

RESPONSES OF ANTERIOR PITUITARY HORMONES TO FEVER DURING COMMUNITY-ACQUIRED INFECTIONS

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Aim: The aim of the study was to determine the responses of adrenal corticotropic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH) and prolactin (PRL) levels during community-acquired infections with fever and to compare changes of these hormones to febrile and afebrile episodes.

Methods: Plasma levels of ACTH, serum levels of cortisol, TSH and PRL of 60 hospitalized patients were evaluated prospectively. Blood samples from study group were taken 2 times; during pyrexia and one hour after decreasing of fever. Only one blood sample was taken from each control patient and time of blood sampling was same for all of them.

Results: 60 hospitalized patients were included to the study. Of these, 29 were study group, 31 were control group. In febrile patients with infection; plasma ACTH levels was higher than the control group (37,35±35,82 pg/mL vs 22,78±28,84 pg/mL) but no statistical significance was found (p=0,101). Serum cortisol levels was higher than the control group (28,88±13,12 ug/dL vs 17,68±7,88 ug/dL) (p<0,001). There were no differences in serum PRL and TSH levels between the two groups. In the study group plasma ACTH and cortisol levels were significantly increased in febrile periods when compared to afebrile periods (32,21±28,51 pg/mL vs 18,93±22,86. pg/mL; p=0,002) and (28,32±12,96 ug/dL vs 23,09±15,05 ug/dL; p=0,024) respectively. In PRL and TSH levels there was no statistically significance.

Conclusion: We concluded that plasma ACTH and serum cortisol elevations are common in acute infectious diseases, and they are more sensitive to increasing of body temperature. The two peptides may be involved in central mediation of fever, perhaps limiting the febrile response acting as neuromodulators in central thermoregulatory pathways.

Key words: Anterior pituitary hormones, fever, infection

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INTRODUCTION

Fever is a part of the acute phase response (APR) to infection and systemic inflammation. It is a part of a complex physiological response of the host against microorganisms or foreign non-microbial agents invading the body (1,2). The fever is induced by inflammatory mediators released by immune cells activated by contacts with foreign molecules (1,2). Recent studies have demonstrated that there are bidirectional circuits between the central nervous systems.(CNS) and the immune system 3,4. The hypothalamic-pituitary-adrenal (HPA) axis plays an important role between the immune

system and the CNS (4,5,6). Interactions between the immune and neuroendocrine systems are mediated by several factors including neurotransmitters, cytokines, humoral mediators and hormones such as glucocorticoids, prolactin (PRL) and thyroid hormones (4,7). However, the interaction between fever during infection and endocrine response has not yet been clearly described (4). In the study reported here, we investigated plasma corticotropin (ACTH), cortisol, thyroid-stimulating hormone (TSH) and PRL levels during acute infection in patients having fever.

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Table 1. Patient characteristics

Group	Study group (febrile patients)	Control group (afebrile patients)
n	29	31
Male/Female	12/17	14/17
Age (Years ,Mean±SD)	62,79±16,99	64,16±13,83
Type of infection (n)		
Pneumoniae	14	
Hepatobiliary infections	7	
Urinary tract infection	3	
Primary bacteremia	2	
Other infections	3	
Underlying diseases (n)		
Congestive heart failure	5	6
Diabetes mellitus	3	7
Chronic obstructive pulmonary disease	3	
Hepatobiliary cancer	3	
Chronic kidney failure	2	3
Diabetes mellitus with chronic kidney failure	2	2
Ischemic heart disease	1	4
Solid tumours of lung and gastrointestinal tract		6
Diabetes mellitus with ischemic heart disease		2
Hepatobiliary cancer with chronic kidney failure		1

MATERIAL AND METHODS

Subjects

This prospective study was carried out in the Departments of Internal Medicine and Infectious Diseases of a University Hospital over a six month period. A total of 60 hospitalized patients were enrolled in the study. The study group was composed of 29 patients with fever and various community-acquired infections but no evidence of ACCP/SCCM criteria (8) for sepsis. 31 of them with diseases of a non-infectious etiology such as cardiac failure etc served as control group. The controls did not have fever and any kind of infection.

Methods

Fever was defined as axillar temperature >37,3 degrees C. After informed consent, according to their history and

physical examination; the erythrocyte sedimentation rate, hemoglobin, platelet count, leukocyte count, serum biochemical analysis, urinary analysis, blood, urine, feces, sputum cultures, C-reactive protein (CRP) and chest X-ray were performed for diagnosis as a first step. Advanced analysis such as serology for some viral infections, brucella, echocardiography, sinus x-rays, ultrasonography, computed tomography of abdomen and chest were also done if necessary. All of the patients received appropriate antibiotics after diagnosis of infections. Exclusion criteria from the study were pregnancy, acute cerebrovascular accident, thyroid diseases, adrenal diseases, endocrine tumors of the abdomen, brain and endocrine organs.

Blood samples were collected in EDTA-K3, placed on ice for ACTH analysis, and

Table 2. Mean (\pm SD) changes in hormone levels of study and control patients

Hormones	Study Group	Control Group	p Value
ACTH (pg/mL)	37,35 \pm 35,82	22,78 \pm 28,84	0,101
Cortisol (ug/dL)	28,88 \pm 13,12	17,68 \pm 7,88	0,0001
PRL (mIU/L)	294,46 \pm 169,64	296,22 \pm 128,87	0,964
TSH (uIU/ml)	1,16 \pm 1,11	1,20 \pm 1,12	0,887

in tubes without anticoagulant for the determination of TSH, PRL and cortisol. The tubes used for ACTH determination were covered by a bandage to prevent for exposing to sunlight.

In study group first samples of blood were collected immediately for the determination of ACTH, TSH, PRL and cortisol levels when the patients admitted to hospital with infection and fever. One hour after the disappearance of fever, we collected second blood samples for the determination the levels of the same hormones.

The blood samples of control group were collected between pm 01.00-02.00 hours to exclude the day and night difference owing to the diurnal rhythms of ACTH and cortisol. Timing of blood sampling was same for all control patients.

All samples were centrifuged in a conventional centrifuge at 3000xg for 10 min. Serum and plasma samples were placed in plastic tubes and stored immediately at -80 degrees C until required for assay.

Plasma ACTH, serum cortisol and PRL levels were measured by chemiluminescence method on an IMMULITE analyzer (Diagnostic Products Corporation) and reagents supplied by BioDPC. Serum TSH level was detected by electrochemiluminescence assay on the ELECSYS™ system (Roche Diagnostics).

Statistical analysis

SPSS software (Statistical Package for the Social Sciences, version 10.0, SSPS Inc, Chicago, Ill, USA) was used. Data were expressed as means \pm SD. Independent-Samples T test was used to determine the significance of differences between two groups, $p < 0.05$ was considered as statistically significant. Paired-Samples T test was used for comparisons of fever-induced changes in the study group. The demographic, clinic characteristics of the patients were compared using chi-square test. $P < 0.05$ was accepted as significant

RESULTS

Totally 60 hospitalized patients were included in the study (29 patients with fever and 31 controls). Demographic characteristics of the patients, underlying diseases of both study and control groups and infectious diseases of study group are shown in Table 1. The group with infection and fever had higher serum CRP concentrations (162,95 \pm 89,40 vs 40,37 \pm 59,80 mg/dL; $P = 0.003$) than the control group. There were no differences in the erythrocyte sedimentation rates, hemoglobin levels, platelet and leukocyte counts between the two groups.

In febrile patients; mean plasma ACTH levels were higher than the control group but the difference was not significant. Serum cortisol levels were significantly higher than the control group. There

Table 3. Mean (\pm SD) changes in hormone levels during febrile and afebrile periods in infective patients

Hormones	Study Group	Control group	p value
	Febrile period	Afebrile period	
ACTH (pg/mL)	32,21 \pm 28,51	18,93 \pm 22,86	0,002
Cortisol (ug/dL)	28,32 \pm 12,96	23,09 \pm 15,05	0,024
PRL (mIU/L)	296,10 \pm 171,58	261,98 \pm 153,60	0,218
TSH (uIU/ml)	1,19 \pm 1,08	1,19 \pm 1,12	0,968

were no differences in serum PRL and TSH levels between the patients and the controls, respectively (Table 2).

When we compared hormone levels between the febrile and afebrile periods in the study group, some alterations were determined. The differences of the mean hormone levels between two periods are shown in Table 3. Serum ACTH and cortisol levels were also higher in febrile patients when compared to absence of fever.

DISCUSSION

Human body has a complex defence mechanism against to systemic infections with bacteria, viruses or parasites (2,9,10). These microorganisms are exogenous pyrogens that initiate a number of biological responses in the host which is called as APR (9,11). APR is characterized by high circulating levels of prostaglandins and cytokines, which are produced predominantly by monocytes and macrophages (1,9,11). They are called as endogenous inflammatory mediators (9,10,12). Cytokines are immunoregulatory molecules and play a key role between the immune function and neuroendocrine system (11,13,14). The most important cytokines are interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) (11,14,15). During host response against to microorganisms, fever is one of the most seen symptom induced by pyrogenic cytokines (9,10). The febrile increase of body temperature can admit of two interpretations namely it is regarded as a component and/or as a conclusion of the complex host response to infection (9,10). Essentially there are two results of effect of fever to the host during infection (9,10). That means fever can reduce bacterial proliferation by iron deprivation and restrict the synthesis of bacterial cell wall thereby facilitates to kill the pathogens so bacterial load is decreased. It is clear that this effect is beneficial for the host (9,10). But fever may become destructive over a certain temperature and this is the harmful effect of fever to the host (9,10). Therefore fever is controlled by a number of feedback mechanisms (10,12,16). The preoptic area (POA) of hypothalamus is the centre point of thermoregulation (13,17). Cytokine release are sensed by the CNS and transmitted to the hypothalamus to

raise the thermoregulatory set-point. The pathways responsible for transfer of the pyretic signals from the blood to the brain are not clearly understood (13,14,17).

Several studies confirm that cortisol, ACTH, PRL and TSH have an important role in the regulation of the neuro-immuno-endocrine axis (7,18-23). But usually they take place at the different stages of this neuroendocrinologic mechanism. It has been reported that high levels of glucocorticoids and ACTH depress the immune response by inhibiting the production of prostaglandins and inflammatory cytokines so febrile response is antagonized (20,24,25), whereas PRL increase the response by stimulating lymphocyte proliferation and macrophage function (21,26). It is reported that PRL secretion is increased by all kind of stress, particularly sepsis (7,27). Denhardt, reported PRL levels were regularly elevated in sepsis although to variable degrees (27). And also it has been reported that thyroid hormones were necessary for a proper response of PRL release during sepsis (7).

In the present study cortisol, ACTH, PRL and TSH were investigated to determine the neuroendocrinological changes during pyrexia in hospitalized medical patients. We determined that ACTH and cortisol levels were higher than the other two hormones during pyrexia. This result suggest that the mechanisms regulating ACTH and cortisol secretion are more sensitive to increasing of body temperature than those of the other pituitary hormones studied. ACTH and cortisol should be regarded as acute responders to infection and fever. It is clear that they are more sensitive and important in the regulation of thermogenesis. The result of our study compares well with the literature (28,29,30). On the other hand some studies offered contrarily results, namely, Brandenberger et al, observed no significant changes in ACTH levels during the exposure to heat stress (31). Mphahlele et al, detected that hypothalamic-pituitary-adrenal axis response failed to elicit cortisol increase because of the sustained fever (12). This variability may be related to type of stress, cause and length of fever or time of blood sampling according to the protocol of study. In the present study there wasn't any significant increase in PRL and TSH levels. Lack of

sepsis in our patients might be the reason of these results for PRL. The results of several studies confirm that PRL levels are elevated during sepsis (7,21,22,27). Sepsis as a unique stressor is a much more potent stimulus of PRL release than infection without sepsis and fever.

We evaluated only TSH levels in our study and there was no difference between febrile and afebrile periods. It is known that thyroid hormone levels can be influenced by non-thyroidal illness like sepsis (32,33,34). On the other hand it is reported that alterations of other thyroid hormone levels such as thyroxine (T4), triiodothyronine or reverse T3 and diiodotyrosine (DIT) during infection and fever were more noticeable than TSH (27,35,36). So and this may explain our results. A similar result was reported by Talwar that endogenous TSH levels were maintained during fever (37).

This suggest that PRL and TSH are necessary to keep the homeostasis of body during inflammation and infection but they don't have an important role as much as ACTH and cortisol to keep the body temperature in normal levels. It is obvious that endogenous antipyresis is mediated by actions of ACTH and cortisol (10,20,24).

In summary, our study provides even more substantial evidence for the critical role of ACTH and cortisol in controlling fever during infection. Increasing levels of ACTH, and cortisol is the important part of the general adaptation of host to stress, and contributes to the maintenance of homeostasis.

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