemic protective reactions [9, 10, 12] and are able to intensify stress-induced glucocorticoid secretion [4, 7].

The facts described above suggest that one cause of sex differences which we found in stress reactivity may be the different role of emotional excitation in the two sexes in realization of the hormonal response.

The aim of the present investigation was to study stress reactivity in female and male albino rats exposed to surgical stress under pentobarbital anesthesia, which blocks emotional excitation during stress.

EXPERIMENTAL METHOD

The close relationship of this model of stress to medical practice and the absence of any clear ideas on activity of adaptive mechanisms at different stages of surgical stress [11] induced us to analyze stress reactivity to a whole range of activities accompanying operations. Some animals were exposed to preoperative stress, including being carried into the experimental room, removal from the cage, handling, weighing, and intravenous injection of physiological saline. After these procedures, which took 15-20 min, the animals were decapitated. Other animals at the stage of preoperative stress received an intraperitoneal injection of pentobarbital and were decapitated 15-20 min later, during which time anesthesia developed. Yet another group of animals underwent laparotomy. Some of these animals were decapitated immediately after

Department of Biochemistry, Biophysics, and Physiology, N. G. Chernishevskii Saratov University. (Presented by Academician of the Academy of Medical Sciences of the USSR K. V. Sudakov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 113, No. 1, pp. 26-28, January, 1992. Original article submitted June 11, 1991.

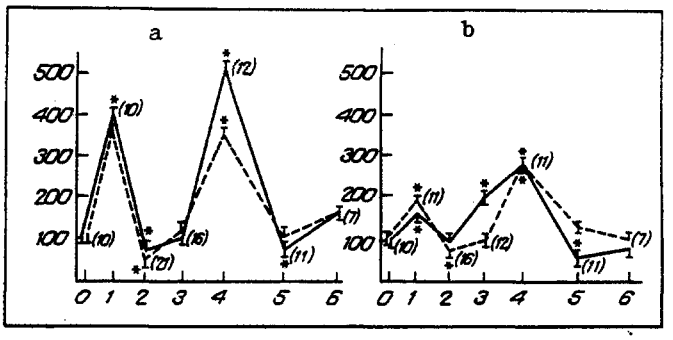

Fig. 1. Time course of changes in coticosterone concentration in females (a) and males (b) during surgical stress. Abscissa, stages of surgical stress: 0) intact animals, 1) preoperative stress, 2) anesthesia, 3) laparotomy, 4) reawakening of the animals, 5) 24 h, and 6) 48 h after the operation; ordinate, corticosterone concentration (in per cent of control) in adrenals (broken line) and in blood plasma (continuous line). Asterisk indicates that shift relative to control is significant ($0.001 < p < 0.05$). Number of animals shown between parentheses.

the operation, i.e., in a state of deep anesthesia, whereas the rest were decapitated 60 min after reawakening. The indicator of arousal was recovery of the voluntary movements by the rats, in the form of moving around the cage, and consuming milk and food. The late aftereffect of stress were studied 24 and 48 h after the operation. Changes in the corticosterone level in the adrenals and in plasma obtained from blood collected during decapitation of the rats served as the indicator of stress reactivity. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The sensitivity of the females to preoperative stress was much greater than that of the males. The corticosterone concentration in the adrenals and plasma of the females increased by 3.7 and 4.0 times respectively (Fig. 1a), but in the males by only 1.8 and 1.6 times (Fig. 1b). In the course of the experiments sex differences were found in sensitivity to pentobarbital. In females an anesthetic effect occurred after nembutal in a dose of 35 mg/kg, compared with 45 mg/kg in males. Anesthesia lasted 2-3 h in the females and a little over 1 h in the males.

The development of an anesthetic state under the influence of pentobarbital was accompanied in most (79%) females by a sharp fall of the corticosterone level in the adrenals and plasma compared with characteristic values for the preoperative period. Moreover, the hormone concentration in the "sleeping" females was only half of that observed in the basal levels (Fig. 1a). Only in 21% of females, against the background of deep inhibition, did the corticosterone concentration remain just as high as in the preoperative period. The dominant component of preoperative stress is psychoemotional. Consequently, sensitivity of most females to it was completely suppressed during blockade of emotional excitation due to pentobarbital anesthesia.

A rather different picture was observed during surgical intervention leading to the formation of a steady flow of afferent nociceptive impulsation. In most females (75%) which did not recover from the state of anesthesia, laparotomy was accompanied by an approximately twofold increase in the corticosterone concentration in the adrenals and plasma compared with the low values observed in "sleeping" females before the operation (Fig. 1a). However, this increase only reached basal levels, i.e., it evidently did not correspond to such severe stress. This is confirmed by the fact that 60 min after reawakening of the animals the hormone concentration in the adrenals and plasma was 3.5 and 5.2 times higher than the basal values (Fig. 1a). It must be pointed out that in 25% of the sleeping females laparotomy led to a threefold increase in the corticosterone level compared with normal, a result which reflects the possibility that certain individuals could respond to stress even through they had developed anesthesia. On the whole, however, against the background of deep inhibition of the CNS, leading to blockade of emotional excitation, in the overwhelming majority of females the response to preoperative stress was completely blocked and the response to surgical intervention was sharply inhibited.

Changes in stress-reactivity in males under the influence of pentobarbital were less marked than in females. In the majority (69%) of males anesthesia lowered the corticosterone level characteristic of the preoperative period (Fig. 1b). Under these circumstances, however, only in the adrenals did the hormone concentration fall below normal. On the whole, whereas in females the development of inhibition was accompanied by lowering of the corticosterone level in the adrenals and plasma by 9 and 7 times compared with characteristic values for the preoperative period, in males it fell by only 3 and 2 times. Moreover, in a high proportion of males (31%) the development of anesthesia was accompanied by a typical stress reaction, the hormone concentration in the adrenals and plasma being increased by 2.2 and 3.0 times. No such reaction to pentobarbital was observed in females.

Laparotomy against the background of anesthesia led to elevation of the corticosterone level in the adrenals by 1.5 times compared with its values in "sleeping" males. The plasma hormone concentration rose under these circumstances by 2.2 times, but on reawakening of the animals it increased further by only 45%. Abolition of the inhibitory effect led mainly to an increase in the corticosterone concentration in the adrenals of the males undergoing the operation (Fig. 1b).

Such different aftereffects of pentobarbital anesthesia in females and males equalled in amplitude the stress-induced rise of the hormone levels in response to laparotomy. In absolute values the plasma corticosterone concentration in males was actually twice as high as in females. Reawakening of the animals which sharply increased the stress-reactivity of the females, led to restoration of the typical relationships between the sexes in their stress reactivity.

Thus the development of the narcotic state, leading to blockade of the emotional component of the stress-induced reactions, is accompanied by greater depression of stress reactivity in females than in males. These findings suggest that in females, compared with males, the emotional excitation arising during exposure to stress plays a much greater role in the realization of the hormonal response, and ensures higher adrenocortical sensitivity to stress. Data in [13], showing that painful emotions are stronger in stress situations and the cortisol level is raised by a greater degree in women than in men, can be interpreted in the same light.

It is important to note that the sensitivity of females is higher than in males not only during physiological stress in the preoperative period, but also during laparotomy. Evidence of the severity of surgical stress is the fact that plasma corticosterone levels in females and males were not restored to normal until 48 h had elapsed. Consequently, sex differences in stress reactivity are a constant phenomenon, manifested in all kinds of stress situations. This conclusion, based on a concrete model of surgical stress, closely linked with medical practice, may be interesting for clinicians, whose therapeutic tactics, with a few exceptions [5, 8], do not take account of sex differences in adaptive systems.

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MAST CELL – LEUKOCYTE INTERACTION IN INCREASED VASCULAR PERMEABILITY OF AN INFLAMMATORY FOCUS

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UDC 616.381-002-092.9:[612.112.93+612.112.9

KEY WORDS: inflammation, vascular permeability; mast cells; leukocytes

The results of in vitro studies of modulation of the functions of different kinds of leukocytes (neutrophils, eosinophils, monocytes, lymphocytes) by biologically active substances of mast cells (MC), on the one hand [6, 11], and the degranulating effect of products of leukocytes (lysosomal enzymes and nonenzymic cationic proteins, cytokines, free radicals, lymphokines) on MC, on the other hand [3, 8-10, 12], point to possible interaction between MC and leukocytes in the pathogenesis of inflammation.

The aim of this investigation was to study the kinetics of peritoneal MC during the exudative phase of infectious peritonitis in rats under natural conditions of inflammation and during its development against a background of isolated and combined removal of MC and leukocytes.

EXPERIMENTAL METHOD

Experiments were carried out on 317 male Wistar rats weighing 180-200 g. Peritonitis was produced by intraperitoneal injection of $2 \cdot 10^9$ ($0.5LD_{50}$) cell bodies of a 24-h culture of *E. coli*, isolated from a patient with peritonitis, in 1 ml of isotonic sodium chloride solution. Vascular permeability in the peritoneal cavity at different times after reproduction of peritonitis was judged from the concentration of 1% trypan blue (5 ml/kg) in isotonic sodium chloride solution [1], injected intravenously 5 min before decapitation, in the peritoneal washings. The washings were obtained by irrigating the peritoneal cavity with 5 ml of isotonic sodium chloride solution containing 5 U/ml heparin. The concentration of the dye in the washings was determined on a KFK-2 photoelectric colorimeter at a wavelength of 590 nm (after deduction of a figure for turbidity of the exudate, determined at 400 nm). The peritoneal MC were disintegrated 10 days before reproduction of peritonitis by intraperitoneal injection of 10 ml/100 g body weight of sterile distilled water [1, 4]. Leukopenia was induced by a single intravenous injection of 0.75 mg/kg of vinblastine sulfate (Richter, Hungary) 4 days before reproduction of peritonitis [15].

EXPERIMENTAL RESULTS

The increase in vascular permeability (VP) of the peritoneal cavity in rats during the natural development of inflammation was phasic in character and included immediate and delayed phases (Fig. 1). The immediate phase was observed in the first 15 min after reproduction of peritonitis. Toward the 30th minute VP was appreciably reduced, but was nevertheless higher than initially. The delayed phase reached a peak toward 5 h, and VP returned to normal by the 5th day.

Department of Pathological Physiology, Khar'kov Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR E. D. Gol'dberg.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 113, No. 1, pp. 28-30, January, 1992. Original article submitted July 16, 1991.

 0007-4888/92/0001-0038$12.50