REVIEW

Endocrine Changes after Burn Trauma—A Review

Rajko Doleček

Department of Medicine, Burns Unit, Regional Hospital KUNZ in Ostrava
Czechoslovakia

(Received for publication on May 16, 1989)

Abstract

After burn trauma, a very marked endocrine response occurs. Almost all the known hormones take part in it. Their response influences very much the postburn metabolic changes and participates in the integration of the body's response with the nervous and immune systems. In this review, mainly the changes in various hormone levels are described, as well as the possible role of the acute phase response after burn trauma, and the communications between the endocrine and immune systems, the cells of the latter are able to respond to various hormonal stimuli and to secrete various hormones themselves. Some of the hormones are very sensitive indicators of the burn stress, e.g., the T₃ levels (very low), testosterone in males (very low), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) (very low), ADH, catecholamines, renin and angiotensin II, cortisol (high), 17-β-estradiol in males (usually elevated). Other hormones are usually elevated, but not always (ACTH, aldosterone, prolactin, glucagon, immunoreactive insulin, β-endorphin, rt₃, 11-β-hydroxyandrostenedione), but there are hormones that are usually low (T₄, FSH, androstenedione, progesterone—the latter especially in females). Calcitonin, parathyroid hormone, growth hormone are sometimes elevated, as well as LH (measured with RIA methods). TSH is usually normal, the biologically measured LH was reported to be low. The levels of the sensitive indicators of burn stress may be used to evaluate the effect of treatment: if the burn patient is properly treated, the indicators may become earlier normal.

Key words: burn trauma, thirty different hormones, endocrine and immune response, sensitive indicators of the burn stress, acute phase response

Reprint requests to: Dr. Rajko Doleček, Urxova 2, Ostrava 4, 708 00, Czechoslovakia
There are three main integrating systems in the human body: the nervous, the endocrine, and the immune systems. All of them are very active after burn trauma. The activity of the nervous system is difficult to measure, but the endocrine changes after burn trauma are easily measurable. In the last one to two decades, the changes in the immune system after burns are measured more reliably as well. The concept of the classical stress response to burn trauma has been reevaluated—it must include now the acute-phase response as well (see Fig. 1). One facet of the close relationship between the endocrine and the immune system is presented in Fig. 2.

After burn trauma, the endocrine and the metabolic responses have many problems to solve:

1. to supply sufficient quantities of substrates ("fuel") to cover the highly increased energy expenditures,
2. to supply sufficient quantities of amino acids for the necessary reparative syntheses, for the immune response, to create new enzyme systems, etc.,

Fig. 1  A simplified scheme of the stress response to burn trauma and its connection with the acute-phase response.
SAS—sympatho-adrenal system, CRH—corticotropin-releasing hormone.
Fig. 2 The "dialogue" between the endocrine and the immune system.

→ stimulation, ↔ suppression.

CRH—corticotropin-releasing hormone, POMC—proopiomelanocortin.
Practically all the known hormones, both the “classical” ones, and the “new” ones (e.g., various cytokines) participate in these activities.

The endocrine studies in burned humans started in the early fifties. The adrenal hormones, catecholamines, and the thyroid gland activity were measured at that time with the methods available. The radioimmunoassay (RIA) methods revolutionized the endocrine studies and made the relatively easy measurement of many hormones possible. More than 30 hormones and their metabolites have been measured so far after burns. In this review the findings resulting from our own studies, started 35 years ago, will be presented, as well as those from the studies of other authors. Most of our results have been included in two publications.1,2

The present review will cover mainly the changes of levels of various hormones after burn trauma, without explaining their pathophysiologic implications, because it would at least double or triple the size of this review. Nevertheless, in a few instances, this has been done to shed some light on still very controversial problems (e.g., the possible role of DHEA, DHEA-S).

**Hypothalamic and Pituitary hormones**

The serum levels of the antidiuretic hormone (ADH, vasopressin) are increased after burn trauma, sometimes very much, if measured both by the biological method1 and by RIA method.3-5 Its levels are very high during and just after resuscitation, but they are often elevated even in the apparently volume-repleted patients. Even the syndrome of inappropriate vasopressin secretion was described after burn.5 In addition to the fluid and electrolyte shifts, some other mechanisms prolong later in some patients the presence of elevated ADH levels.

**FSH** is a very sensitive indicator of the burn trauma, in both males and females, its low levels may persist for many weeks after a major burn, they correlate with the very low testosterone levels in the burned men.6,8 The low levels of FSH after burn were repeatedly described.6-9 After LHRH stimulation, the FSH levels increase after burn injury, but much less than in the normal, healthy controls. Especially low or practically absent response of FSH was noted during the second and third postburn week.8

**LH** levels, as measured by RIA methods, were not uniformly altered after burn trauma, they were in the mean more or less normal,6-10 occasionally even elevated (e.g., during some postburn complications, during the first two postburn days).2,6,8 Never-
theless, very low LH levels were described in some critically burned patients. But if a biological method was used to measure the postburn LH levels, they were low. The response of LH to LHRH stimulation was normal after burn, with the exception of the second and third weeks, when the response was significantly lower than in the first and in the later postburn weeks. There is a marked discrepancy between the low postburn testosterone levels in males and the normal or even elevated LH levels, and the normal or even elevated LH response to LHRH.

Prolactin (PRL) serum levels are often elevated after burn trauma, especially in the burned women, but those elevated levels are not such a constant indicator of the burn stress as e.g., the levels of cortisol. Normal PRL levels may be found even after a severe burn. After TRH administration, PRL levels increased in the burned.

TSH serum levels are only very exceptionally elevated after burn trauma—they are almost always within normal limits, but if measured with sensitive methods, they may be low. In the later phases of the post burn syndrome, they may be elevated. They usually respond to TRH stimulation, but the response is significantly lower in nonsurvivors. Neither the low triiodothyronine syndrome after burn injury, nor the low T₄ (thyroxine) levels after burn are followed by an increase in TSH levels.

Lee et al., reported about the hypothalamic-pituitary dysfunction in critically ill post-menopausal women. They stressed that the hypothalamic-pituitary-gonadal axis is more frequently affected than the hypothalamic-pituitary-thyroid axis. The hormones and metabolism in critical illness are discussed extensively elsewhere.

From the large molecule of proopiomelanocortin (POMC), the ACTH levels were measured repeatedly. They are very often elevated after burn trauma, but not always, there may be even discrepancies between cortisol and ACTH (e.g., normal ACTH—elevated cortisol, and vice versa). In more severe burns, the ACTH levels tend to be usually higher, but this observation was not made by all authors. Some of the above discrepancies may be explained by the effects of interleukin-1 on the anterior pituitary and on the adrenals (Fig. 1). In addition to ACTH, from the POMC molecule, β-endorphin levels have been measured after burn trauma. They were found elevated, but their elevated plasma levels did not mean that analgesia was present. To achieve analgesia, opioids must be available at specific sites.

The growth hormone (hGH) levels are usually not elevated after burn trauma, but elevated and even high levels have been found. The mean hGH levels after burn are higher than the levels of hGH in normal controls, but they both are within normal limits (below 5 ng/ml). The response of hGH and blood glucose levels to insulin caused hypoglycemia (insulin tolerance tests) is rather low during the first two postburn weeks, but later in increases significantly.
Renin and Angiotensin II

Renin levels after burn trauma are very high, these high levels may persist for many days. The high levels of angiotensin II have been described as well. The above high levels sometimes persist even in already volume-repleted burn patients. Both the renin and angiotensin II levels are important indicators of the burn stress. But there may be discrepancies in the renin-angiotensin II-aldosterone system in the critical illness (see later).

Adrenals

The adrenals, their cortex, are the most important "classical" endocrine gland that enables the survival of burn patients. The patients without the pituitary gland can survive the critical illness (and the burn trauma), if their replacement therapy with cortisol is adequate. In this respect, cortisol is the most important hormone. It must be remembered that its daily production in normal, unstressed, healthy individuals is 15–30 mg/24 hrs. In severely stressed humans it may reach values about 300 mg/24 hrs. If the needed replacement therapy in humans without adrenals is administered in time, the patient requires much less cortisol than if the treatment is initiated when the adrenal crisis is imminent or already beginning: the daily dose necessary for survival in that case may be as high as 1,000 mg or even more.

There are five main groups of adrenal steroids: glucocorticoids (cortisol is the most important in humans, corticosterone in rats), mineralocorticoids (aldosterone), adrenal androgens (androstenedione, 11-β-OH androstenedione, DHEA, DHEA-S), estrogens (17-β-estradiol), and gestagens (progesterone).

Glucocorticoids: The most important glucocorticoid for humans, as stated above, is cortisol. Its levels after burn trauma are increased, sometimes very much. Only exceptionally are found their normal levels. The earliest publications about 17-hydroxy-corticosteroids (17-OHCS) in urine and plasma after burn trauma in humans appeared in the early fifties. For a review see e.g.1,2,13,14,16,25,27–29 The circadian rhythm of plasma cortisol disappears after burn trauma for some time,25 or is at least less obvious.16 But it must be noted here that sometimes even major burns may be accompanied by more or less normal cortisol levels, at least for some time only. The levels of cortisol in burned women are less elevated than its levels in burned men from the same burn unit.2 But generally, the cortisol levels seem to be elevated in proportion to the burn size.13,14,16 The data from different places must be interpreted cautiously, because they may depend very much on the type of treatment as well.

Mineralocorticoids: Aldosterone levels, both in urine and in plasma, are mostly elevated after burn trauma, but not as consistently as the cortisol levels.1,2,13,14,25–27,30
Their increased values may persist for many weeks—they are elevated even in patients with already no obvious water-and-electrolyte problems. The peak aldosterone plasma values may be as high as 500 pg/ml, and even higher. During severe stress, in the critically ill, the dissociation of renin and aldosterone values were described as a new entity: low to very low levels of aldosterone were present despite high levels of renin. Finding et al. interpreted it as an additional adrenal adaptation designed to promote cortisol production in critically ill patients. Similar observations were made in the burned patients.

Adrenal androgens: Adrenal androgens or N (nitrogen) hormones, or adrenal anabolic hormones represent an important group of adrenal hormones whose exact role is not yet fully understood. This role must be important, because they represent 40–50% of the adrenal cortex capacity. They are precursors of estrogens (17-estradiol) and androgens (testosterone), they may serve as a counterregulation to the catabolic glucocorticoids. Even a pituitary adrenal androgen stimulating hormone (AASH) was postulated. The levels of dehydroepiandrosterone sulfate (DHEA-S) and of dehydroepiandrosterone (DHEA) were uniformly low after burn trauma. While DHEA-S increases significantly after ACTH, it is very low after burn trauma, in the old age, during severe illness. Androstenedione postburn levels are mostly low, but occasionally they may be even elevated. A relatively sensitive indicator of the burn stress is another adrenal androgen, 11-OH androstenedione. Its levels are very often high after burn trauma. DHEA and DHEA-S may have a very important metabolic role: they control the hexosemonophosphate shunt or pentose phosphate pathway which has two purposes: the generation of NADPH for reductive biosyntheses, and the formation of ribose 5-phosphate for the synthesis of nucleotids. If low levels of DHEA and DHEA-S are present, the pentose phosphate pathway is more active, more NADPH is available, and a “hyperproductive syndrome” may develop. Increased levels of NADPH are indispensable for the proper functioning of various microbicidal systems (e.g., the myeloperoxidase system).

Estrogens: After burn trauma, 17-estradiol levels in males are elevated, sometimes very much. In females, they do not decrease either, they may even reach very high normal levels, or even be as high as during ovulation. In males, the only source of these high levels of 17-estradiol are the adrenals—the activity of male gonads is very depressed after burn trauma, both their gametogenesis and testosterone production. The amenorrhea in burned females is not caused by the lack of estrogens (17-estradiol) whose normal or even elevated levels may persist for many weeks after burn trauma. It is interesting to note here that in the adult persons, but not in the old ones, 17-estradiol does not rise after ACTH, but in the elderly, after 70 years of age,
it increases significantly after ACTH. It is not clear what causes this change in adrenal response. A similar mechanism may operate after burn stress: ACTH, or the burn stress only (?), activate the adrenals in such a way that they secrete large quantities of 17-β-estradiol.

Gestagens: As for plasma progesterone levels after burn, they were in most cases low to very low in the adult, premenopausal women, without their usual elevation in the secretory phase of the menstrual cycle. But, occasionally, this elevation occurred in minor burns. In the burned men, their plasma progesterone levels were mostly low normal, with occasional elevated levels. Those above observations cannot explain the source of progesterone, but again here the adrenals are probably the source, because the ACTH stimulation in healthy controls usually increases the progesterone levels.

There is a major difference between men and women in their testosterone response to ACTH: in men, testosterone drops significantly after ACTH, in women it increases significantly.

Thyroid hormones

The thyroid hormones, especially the triiodothyronine (T₃) levels, are sensitive indicators of the burn stress. The postburn hypermetabolism is not related to the thyroid gland activity. Cope et al. did not find any alternation in the thyroid gland activity after burn when they used ¹³¹I uptake and PBI (protein-bound iodine) values to measure it. Caldwell found in the experimentally burned rats that they were able to increase their oxygen consumption without any change in thyroid gland activity. Even the thyroidectomized rats were able to increase their oxygen consumption after burns. After burn trauma, major histological lesions of the thyroid gland are usually found. In the postburn period, the T₃ levels are uniformly low for several weeks, they depend to some extent on the burn size. The nonsurvival after burn was more correlated with T₄ serum levels. The T₄ values after burn are low too, but not as low as T₃. The reverse T₃ (rT₃) levels rise after burn trauma in the majority of cases, but the results from different laboratories and burn units differ somewhat. The free T₃ and T₄ (FT₃, FT₄) levels were much lower in clinically unstable patients than in the clinically stable ones. There is a reciprocal relationship between plasma concentrations of T₃ and both epinephrine and norepinephrine in untreated burn patients: treatment of them with triiodothyronine does not alter the level of hypermetabolism after thermal injury. If TSH tests are carried out, the mean response of the thyroid gland, of both T₃ and T₄, is normal. The levels of rT₃, naturally, do not increase after TSH. The low levels of T₃ and T₄ after burn trauma are not accompanied by elevated TSH levels. As for the TRH-TSH tests after burn, see above (the pituitary hormones).
Endocrine Changes after Burn Trauma—A Review

Gonads

After burn trauma, the male gonads are seriously affected, their severe histological lesions were repeatedly described. Doleček et al. described both the histological lesions, and the endocrine changes as well. The postburn low testosterone levels were reported repeatedly. These low levels of testosterone last in the mean for 5–6 weeks, the very low levels for 4 weeks. If hCG (human chorionic gonadotropin) is administered to the burned males, testosterone levels increase, but this increase is not present usually in the critically burned. The burn trauma adversely affects the gametogenesis, but this unfavorable changes need some time to develop. Occasionally, these changes may be probably reversible. In one severely burned young man (21 year old), complete azoospermia was found one year after burn, but the next year already $14 \times 10^6$ sperms per ml were found. The low testosterone levels are correlated to some extent with the low FSH levels, but not with the LH values. The testosterone levels may be very low, even below 0.5 ng/ml, and the LH (and only occasionally even the FSH) levels are quite normal and respond quite normally to the LHRH stimulation. The possibility of a discrepancy between the RIA measurement of LH and biologically measured LH must be stressed (see earlier). The low testosterone levels are not accompanied by elevated FSH and LH levels. In burned females, the plasma testosterone values are normal, only occasionally elevated.

Not too much is known about the histological changes in ovaries of burned female patients: some changes were described by Arjev; swelling, destruction of follicles, fibrosis. The normal or even elevated levels of 17-β-estradiol in burned females are very probably of adrenal origin as in males. We found high plasma 17-β-estradiol levels in a severely burned woman one year after menopause (up to 217 pg/ml). Even her progesterone was elevated for her post-menopausal age (1.28 ng/ml). Her LH was at that time 41 mIU/ml, her FSH 27 mIU/ml. Otherwise, progesterone levels in females after burn trauma are generally low.

Catecholamines

The high levels of catecholamines (epinephrine and norepinephrine) in both urine and plasma after burn trauma were published rather early, as well as the possibility of sympathetic nerve depletion in severe thermal injury. Wilmore et al. even described the catecholamines as the mediators of the hypermetabolic response to thermal injury. Until recently, catecholamines, glucagon and cortisol were considered to be the driving force of the hypermetabolic response to burn injury. But the present evidence shows that they are not responsible for all the facets of the postburn syndrome. Various cytokines (e.g., interleukin-1, cachectin) are probably responsible for them. The acute-phase response as elicited by cell damage explains much better many
symptoms and signs of the postburn syndrome (Fig. 1).

**Insulin and Glucagon**

After burn trauma, elevated levels of IRI (Immunoreactive Insulin) were repeatedly described,\(^2,6,10,13,21,22,60,61\) as well as an impaired glucose tolerance. The elevated mean IRI levels persisted for 7 postburn weeks.\(^6,10\) Hinton et al.\(^62\) used the anabolic effects of insulin in the treatment of burn patients. They administered huge doses of insulin and glucose to their patients.

Hyperglucagonemia after burn injury was repeatedly reported,\(^61,63,64,65\) it participates in the development of the postburn catabolic and hypermetabolic state.

**Parathyroid hormone (PTH), calcitonin**

The serum levels of calcium (total and/or ionized) are generally low after burn trauma, and these low levels may persist for many weeks.\(^2,3,14,61,67,69\) Some authors found only low levels of total calcium, but not of the ionized.\(^68\) Increased levels of calcitonin after burn were found repeatedly,\(^2,13,14,69,70\) but not in all patients. PTH in serum was elevated too,\(^13,14\) but its mean values, as found by some authors, reached only the upper normal limits.\(^69,70\) In two cases, PTH reached the levels of patients with parathyroid cancer.\(^2\) In very many burn patients, their cAMP serum levels were high, and these high levels might persist for many weeks.\(^2\) The postburn osteoporosis could be explained to some extent with other factors that could help induce it: the tumor necrosis factor or cachectin stimulates bone resorption and inhibits its formation.\(^71\)

**The acute-phase response**

The acute-phase response\(^57-59\) represents the sum of host responses to various adverse stimuli: injury, burn, inflammation, microbial invasion, immunologic reactions, etc., connected with damage, injury, necrosis of cells. This response includes changes in metabolism, alteration in endocrine glands activity, in immune and nervous system response. The summary of the above changes is included in Fig. 1. The principal mediator of all the above changes is a polypeptide with hormonal activity, a cytokine, interleukin-1, secreted by phagocytic and other cells (monocytes, macrophages, astrocytes, Kouffer cells in the liver, etc.). It is one of the endogenous pyrogens of the human body. The endocrine changes elicited by the acute phase response involve increases in insulin levels, of vasopressin (ADH) and glucagon. This glucagon and insulin release stimulating effect by interleukin-1 (earlier called LEM, leukocytic endogenous mediator) was postulated by Beisel.\(^72\) Glucocorticoids and cyclosporine are potent inhibitors of both lymphokine synthesis and the response of cells to lymphokines.\(^58\) There is even an immunoregulatory feedback between interleukin-1 and glucocorticoid hormones.
The **tumor necrosis factor** (TNF or cachectin) is a cytokine too (lymphokines and monokines “belong” to a larger family of cytokines), it is produced by cells of hematopoetic origin. Its production is elicited by endotoxin, mostly by endotoxin-induced macrophages. It causes coagulopathies, shock, hemoconcentration, fluid and electrolyte sequestration, wide-spread end-organ damage. In this respect see e.g., the multiple organ failure in burned patients. Cachectin is an important mediator of inflammation, it stimulates interleukin-1 production, it is an internal pyrogen as well. Glucocorticoid hormones strongly inhibit cachectin production. It is interesting to note here, that even the D hormone (calcitriol) inhibits the T cell proliferation, primarily through inhibition of interleukin-2 production.

**Communication between the endocrine and immune system**

The relationship between the endocrine and immune system are well known. The pronounced hormonal changes after burn trauma, as described earlier, influence the host immune response significantly.

Communications between the neuroendocrine and immune system are reciprocal. Various pituitary peptides and neuropeptides play a “lymphokine role” in this respect, via e.g., ACTH and opiate receptors on lymphocytes, leukocytes (Fig. 2). The latter produce various neuroendocrine, peptide hormones (ACTH, opioids) when stimulated by virus infection, by bacterial lipopolysaccharide. *In vitro* POMC gene products induced by CRH and suppressed by dexamethasone, may be found in the cells of the immune system. In this respect they behave like the pituitary: they respond to the positive signal from the hypothalamus (CRH), and to the negative from the adrenals (glucocorticoids). At the same time their lymphokines (e.g., interleukin-1) influence significantly the pituitary-hypothalamic area. It is probable that the immune system serves as sensory organ for stimuli (bacteria, viruses) that are not recognized by the central and peripheral nervous system, and leukocytes may pass then their information to the neuroendocrine system by their peptide hormones and lymphokines. In this respect, certain cells of the immune system may serve as “free floating nerve cells,” or as a “mobile brain.” In various types of immune cells, neuroendocrine hormone-like peptides and hormones and their receptors may be found (growth hormone, thyroid stimulating hormone, vasoactive intestinal peptide, somatostatin, etc.). All the above neuropeptides, hormones, lymphokines, serve in the “cross talk between the brain, endocrine system, immune system.” The brain most likely modulates the immune response at both the afferent (activation), and efferent (expression) stage through neuronal and neuroendocrine influences. Basedowsky et al. described an immunomodulatory feedback circuit between interleukin-1 and glucocorticoids in which interleukin-1 acts as an afferent, and glucocorticoids as an efferent hormonal signal.
References

Endocrine Changes after Burn Trauma—A Review

274

66: 33–38, 1988


