Journal of Steroid Biochemistry, 1975, Vol. 6, pp. 869–872. Pergamon Press. Printed in Great Britain.

ROLE OF ADRENAL STEROIDS IN THE REGULATION OF GONADOTROPIN SECRETION AT PUBERTY

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SUMMARY

Plasma levels of androstenedione (Δ^4), testosterone (T), estrone (E_1), and estradiol (E_2), were measured by specific radioimmunoassays in 109 normal subjects, 55 boys and 54 girls 3·5 to 16·3 years of age, and were correlated with maturational parameters such as bone age (BA) and Tanner's stage of sexual development (P). Plasma levels of Δ^4 and E_1 show a significant increment earlier in females than in males, and increase earlier than those of T or E_2 in females. A better correlation was consistently found between plasma levels of Δ^4 or T and BA or P both in males and females.

Plasma levels of Δ^4, T, E_1 and E_2 were also measured in 8 boys and 10 girls undergoing testing with LH–RH for various disorders of sexual development, and were correlated with the maximum plasma LH increment (ΔLH) observed after LH–RH. In these patients a better correlation was found between ΔLH and plasma levels of Δ^4 in males, and between ΔLH and plasma levels of Δ^4 or T in females than between ΔLH and T in males and ΔLH and E_2 in females.

These data seem to indicate that the adrenal gland, through "adrenal" sex steroids such as Δ^4 and E_1, plays a role in the triggering and the maintaining of sexual maturation.

Despite exhaustive work done by various researchers in recent years, the intimate mechanism responsible for the advent of puberty is still unknown. Paradoxically, the more information we gather about the physiology of puberty the more we seem unable to grasp the "primum movens" of pubertal development. The advent of radioimmunoassays for gonadotropins has made it possible to delineate the pattern of their secretion throughout infancy, childhood, and adolescence. In turn this has brought about the discovery that gonadotropin levels start to rise prior to any evidence of secondary sexual development, and that in human females they are high at birth to decline thereafter until 2 to 8 years of age [1–4]. The significance and the cause of these fluctuations are matter for speculation.

More recently radioimmunoassays have become available for the determination of plasma levels of steroids, and a few papers have already appeared on the variations of some sex steroids throughout puberty [5, 6]. On the other hand, some authors have advanced the hypothesis that adrenal steroids may be involved in the onset of puberty in animals as well as in humans [7, 8]. In particular, it has been suggested by Ducharme *et al.* [9] that the sequential increase observed in both sexes in plasma levels of adrenal steroids, such as dehydroepiandrosterone (DHA), androstenedione (Δ^4) and estrone (E_1), during the prepubertal period, may be responsible for the change in the gonadostatic threshold which ushers the onset of pubertal development.

In order to determine more precisely the intimate mechanism of puberty, relationships between plasma levels of adrenal and gonadal sex steroids and various indices of sexual maturation were studied.

MATERIALS AND METHODS

In the first part of this study, plasma levels of androstenedione (Δ^4), testosterone (T), estrone (E_1) and estradiol (E_2) were determined by radioimmunoassay [10, 11] in 109 normal subjects, 55 boys and 54 girls 3·5 to 16·3 years of age. This was done in collaboration with Dr. J. Bertrand's group in Lyon, France. The normal subjects were submitted to a thorough physical examination, and sexual maturation was staged according to the method of Tanner [12]. In the second part of the work, plasma levels of Δ^4, T, E_1, and E_2 were determined in 8 boys and 10 girls undergoing testing with the luteinizing hormone releasing hormone (LH–RH, 100 μg sc) for various disorders of sexual development as shown in Tables 1 and 2. In these patients, plasma levels of LH and FSH were determined by radioimmunoassay [13, 14] using LER 907 as pituitary reference preparation.

RESULTS

Figure 1 shows that although plasma Δ^4 levels rise progressively with age in both normal male and

TABLE 1. PLASMA HORMONE VALUES IN MALE SUBJECTS TESTED WITH LH-RH, 100 μg s.c.

Subject	CA[1]	BA[2]	P[3]	Diagnosis	LH	FSH	Δ^4[4]	Δ^4FSH[4]	E_1	E_2	$\hat{\Delta}$	T
					ng/ml				ng/100 ml			
K.R.	7.6	8.0	1	Obesity, idiopathic gynecomastia	20	<25	30	140	5.1	-	17	9
P.M.	9.6	9.5	1	Cryptorchidism unilateral	12	48	43	407	2.8	7.1	98	10
C.T.	9.4	12.5	1	Obesity, micropenis	14	<25	24	170	11.8	7.2	25	10
M.P.	15.5	12.5	2	Delayed puberty	36	282	211	845	10.5	3.1	64	208
A.R.	14.0	9.0	2	Delayed puberty	<12	47	155	57	5.2	1.5	28	56
P.R.	14.9	13.0	1	Delayed puberty	55	160	251	340	2.9	-	52	24
P.T.	17.0	11.9	1	Delayed puberty	<10	66	265	224	0.4	-	111	67
Y.C.	14.0	14.0	5	Advanced puberty	57	77	140	73	-	-	79	589

1 Chronological age
2 Bone age
3 Tanner stage
4 Maximum increment after LH-RH

TABLE II. PLASMA HORMONE VALUES IN FEMALE SUBJECTS TESTED WITH LH-RH, 100 mg s.c.

Subject	CA[1]	BA[2]	P[3]	Diagnosis	LH	FSH	ΔLH[4]	ΔFSH[4]	E_1	E_2	Δ^4	T
					ng/ml				ng/100 ml			
M.M.	4.0	5.7	2	Precocious puberty	15	130	120	545	51.6	18.2	37	11
S.R.	6.0	7.5	2	Precocious puberty	23	55	42	795	-	-	54	12
L.B.	10.7	12.0	3	Advanced puberty	57	190	751	273	5.6	5.0	92	29
I.St.G.	18.8	13.5	4	Delayed puberty	< 12	110	95	590	5.7	5.6	92	18
L.T.	15.9	14.0	4	Delayed puberty	35	251	605	447	8.2	7.3	275	40
L.P.	15.1	12.0	2	Delayed puberty	19	57	301	195	11.5	4.1	100	22
L.N.	15.4	11.0	2	Delayed puberty	46	265	249	287	3.8	2.1	78	12
Y.G.	13.4	11.5	2	Delayed puberty	22	125	478	505	2.1	2.5	215	30
A.B.	16.2	17.0	5	Uterine agenesis	240	117	760	182	10.2	14.9	157	93
S.B.	16.1	18.0	5	Secondary amenorrhea	64	115	610	445	5.6	5.0	347	85

1 Chronological age
2 Bone age
3 Tanner stage
4 Maximum increment after LH-RH

female subjects, the first sharp increase occurs earlier in females (8–10 years of age) than in males (10–12 years of age). T levels rise abruptly in both sexes after 10 years of age, and in males continue to rise throughout adolescence as shown in Fig. 2. Plasma E_1 levels show a small progressive rise with age in males while, in contrast, a sharp rise is noted in females as early as 8–10 years of age (Fig. 3), which is concomitant with the abrupt rise of Δ^4. There is no sex difference in E_2 levels prior to 10–12 years of age when a significant increase occurs in females while in males an increase is noted only after 14 years of age (Fig. 4). As shown in Figs. 5, 6, 7 and 8, statistically significant correlations were consistently found, both in normal males and females, between plasma levels of Δ^4 or T and bone age (BA) or sexual maturation (P). The correlation was less consistent between E_1 or E_2 and BA or P. Figure 9 shows the correlations between the maximum increment of LH (ΔLH) after the administration of LH–RH and BA or P or plasma levels of Δ^4, or E_1 or E_2 in male subjects presenting with various disorders of sexual development. A significant correlation ($P < 0.05$) was found only

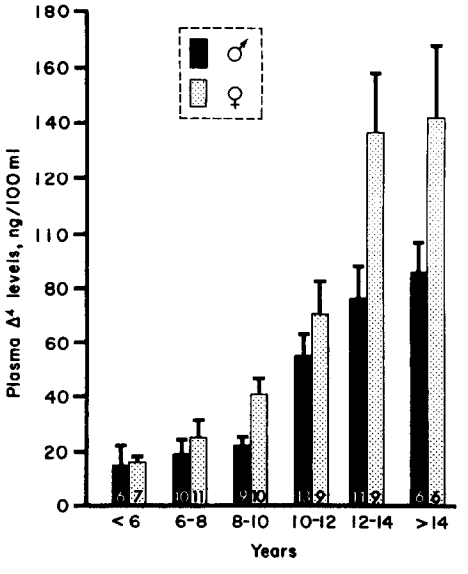

Fig. 1. Plasma levels of Δ^4 in normal male and female subjects of increasing age. Columns are means ± S.E. At the bottom of the columns are shown the number of subjects in each age group.

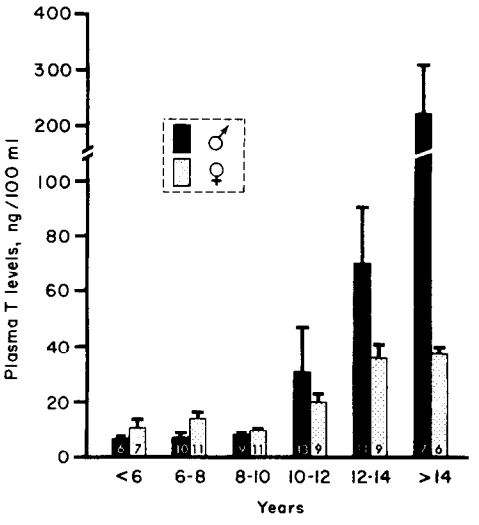

Fig. 2. Plasma levels of T in normal male and female subjects of increasing age.

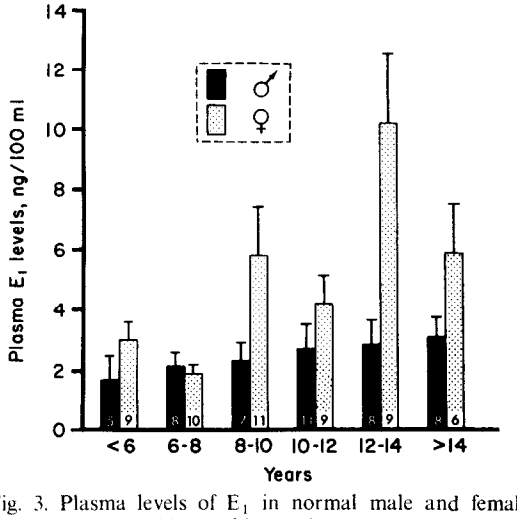

Fig. 3. Plasma levels of E_1 in normal male and female subjects of increasing age.

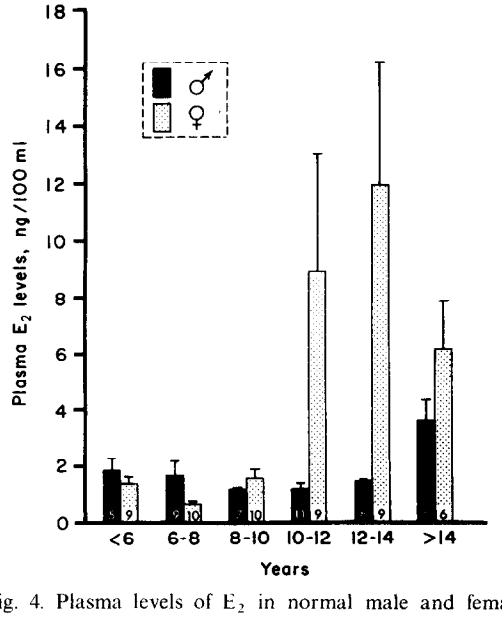

Fig. 4. Plasma levels of E_2 in normal male and female subjects of increasing age.

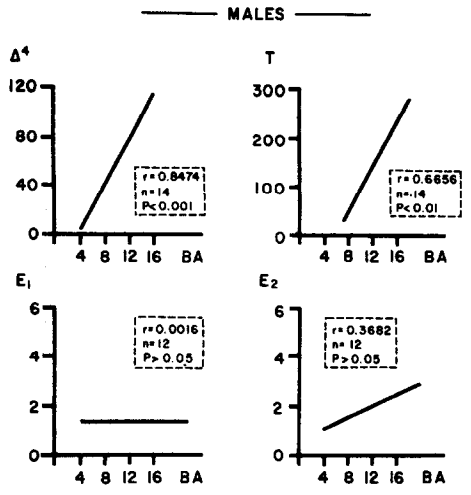

Fig. 5. Linear correlation between BA and plasma levels of Δ^4, T, E_1 and E_2 in normal male subjects.

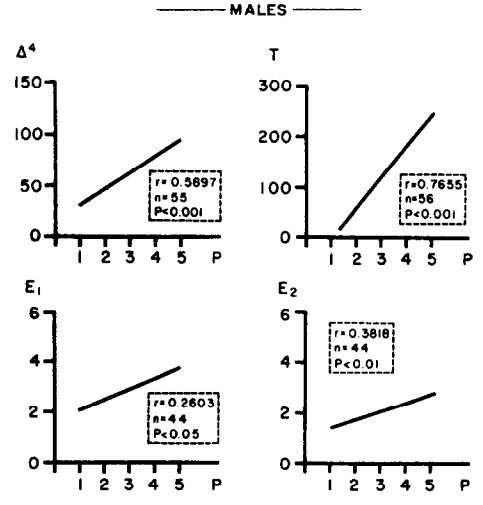

Fig. 6. Linear correlation between Tanner developmental stage P and plasma levels of Δ^4, T, E_1 and E_2 in normal male subjects.

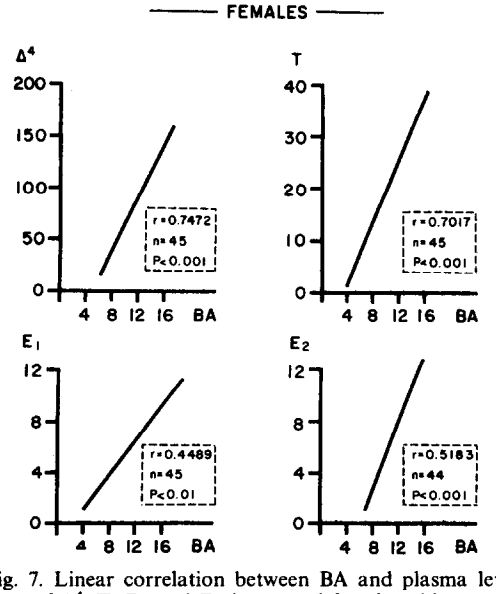

Fig. 7. Linear correlation between BA and plasma levels of Δ^4, T, E_1 and E_2 in normal female subjects.

between ΔLH and Δ^4. Figure 10 shows the same correlations in female patients. A statistically significant correlation was found between ΔLH and BA ($P < 0.05$), ΔLH and Δ^4 ($P < 0.05$) and ΔLH and T ($P < 0.01$).

DISCUSSION

Data obtained with normal subjects show the existence of an interesting correlation between plasma levels of some hormonal steroids and parameters of

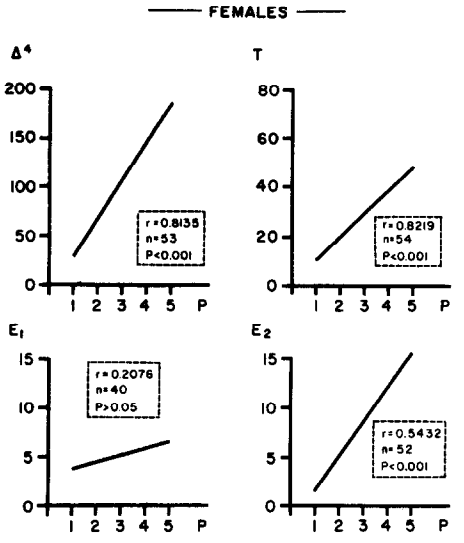

Fig. 8. Linear correlation between Tanner developmental stage P and plasma levels of Δ^4, T, E_1 and E_2 in normal female subjects.

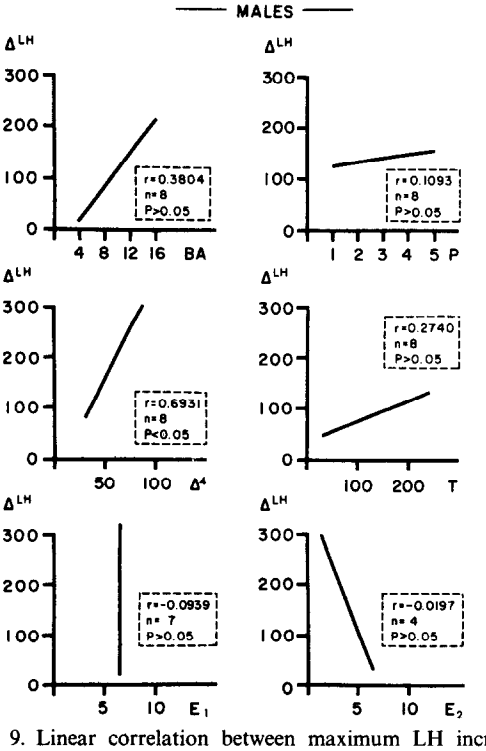

Fig. 9. Linear correlation between maximum LH increment during an LH–RH test (ΔLH) and BA, P, Δ^4, T, E_1 and E_2 in male subjects with various disorders of sexual development.

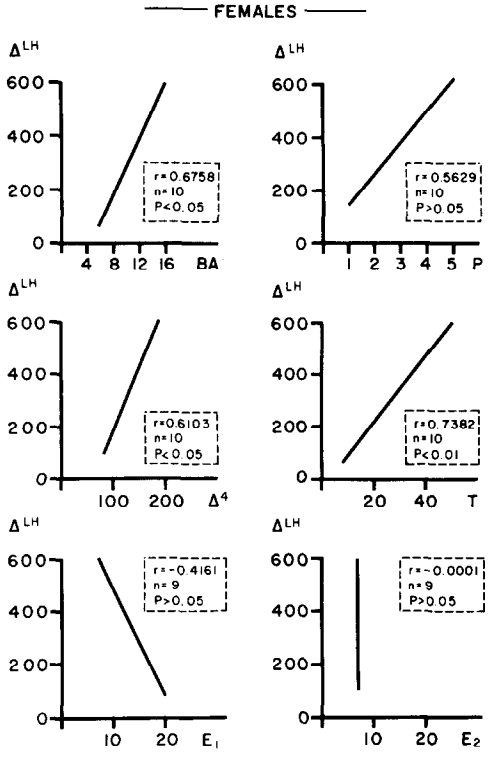

Fig. 10. Linear correlation between ΔLH and BA, P, Δ^4, T, E_1 or E_2 in female subjects with various disorders of sexual development.

sexual development. Plasma levels of Δ^4 and E_1 show a significant increment earlier in females than in males consistent with the earlier onset of puberty in girls. In females, plasma levels of these two sex steroids increase earlier than those of T or E_2. A better correlation was consistently found between plasma levels of Δ^4 or T and BA or P. These data seem to indicate that Δ^4, a steroid reflecting essentially the activity of the adrenal gland, is the best index of sexual maturation and, at least in females, the first to be significantly modified concomitantly with E_1. It is therefore tempting to speculate that Δ^4 and possibly E_1 may play a role in the maturation of the hypothalamus, the first significant increase in plasma Δ^4 levels being determinant in the activation of the hypothalamic-pituitary-gonadal axis. It is interesting to note that plasma levels of LH and FSH show the first significant increase between 9 to 12 years of age in females and between 11 to 14 years of age in males [1–4, 15]. Therefore, the increment in plasma gonadotropin levels occurs approximately 1–2 years after that of plasma Δ^4 levels, and approximately at the same time as that of T and E_2.

Data obtained with males and females presenting with various disorders of sexual development seem to confirm the existence of a close correlation between the activity of the adrenal gland and the activation of the hypothalamic-pituitary-gonadal axis. In effect, a better correlation was found between the maximum LH increment during a LH–RH test and plasma levels of Δ^4 in males, and between ΔLH and Δ^4 or T in female patients than between ΔLH and T in males and ΔLH and E_2 in females. Since it is well known that the LH response to LH–RH is closely related to sexual maturation [16], it appears therefore that even in subjects presenting with abnormalities of sexual development, indices of adrenal activity have a better overall correlation with sexual maturation than indices of gonadal activity.

In conclusion, data obtained with normal subjects and with subjects presenting with various disorders of sexual development seem to indicate that the adrenal gland is the first to be activated in the process of sexual maturation. In addition, all along this process, the activity of the adrenal gland, as indicated by the levels of Δ^4 in males and Δ^4 and T in females, is a better index of the different stages of pubertal development than gonadal steroids. These data seem to indicate that the adrenal gland plays a role in the triggering and the maintaining of sexual maturation.

Acknowledgments—This work was jointly supported by the Medical Research Council of Canada and La Fondation Justine Lacoste-Beaubien. The technical assistance of Ms. G. Alberti, D. Ivelja, J. Gaulin and N. Duff, and the secretarial help of Ms M. F. Rocheleau are gratefully acknowledged. The authors wish to thank Dr. C. Faiman for the gift of reagents for the radioimmunoassay of LH and FSH, and Dr. J. G. Rochefort of the Ayerst-McKenna Company for the generous supply of LH-RH.

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