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Dual function of glucocorticoid hormones in the body and using this duality for preventing complications of glucocorticoid therapy

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Abstract

Glucocorticoid preparations are used in all areas of medicine for more than 70 years as the most effective anti-inflammatory drugs possessing also anti-allergic and immunosuppressive actions. However, the use of these preparations, unique in the combination and expression of therapeutic properties, is associated with nearly inevitable serious adverse effects. The complications of glucocorticoid therapy are caused by the duality of glucocorticoid hormone functions. Glucocorticoid hormones in the body act:

- As the most universal regulators of virtually all metabolic and physiological processes and
- As hormones mainly responsible for the organism behavior under stress conditions.

In clinical practice, glucocorticoid preparations are used mainly as stress-responsible agents, and their regulatory activities are neglected, but they are manifested inevitably as complications. To prevent these complications, it is necessary to follow the regulatory properties of glucocorticoid preparations which are realized through regulation of activities of many enzymes. The hepatic tyrosine amino transferase seems to be, possibly, the best example of the regulatory activity of glucocorticoids. Based on the literature data and results of the author's studies, it is proposed to use blood level of tyrosine as a promising laboratory parameter for monitoring glucocorticoid therapy.

Keywords: Glucocorticoids; Dual function in the body; Tyrosine aminotransferase; Blood tyrosine; Monitoring of glucocorticoid therapy

1. Introduction

For the first time a glucocorticoid (GC) hormone, cortisone, was injected by Dr. Ph. Hench in the Mayo Clinic to a patient with rheumatoid arthritis on September 21, 1948 [1, 2]. In July 1949, Dr. Hench reported at the Rheumatological Congress in New York about the successful use of GC preparations in a number of diseases. This report was a sensation, and led to a wide use of GC preparations in various pathologies. The efficiency of these spontaneous clinical trials was so impressing that in 1950 Dr. Hench and co-workers were awarded the Nobel Prize.

However, rather soon the initial euphoria was replaced by bewilderment and then by disappointment. Reports appeared about serious adverse effects of new drugs: characteristic obesity, hypertension, diabetes, osteoporosis, secondary infections, etc. Moreover, it was very difficult and often impossible to cancel GC preparations because of exacerbation of the underlying disease and atrophy of the adrenal cortex. The complications of GC therapy were nearly inevitable and frequently so severe that in the article on the 25th anniversary of corticosteroid therapy the author considered the appointment of corticosteroids in rheumatism as evidence of the incompetence of the physician [3].

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Unexpectedly, the therapeutic effect of GC preparations was independent on the level of endogenous GC hormones; thus, GC drugs are efficient in *status asthmaticus* on the background of high level of GC hormones in the blood [4].

The independence of the therapeutic effect of GC drugs on the hormonal background of the patient led to an idea about specific therapeutic properties of these drugs. Detailed studies on the anti-inflammatory action of GC drugs showed them to act on all components of the inflammatory process and the immune response: they inhibit inflammatory mediators, stabilize lysosomal membranes, normalize the cell membrane permeability, suppress the lymphoreticular system, antibody synthesis, formation of autoimmune complexes, etc. GC preparations enhance the expression of genes encoding anti-inflammatory proteins and suppress the transcription of genes encoding the synthesis and release of inflammation mediators, induce apoptosis of immunocompetent cells [5-8].

To increase the desired therapeutic effect and decrease the complications, many GC drugs have been synthesized with the stronger therapeutic efficiency and/or with the targeted action [9]. Numerous empirical schemes have been developed for using GC drugs in various diseases and a special attention is paid to the timely medicamentous correction of the adverse effects. These empirical treatment regimens are reproduced without essential changes in the numerous manuals and reference books. However, GC therapy is still associated with the risk of serious complications, and the corresponding reviews are published up to now [10].

The complications of GC therapy are associated not with toxicity of GC preparations, but with the very nature of these preparations and manifestation of the functional duality of their natural prototypes, GC hormones of the adrenal cortex. In the body GC hormones are responsible for two extremely important functions: first, they regulate directly or indirectly virtually all metabolic and physiological processes, and second, they play a very important, if not the determinative, role in the organism response under stress conditions.

Thus, for more than 70 years GC preparations remain the most effective anti-inflammatory drugs possessing also anti-allergic, immunosuppressive, antitoxic, and antishock actions, and for more than 70 years the problem exists of severe adverse effects and the difficulty and in many cases impossibility to withdraw these drugs.

It seems that the surprisingly wide range and expression of the therapeutic properties of GC preparations are due to their being used just in their role as stress-responsible hormones (and in many cases a disease is a stress situation for the body!). Therefore, GC preparations can use all the pathways and mechanisms that have been developed in the course of evolution.

However, the use of GC preparations as anti-inflammatory drugs (i.e. stress-responsible agents) is inevitably associated with the manifestation of their duality, i.e. with their regulatory action on metabolism.

Glucocorticoid hormones of the adrenal cortex regulate metabolic processes through activation or inhibition activities of many enzymes [11]. The hormonal regulation of enzymes was detected in 1951: corticosteroids were shown to activate in the rat liver synthesis of two enzymes, tryptophan oxygenase (EC 1.13.1.12) and tyrosine aminotransferase (EC 2.6.1.5) catalyzing, respectively, the first stages of tryptophan and tyrosine oxidation in the body. Later, the influence of GC hormones on many enzymes was shown, but their effect on the synthesis by hepatocytes of tyrosine aminotransferase (TAT) occurred to be the most striking example of the regulatory action of these hormones [12, 13]. Therefore, the hepatic TAT became one of the most frequent models for study mechanisms of GC action in various systems *in vitro* and *in vivo* [14-16].

However, TAT cannot be determined in blood, and this prevents its using as a laboratory parameter for clinical purpose, but it is a key enzyme of tyrosine metabolism catalyzing its transamination. Introduction of GC preparations activates the TAT synthesis by the liver cells and leads to a dose-dependent decrease in the blood level of tyrosine in animals and humans [17, 18].

It is reasonable to admit that synthesis of the hepatic TAT depends mainly on two factors: the functional competence of the liver cells that determines their ability to synthesize TAT (alongside with other hepatic enzymes) and on the entrance of glucocorticoids (natural hormones or hormonal preparations) into the liver. If the TAT synthesis is insufficient (due to incompetence of the liver cells or a lack of the hormones), the level of tyrosine in the blood should increase. Indeed, in the blood of patients with liver pathology the level of tyrosine is increased [19].

However, since the end of 1958, an increased level of blood tyrosine has been noted by many researchers (mainly in the USSR) in various diseases besides collagenoses and rheumatism: in acute leukemia, pneumonia, etc., including patients with normal functions of the liver [20, 21]. It was most likely that such a nonspecific increase in the blood level of

tyrosine could be caused by an insufficient entrance of GC hormones to the liver and, accordingly, an insufficient hormonal provision of the body.

The systematic comparison of blood tyrosine levels with the introduction of GC preparations or with the levels of endogenous GC hormones was conducted by the author in 1973-1980 in some diseases (systemic lupus erythematosus, bronchial asthma, congenital adrenal hyperplasia) in cooperation with clinicians, and also in adrenalectomized rats. Tyrosine level was measured in blood serum by spectrophotometry, as described in the work [22].

In the XX century, these works were published only in Russian and were not continued. However, since GC drugs are still actively and widely used in medicine and the problem of their adverse effects is still urgent, I thought it expedient to republish the main results of these studies. The most interesting data, as well as references to the original Russian reports, were presented in English in the previous publications [23-25**]**. In the paper presented below, I would like to summarize briefly the most important results.

2. Experimental data

Young Wistar rats were subjected to bilateral adrenalectomy, and tyrosine level was measured in the blood samples taken from the tail tip of the adrenalectomized rats after their general condition became normal (judging by normalization of their body mass – beginning from the 7th day after the operation) after injection and withdrawal of hydrocortisone (Fig. 1).

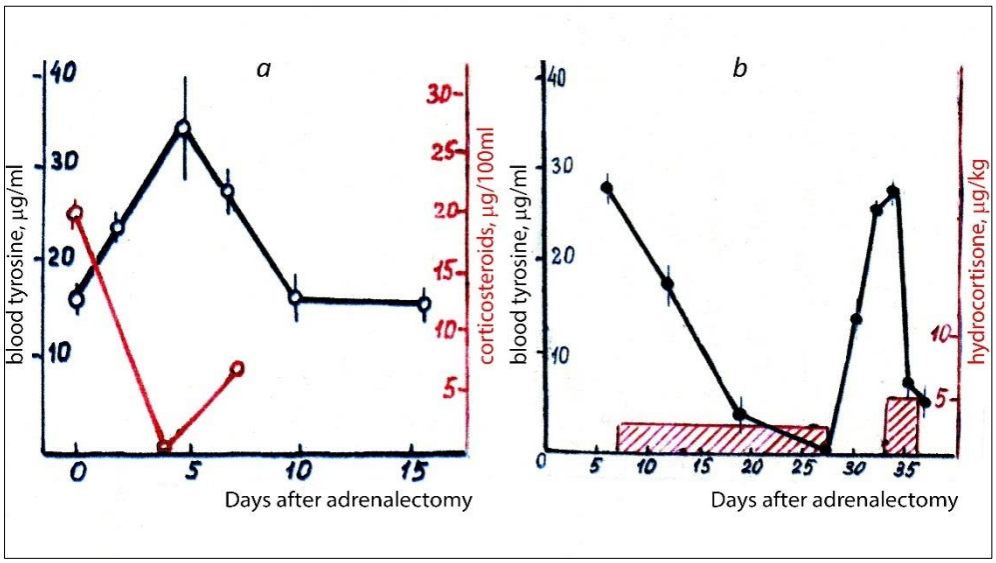

Figure 1 ***a)*** Changes in the blood levels of corticosteroid hormones (red curve) in rats after adrenalectomy (according to the work [26]) and in blood tyrosine level (black curve). (Secretion of corticosterone in the adrenalectomized rats recovers due to presence of the so-called "brown adipose tissue" capable of secreting corticosteroids). *b*) Changes in blood level of tyrosine (black curve) in the adrenalectomized rats after daily injectionsof hydrocortisone and its withdrawal(red patching).

Thus, Fig. 1 clearly shows that the blood tyrosine level depends on the entrance of corticosteroids (natural hormones or the preparation) into the animals.

3. Clinical models

Congenital Adrenal Hyperplasia, or Adrenogenital Syndrome (AGS), and Systemic Lupus Erythematosus (SLE) were studied as two fundamentally different situations of GC therapy.

I.The GC therapy in AGS is an example of substitutive GC therapy when GC drugs are given lifelong to compensate the insufficient synthesis of GC hormones in the adrenal cortex. AGS is caused by a genetically determined deficiency of enzyme(s) responsible for biosynthesis of GC hormones in the adrenal cortex that results in the excess synthesis of androgens. The insufficiency of GCs leads to hyperproduction of adrenocorticotropic hormone (ACTH), the constant

stimulation of the adrenal cortex, and the permanent hyperproduction of androgens. AGS manifests itself very early by the characteristic clinical picture, and GC preparations must be prescribed as early as possible to break the vicious circle and provide the normal physical and sexual development of the affected children. The dose of GCs must be strictly individualized and corrected regularly during the whole life of the patient [27, 28].

Just correcting the dose of GC preparations presents some difficulties, but on the other hand, in the affected children observation of the growth and sexual maturation allows the Pediatrician to assess rather objectively whether the dose of GC preparation is adequate for compensating the real requirements of the given child.

OurworkwasperformedattheInstituteofExperimentalEndocrinologyandChemistryofHormones (in collaboration with Prof. MA Zukovsky and Dr. ESKuznetsova). Under study were 38 children (33 girls and 5 boys, 3-18 years old). Itwas foundthat the blood tyrosine level was normal in the affected children with the complete clinical compensation and was increased in the non-compensated (or untreated) children (Fig. 2). It was interesting that blood tyrosine level was normal in three non-compensated children with the skin hyperpigmentation (it should be reminded that a part of free tyrosine is converted to melanin!). Prescribing GC drugs to untreated children with AGS led to decrease in the blood level of tyrosine, and the Pediatrician could rather easily choose the best individual regimen of GC therapy varying GC doses and regimen and measuring blood tyrosine level. Thus, the determination of tyrosine level makes it possible to simplifyand accelerate the finding the optimal individual dose of the hormonal drug for the given child.(The tyrosine-based correcting the GC dose in adult patients would be very useful, because for them there are no reliable laboratory parameters of the GC dose adequacy).

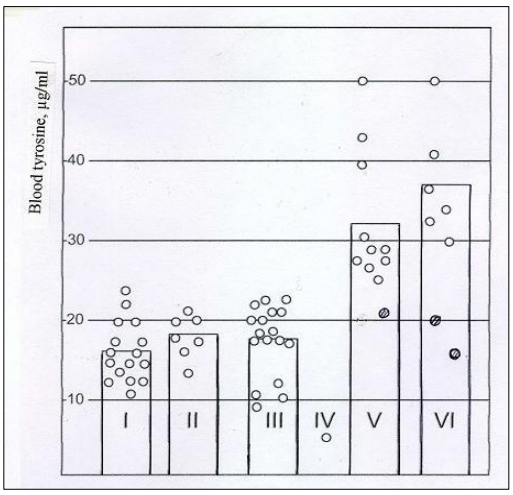

Figure 2 Blood levels of tyrosine in healthy donors and in children with AGS (the mean and individual values).I – Healthy adults; II – Healthy children; III – Compensated children with AGS; IV – An affected girl with overdosed GCs; V and VI – Non-compensated affected children (irregularly treated and untreated), the hatched circles correspond to patients with Melanodermia

Thus, in children with the inborn deficiency of GC hormones the normal blood tyrosine level indicated that the substitutive GC therapy really compensated the genetic defect and may be considered a representative indicator of the body provision with GC hormones.

II. Glucocorticoid therapy made it possible to save the life of many patients with systemic lupus erythematosus (SLE) [28]. In this severest collagenosis all therapeutic properties of GC preparations are realized: anti-inflammatory, anti-allergic, anti-immune; but the side effects are also virtually inevitable. At the extremely rich experience of GC therapy in SLE, the clinicians are forced to acknowledge that "*the use of glucocorticoids in systemic lupus erythematosus…after 60 years is more an art than science*" [29] and that the problem of glucocorticoid use in lupus "*hasn't gone away*" [30].

In our work, carried out at the Clinic for Therapy and Occupational Diseases, I Moscow Medical Institute (in collaboration with Dr. IA Borisov, Dr. TA Nikishova, and Prof. VV Sura), 80 patients with SLE were under study during four years. Tyrosine levels were determined in blood samples taken for biochemical analysis, usually every 7-14 days. After the patients were discharged from the Clinic, the tyrosine level behaviors in their blood were compared with the records in their stories concerning the regimen of given therapy and clinical and laboratory data during the hospitalization. Thus, this study may be considered a "retrospective experiment".

The most interesting were the observations on **32** patients with SLE who were given an increased dose of GCs because of clinical exacerbation of the disease. In **20** patients GC drugs were given on the background of elevated tyrosine, and in **17** of them the effect of GCs was positive and the level of tyrosine decreased in **13** concurrently with the improvement of clinical and laboratory parameters; side effects appeared ***after reaching*** the normal level of tyrosine, i.e. ***after normalization*** of the tissue provision with GCs. In **12** patients GC drugs were given on the background of normal blood tyrosine: in **9** of them no clinical effect was observed, but in **4** patients ***side effects*** appeared rapidly.

These data are also presented below in the Table.

Table 1 Changes in blood tyrosine level and effect of GC therapy in patients with SLE upon prescribing GC preparations

Blood tyrosine (μg/ml) on prescribing GCs	**Number of patients**	**Results of GC therapy**		**Changes in blood tyrosine level**	
		Improvement	**Absence of effect**	**Decreased**	**Without changes**
Elevated	20	17		13	4*
49.1 ± 0.8			3	bot h be	h av i ors
In normal limits	12	3**		3	
< 2.65			9		9(4***)

Note: *signs of the liver affection; **a slight improvement, possibly, due to other cytostatics and/or heparin; ***a rapid appearance of side effects

Thus, GC therapy in SLE was favorable when prescribed on the background of elevated blood tyrosine levels, i.e. at the insufficient hormonal supply, and was ineffective on the background of normal level of tyrosine, i.e. at the sufficient provision with GCs (all patients under study received supporting doses of GCs). The side effects caused by hypercorticism were observed at the normal tyrosine level, i.e. at the sufficient hormonal provision.

4. Conclusion

Blood tyrosine level may be considered a representative index of tissue provision with glucocorticoids, natural hormones or preparations (on taking into account the functional competence of the liver !).

However, this observation is insufficient for introducing blood tyrosine level as a laboratory parameter suitable for using in clinical practice. Certainly, the clinician has to clearly understand the physiological role of GC hormones in health and disease, and on usingGCpreparations as anti-inflammatory drugs, it is fundamentally important to remember about thefunctional duality of GCsand not neglect their regulatory action onmetabolic processes. The synthesis of hepatic tyrosine aminotransferase *in vivo* and *in vitro* is a well-studied, demonstrative, and representative example of a GC-dependent enzyme. TAT cannot be measured in blood, but it determines the blood level of tyrosine which may be considered an index of the body provision with GCs (natural hormones or preparations).

Introduction of blood tyrosine as a laboratory parameterfor monitoring GC therapy seems promising for reducing the risk of the side effects and probably for avoiding them.Certainly, it is necessary to develop schemes which would allow a clinician to use results of blood tyrosine determination in his therapeutic practice. It is not necessary to measure blood tyrosine for determination the requirement for GCs at the acute state of a patient (even a high single dose of GCs usually is not dangerous), but the monitoring of next doses of GCs would be extremely useful. It is important to develop schemes for prolonged GC therapy and especially for decreasing the dose.In any case, the tyrosine-based monitoring of GC therapy seems promising, but it has to be strictly individualized.

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