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Age- and Sex-Related Characteristics and Mechanisms of Adaptations during the Prepubertal and Pubertal Periods of Development

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Abstract—Integrated study of the functional state of the sympathoadrenal system and the adrenal cortex in children of both sexes aged 10–15 years. The study was conducted on the basis of the daily adrenaline, noradrenaline, 17-ketosteroid, and 17-oxycorticosteroid excretion values, which allowed certain synchrony to be established in the manifestation of the activity of the transmitter link of the sympathoadrenal system and the adrenal cortex androgenic and glucocorticoid functions with age, during sexual maturation. The heterogeneous character of maturation was found in the sex groups: in girls at an age of 10 and 12 years and in the boys at an age of 14–15 years. Changes in the excretion of the hormones and hormone metabolites with different directions and rates in the age–sex groups were observed throughout the academic year. In 14- to 15-year-old boys, a sharp increase in the daily excretion of the glucocorticoid metabolites accompanied by a substantial decrease in the age-related noradrenaline excretion values and the sex hormone metabolite values at an age of 15 years was observed. In the girls, these values varied within the age range, which indicates a more perfect character of the neuroendocrine regulation of their physiological functions in the period of sexual maturation.

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INTRODUCTION

During the postnatal life of humans, their genetic program is executed, and the level of physical and sexual maturity is achieved at which reproduction is possible [1]. This occurs in concert with the hormonal functions and their central nervous regulation. According to the principle of heterochrony of development of functional systems [2], at every stage of ontogeny, the neuroendocrine mechanisms necessary for vital functions and the optimal adaptation of the body to the age-specific conditions of life are the first to mature. The nervous and hormonal mechanisms of the sympathoadrenal system (SAS) and the pituitary–adrenal system actively interacting at different levels play an exceptional role in this process [3–12]. Due to their mobilizing, homeostatic, and tonic role, catecholamines (CAs) and corticosteroids (CSs) are involved in the adjustment of the body and in all interrelations with its autonomic functions [13–16]. The SAS (its sympathetic part) is a nervous regulatory link that is necessary for the humoral mechanism of adaptive endocrine reactions to be triggered [17–19]. The pituitary–adrenal system plays the key role in the mechanism of transition of temporary adaptive responses into definitive, long-term adaptation, because CSs not only mobilize the plastic functions of the body, but also prevent excessive tissue responses to stress, through the temporary regulatory inhibition of the hormone synthesis [20–22]. In the process, the adrenal cortex (AC) androgens may act as a defensive mechanism lowering the high glucocorticoid level by the inhibitory influence on the enzymatic processes of the CS biosynthesis, thus warding off the danger of their catabolic effect on the body [23].

The neuroendocrine regulation of the functions of a child's body and its adaptation to physical and mental stress are characterized by relative immaturity and functional instability expressed in physiological variations in the production of hormones and neurotransmitters and a change in the sensitivity of the receptor apparatus of the nervous system and target tissues [24]. Of special importance in the development of the body is the adolescent period, when complex mechanisms of sexual maturation and a characteristic physiological hyperfunction of the hypothalamic region of the brain and the pituitary are triggered [25–30]. An increase in the production of adrenaline (A), noradrenaline (NA), their precursors, as well as AC glucocorticoids, mineralocorticoids, and androgens, combined with the pubertal enhancement of the thyroid function, causes a powerful flow of sympathetic impulses to different organs and systems, thereby increasing the stress and vulnerability of a child's body upon exposure to external unfavorable factors, e.g., physical and mental overwork, low physical activity, and emotional stress [31]. In this connection, adolescents run an increased risk of their physiological endocrine reorganization developing into endocrine and neurovascular dysfunctions [32, 33]. Despite the large amount of literature data on the age- and sex-related features of the functional maturation of the SAS and AC in children, they are very contradictory

[34–40]. They have mainly been obtained from sick children [41–43] and do not reflect the pattern of interrelations, the ratio between the functional activities of the SAS and AC in the process of development and learning activity of schoolchildren. Undoubtedly, a combined study of the functional state of the SAS and AC in adolescents will extend the knowledge on the neuroendocrine mechanisms of sex maturation from the point of view of the hypothalamic–pitutary–cortical–medullary interrelations. Understanding the patterns of the neurohumoral regulation of adaptations in modern schoolchildren is very important for the scientific basis of the system of health care of the growing generation.

Therefore, we studied the functional state of the SAS and AC in children aged 10–15 years as dependent on the age, sex, and stage of sexual maturation in the course of the academic year.

METHODS

Boys and girls aged 10–15 years from secondary school no. 143 of Kazan, classified with health groups 1 and 2, were enrolled in the study. A total of 42 girls and 39 boys were selected, and they were under constant observation for six years.

The state of the SAS was judged by the daily A and NA contents of urine using the fluorometric method [44]. The NA/A factor, whose increase or decrease indicates an increase in the activity of the neurotransmitter and hormonal link of the system, respectively, was used [45, 46]. The AC state was assessed by the daily urine concentration of 17-oxycorticosteroid (17-OCS), which is one of the main metabolites of cortisol, cortisone, and their derivatives, as well as by the level of excretion of 17-ketosteroids (17-KSs), two-thirds of which is synthesized from AC androgens (androstendione, dehydroepiandrosterone, etc.) and one-third, from gonad androgens [47]. The method based on Zimmerman's reaction with *m*-dinitrobenzene was used for determining 17-KS; the 17-OCS content was determined based on the reaction with phenylhydrazine after enzymatic hydrolysis [48]. The absolute excretion values and the relative values calculated per kilogram of body mass were analyzed. Daily urine was sampled three times during the academic year; age-related changes were assessed using the October data.

The stages of sex maturation were determined, according to Tanner's method, from the degree of maturation of secondary sex characteristics.

The data obtained were processed by the standard variation statistic methods using the Microsoft Excel Windows 98 software. The *T*-test based on Student's *t* test was used to assess the significance of the differences.

RESULTS AND DISCUSSION

The analysis of the age-related dynamics of the parameter values of the systems studied showed that the increase in the functional activity of the hormonal and neurotransmitter links of the SAS and the AC androgenic and glucocorticoid functions observed in children in the pubertal period of ontogeny manifests itself heterochronously in the sex groups (table). For example, the daily A excretion in children of both sexes changed insignificantly in the period from 10 to 15 years; we only noticed its increase in 14-year-old boys (0.97 μg/day, $p < 0.05$), which agrees with the concepts on an earlier maturation of chromaffine tissue in relation to sympathetic innervation in ontogeny [49] and is consistent with the data on its being completely established in children at an age of 7 to 10 years [50–52]. The changes in NA excretion were more distinct. It fluctuated, decreasing in boys aged from 12 to 13 years and increasing by 5.38 μg/day at 14 years ($p < 0.05$); in girls, the excretion of NA increased in the period from 11 to 12 years. Subsequently, it decreased in both sex groups. However, the NA excretion in schoolgirls had specific features: its maximal level was observed as early as 10 years of age, which does not exclude the pubertal NA increase of 3.77 μg/day $p < 0.05$) noticed earlier than in boys, at an age of 12 years. The functional activity of the sympathetic link of the SAS in girls manifests itself at an earlier age compared to boys and girls of the same age examined 15 to 25 years ago [37, 53]; this indicates the predominance of the nervous mechanisms of regulation in them and is considered to be more optimal for the maintenance of long-term excitation of physiological systems in children [24]. However, analysis of the relative A and NA excretion values shows them to decrease in the period from 10 to 15 years (except for boys aged 11 years, whose NA excretion per kilogram of body mass is higher than in 10-year-old boys). This is explained by the fact that the increase in its absolute value occurs against the background of a more considerable gain in weight in the prepubertal and pubertal periods. With age, boys showed a gradual Na/A ratio increase (with a certain decrease at the age of 13 years, when the NA excretion is relatively low), while in girls the greatest increase in this ratio occurs between 10 and 12 years. Against the background of heterochronous maturation of the SAS links, a change in the NA/A ratio reflects an increase in the activity of its neurotransmitter division with age in both sex groups [37, 38].

Comparative analysis of the state of the SAS and AC in children revealed a certain synchrony in the manifestation of their functional activity with age, which is most clearly seen in the case of the sympathetic link of the SAS and the glucocorticoid function of the AC. For example, from 13 to 14 years of age, a significant increment in the NA excretion in boys was accompanied by an equally substantial increase in the daily 17-OCS excretion of 1.59 μm/day ($p < 0.05$); on the contrary,

The excretion of catecholamines and metabolites of androgen and glucocorticoid in 10- to 15-year-old children ($M \pm m$)

Age, years	Parameters								
	adrenaline (A)		noradrenaline (NA)		NA/A	17-ketosteroid		17-oxycorticosteroid	
	μg/day	μg/(day kg)	μg/day	μg/(day kg)		μm/day	μm/(day kg)	μm/day	μm/(day kg)
	Boys								
10	7.26 ± 0.87	0.20 ± 0.01	19.75 ± 1.34	0.55 ± 0.03	2.72	14.47 ± 1.80	0.40 ± 0.01	5.59 ± 0.61	0.15 ± 0.01
11	7.35 ± 0.45	0.22 ± 0.01	20.58 ± 1.85	0.63 ± 0.05	2.80	18.67 ± 2.62	0.57 ± 0.03*	6.76 ± 0.62	0.20 ± 0.02*
12	7.38 ± 1.05	0.20 ± 0.01	21.97 ± 1.72	0.59 ± 0.03	2.97	20.42 ± 2.22	0.55 ± 0.03	6.47 ± 0.70	0.17 ± 0.01*
13	6.74 ± 0.35	0.15 ± 0.01*	18.04 ± 1.45	0.40 ± 0.02*	2.67	25.79 ± 1.45*	0.58 ± 0.03	6.00 ± 0.29	0.13 ± 0.01*
14	7.71 ± 0.86	0.14 ± 0.01	23.42 ± 2.00*	0.42 ± 0.03	2.94	29.19 ± 1.76	0.53 ± 0.02*	7.59 ± 0.55*	0.13 ± 0.01
15	7.61 ± 0.91	0.12 ± 0.01	22.82 ± 1.35	0.37 ± 0.01	2.99	38.04 ± 2.94*	0.61 ± 0.03*	10.07 ± 0.85*	0.16 ± 0.01*
	Girls								
10	7.02 ± 0.34	0.20 ± 0.01	19.86 ± 1.81	0.51 ± 0.03	2.80	15.26 ± 1.42	0.45 ± 0.02	6.97 ± 0.96	0.13 ± 0.01
11	6.53 ± 0.31	0.17 ± 0.01*	15.70 ± 1.01*	0.46 ± 0.02	2.40	17.83 ± 1.94	0.48 ± 0.02	5.21 ± 0.41	0.15 ± 0.01
12	6.71 ± 0.53	0.15 ± 0.01	19.47 ± 1.58*	0.39 ± 0.02*	2.90	22.86 ± 1.32	0.55 ± 0.03*	6.95 ± 0.51*	0.15 ± 0.01
13	6.35 ± 0.24	0.14 ± 0.01	18.32 ± 2.01	0.42 ± 0.03	2.88	23.02 ± 1.84	0.50 ± 0.02	6.56 ± 0.87	0.15 ± 0.01
14	6.13 ± 0.35	0.12 ± 0.01	17.49 ± 1.86	0.36 ± 0.02*	2.85	28.31 ± 1.58*	0.55 ± 0.03	6.72 ± 0.79	0.13 ± 0.01
15	5.86 ± 0.30	0.10 ± 0.01	16.71 ± 1.20	0.30 ± 0.02*	2.85	35.24 ± 2.84*	0.64 ± 0.03*	8.18 ± 0.78	0.14 ± 0.01

* The difference from the previous age group is significant at $p < 0.05$.

from 12 to 13 years, these parameters tended to decrease. In girls, the earlier maturation of the neurotransmitter link of the SAS accompanied by the highest daily NA excretion at 10 years of age was combined with no less intense excretion of glucocorticoid metabolites, which was 1.33 times higher than in 11-year-old girls; at an age from 11 to 12 years, both variables increased ($p < 0.05$). Along with this, we found opposite changes in the parameters in question: the tendency for the NA excretion to decrease in boys aged 15 and in girls aged from 13 to 15 years does not agree with a sharp increase in the activity of the AC androgenic and glucocorticoid functions at this age: the increment in the daily 17-KS and 17-OCS excretions in boys aged from 14 to 15 years was 8.85 ($p < 0.05$) and 2.48 μm/daily ($p < 0.05$); in girls, 6.93 ($p < 0.05$) and 1.46 μm/day, respectively, which was accompanied by an increase in their relative excretion values and characterized this age as a period of active development of the AC androgenic and glucocorticoid function. Opposite changes in androgenic and glucocorticoid excretions was observed in the group of boys: against the background of a progressive, linear increase in the 17-KS content, the tendency towards a decrease in the 17-OCS concentration with age was observed between 11 and 13 years. This is likely to reflect the biological antagonism between androgens and glucocorticoids exerting a protein-anabolic and a catabolic influence on the body [54] and gives evidence for an increasing role of AC androgens and gonads in the regulation of growth [27, 28]. The results of the work agree with the earlier data that indicate negative correlation of the 17-OCS content and positive correlation of the 17-KS content with the growth rates of schoolchildren aged 11 and 15 years [55]. It is necessary to note an earlier activation of the AC androgenic function in the girls compared to the boys, i.e., at the age of 12, when a significant increment in the 17-KS excretion (5.03 μm/day, $p < 0.05$), which indicates an important role of androgens in the physical and sexual maturation of the female body [29, 30, 56].

Since the development of the neuroendocrine system in the adolescent period is mainly determined by

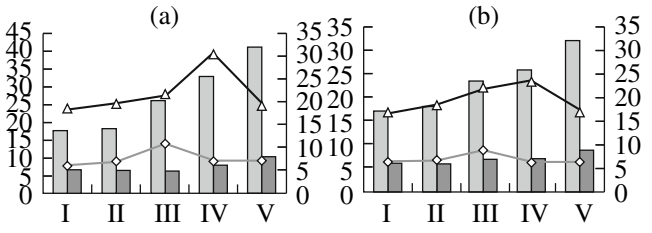

Fig. 1. Excretion of adrenaline (A, diamonds), noradrenaline (NA, triangles), 17-ketosteroids (17-KS, light bars), and 17-oxycorticosteroids (17-OCS, shaded bars) in (a) boys and (b) girls at different stages of sexual maturation. Abscissa: the stages of sexual maturation. Ordinate: on the left, the excretion of 17-KS and 17-OKS, μm/day; on the right, A and NA, μg/day.

the level of sexual maturity, the functional states of the SAS and AC were studied not only as related to age, but also as related to stages of sexual maturation in different sex groups (Fig. 1). It was established that the functional activity of the SAS links (the AC androgenic and glucocorticoid functions) and their ratio change as children mature sexually. For example, from stage I to stage III, unidirectional, positive shifts were observed in the studied values in both sex groups: A and NA excretions in boys increased by 4.77 ($p < 0.05$) and 3.09 μg/day; in girls, by 2.66 ($p < 0.05$) and 5.18 μg/day ($p < 0.05$), respectively. In addition, a significant increment in the 17-KS excretion was observed in both sex groups; i.e., the morphofunctional shifts in the hypothalamus–pituitary structures leading to changes in the activity of peripheral glands are accompanied by a sharp increase in the functional activity of the hormonal and neurotransmitter links of the SAS. This suggests a close functional interrelationship between the SAS and AC and their mutually enhancing biological effects in adolescents at the stage of gonad activation. At stage IV of sexual maturation, characterized by vigorous formation of both the adrenal cortex and the gonads [28], specific features were found in the sex groups: in boys, we observe a substantial 17-KS and 17-OCS ($p < 0.05$) increase associated with an increasingly higher excretion of NA, which is likely to cause, along with other CNS neurotransmitters, humoral transmission of nervous influences at the hypothalamic level and, as a consequence, activation of the AC [18, 19]. In girls, relative stabilization of these values with a decline in excretion A was found. At stage V of sexual maturation, the changes in these parameters in both groups were opposite: the daily NA excretion decreased, with the A level being stable, and the excretion of 17-KS and 17-OCS continued to increase by 9.24 and 2.44 and by 6.77 and 1.90 μm/day in boys and girls, respectively. This indicates that the pubertal formation of the pituitary–adrenal system was incomplete in the children studied, which agrees with the literature data on later pubertal changes in the regulation of the pituitary–adrenocortical system, with the definitive levels of the cortisol and dehydroepiandrosterone concentrations established only at an age of 21 years [28].

We carried out analysis of the functional state of the SAS and AC throughout the academic year, in the course of which it was rather difficult to take into account the relative influence of internal and environmental factors on the child's body; these included the age-related changes, mental and physical stress, and seasonal variations in the activity of neuroendocrine regulation, which were interconnected and affected one another. It was established that the level of excretion of the hormones and hormone metabolites studied varied during the academic year; the ratio of their functional activity was different in the age–sex groups (Fig. 2). Specifically, in 14-year-old boys, the excretion of CA and glucocorticoids throughout the academic year was characterized by relative stability with a strong tendency of the NA level to increase at ages of 11 and 13 years from October to May, as distinct from androgens, whose excretion, beginning at the age of 12 years, significantly increased (except for the 15-year-olds), reflecting the age-related tendencies of the formation of the AC androgenic function and gonad activation [39, 54]. This was the most pronounced at the age of 14 years, when the increment in the of 17-KS excretion was 10.27 μm/day ($p < 0.05$) compared to October. We noted undulatory changes in the androgen metabolite excretion during the academic year in boys aged 12, 13, and 14 years, with a decline in its rate in winter and a rise in spring ($p < 0.05$), which is supposedly explained by seasonal fluctuations in the functional activity of the adrenals and sex glands and is consistent with the notions on the neuroendocrine seasonal rhythms [57, 58]. We noted that in boys aged 14 and 15 years, against the background of an age-related increase in NA excretion (table), it decreases significantly by 5.09 and 6.02 μm/day ($p < 0.05$) at the end of the academic year compared to its beginning, at the former and the latter ages, respectively. This fact suggests, on the one hand, an increase in the activity of the nervous link of the SAS in the pubertal period and, on the other hand, the low efficiency of its functioning in the process of academic activity of the adolescents [37, 46]. The changes in the AC glucocorticoid function were the opposite: the 17-OCS excretion, which was, in 14- and 15-year-old boys, 7.59 ± 0.55 and 10.07 ± 0.85 μm/day at the beginning of the academic year, increased at the end of the academic year, exceeding its age-specific norm by a factor of 1.5. This may indicate a long-lasting and significant exertion of the adrenal–pituitary system, which is known to be accompanied by a decrease in the sensitivity of central corticosteroid receptors to the inhibitory effect of cortisol [7, 59], a sharp increase in its blood content, and increased degradation. Despite the fact that the glucocorticoid increase is the main adaptive reaction of the body, an increased cortisol level is dangerous due to its catabolic influence on the child's body, the suppressing action on the lymphoid tissue and immune reactions [24, 54]. Moreover, a high CS concentration may cause inhibition of androgen biosynthesis [60]; there-

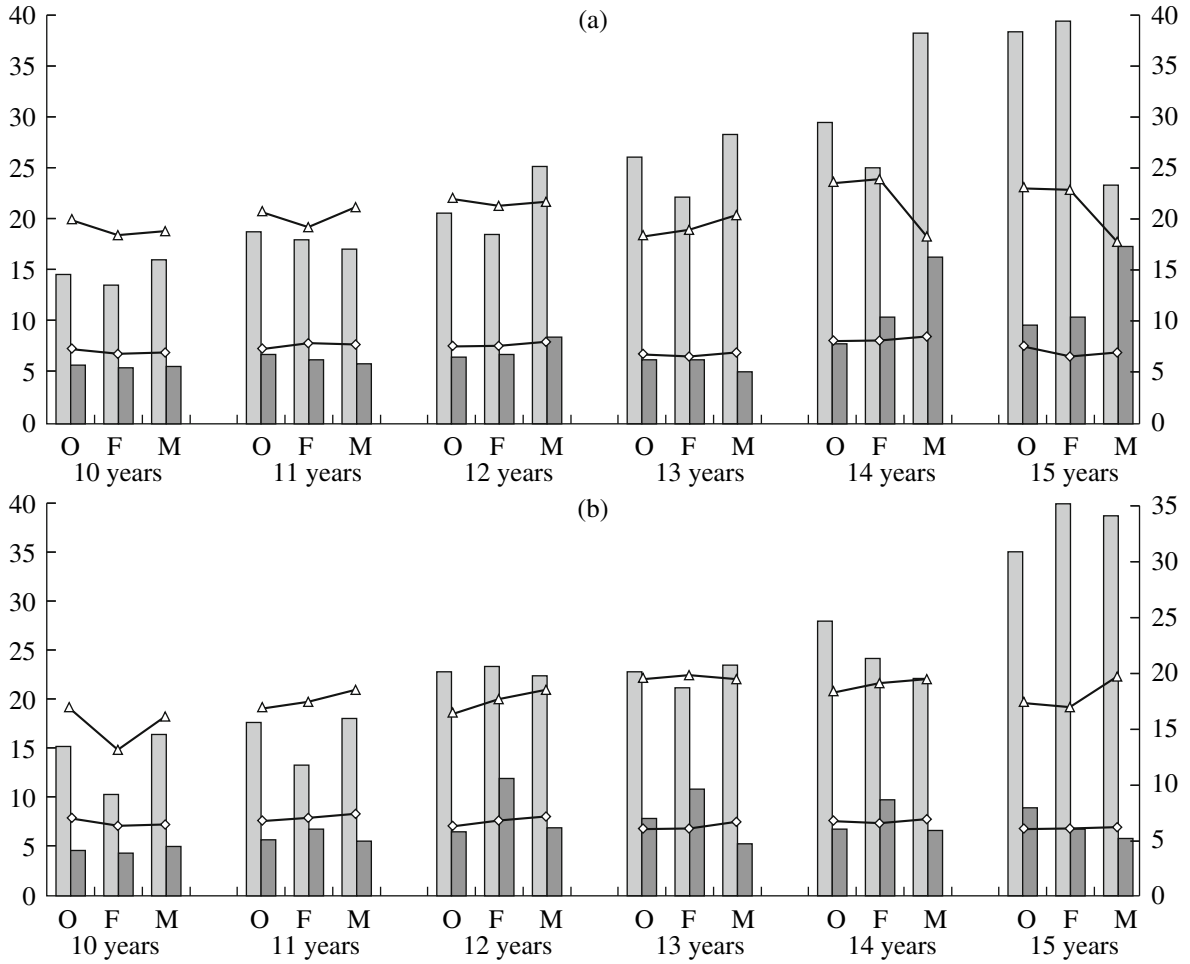

Fig. 2. The change in the excretion of adrenaline (A), noradrenaline (NA), 17-ketosteroids (17-KS), and 17-oxycorticosteroids (17-OCS) in (a) boys and (b girls aged 10–15 years during the academic year. Abscissa: the age (years) and the academic year period (O, October; F, February; M, May). Ordinate: on the left, the excretion of 17-KS and 17-OKS, μm/day; on the right, A and NA, μg/day. See Fig. 1 for the other designations.

fore, it is not ruled out that the sharp increase in the excretion of 17-OCS observed in 15-year-old boys led to a significant decline of the concentration of androgen, whose daily urine content at the end of the academic year was 28.19 ± 2.48 μm/day, which was significantly lower than at the beginning of the academic year and 1.4 times lower than the normal age-related values in 15-year-old schoolchildren. This is extremely unfavorable and may affect sexual maturation in boys [61, 62].

An entirely different situation was observed in girls: at all the stages of the study, the pattern of the daily NA excretion was stable, which, on the whole, agrees with its age-related trends (table) and indicates a high level of mobilization preparedness of schoolgirls, which is likely to be determined by the earlier maturation of the sympathetic link of the SAS. The daily excretion of glucocorticoid metabolites followed a marked oscillatory pattern: in 11- to 14-year-olds, we observed an increase in 17-OCS in the period from the beginning to the middle of the academic year ($p < 0.05$) and a decrease in their excretion in the period from February to May, especially pronounced at 13 and 14 years of age ($p < 0.05$). The danger of exhaustion of glucocorticoids against the background of stable tonic sympathetic influences (the α-adrenoreceptor mechanism at the hypothalamic level simulating the secretion of corticoliberin as a consequence of the excessive catabolic influence of adrenocorticotropic hormone and glucocorticoids [63, 64], especially in the pubertal period) is likely to be prevented in 12- to 14-year-old girls by the temporary regulatory inhibition of the hormone synthesis (and a decrease in 17-OCS excretion) observed at the end of the academic year. This is regarded as an important defensive response of a child's body aimed at preserving the adaptation reserve and increasing the total resistance [65]. The androgen pattern in girls was stable enough and did not coincide with periodic variations in the glucocorticoid excretion values. Schoolgirls aged 15 years are an exception, in whom the change in the excretion of these metabolites was the opposite: a drastic increase in the 17-KS concentrations and their

high values throughout the academic year (varying between 35.24 ± 3.10 and 40.28 ± 1.94 μm/day) were observed in combination with a decrease in the excretion of glucocorticoid metabolites, the decrement being 2.04 μm/day from the beginning to the end of the academic year ($p < 0.05$). This agrees with the concepts on the inhibitory influence of androgens on the enzymatic processes of steroid biosynthesis in the adrenals [60, 66]. In addition, AC androgens may control stable adaptation [23] by lowering, in this case, the high glucocorticoid level in girls.

CONCLUSIONS

Thus, this study showed that the sexual maturation and academic activity of 10- to 15-year-old adolescents are ensured by complex, interdependent reactions of the SAS and AC, which confirms the literature data on the presence of a close functional interrelation between CA and CS at different levels of the neurohumoral regulatory mechanism. Along with a certain synchrony in the functional activity of the neurotransmitter link of the SAS and the AC androgenic and glucocorticoid functions, we note their heterochronic maturation in the sex groups, as well as different rates and oppositely directed changes in the excretion of NA and androgen and glucocorticoid metabolites during the academic year, which testifies to the characteristic features of the neuroendocrine mechanism of adaptive activity in boys and girls in the period of sexual maturation.

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