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AGE, ENVIRONMENTAL FACTORS AND PROSTATIC CANCER.

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ABSTRACT

Although prostatic cancer is evident late in life, pathological evidence suggests this disease is initiated earlier in life. As prostatic cancer is an endocrine associated disease and as adult hormone profiles are established during puberty, it was of interest whether difference in pubertal hormone levels occurred in populations at low or high risk for prostatic cancer. Accordingly we have investigated the hormone profiles in rural Black South African and urban white boys during puberty. It has been suggested that the timing of puberty is modified by environmental factors and that there is a concomitant control of gonadotrophin release and food intake by CNS-peptide hormones. It is therefore postulated that dietary factors during puberty modify the gut-CNS peptide hormones which in turn control the hypothalamic-pituitary-testicular axis. Distinct difference in plasma androgen and gonadotrophins between the two races are in part concordant with a modification of CNS-peptide hormones by environmental factors during puberty.

INTRODUCTION

In a cancer conscious society, interest has arisen in the environmentally related cancers, especially those associated with lifestyle and diet (1) which are therefore preventable. A number of studies have associated dietary factors in western societies with increased risk of prostatic cancer (2-5). Epidemiological studies have reported a lower death rate from prostatic cancer in black South African (SA) men compared to white North American (NA) men (6,7). While the development of this disease has a multiple etiology, modification of the incidence of this endocrine related cancer by lifestyle and diet have been reported (8,9). Inspite of the fact that prostatic cancer develops late in life, pathological evidence suggests that latent lesions in the prostate are evident in younger men and that a western lifestyle is probably one of the factors which activate these lesions (10,11).

Rural black SA men who maintain physical activity until late in life and who eat a limited vegetarian diet have been reported to have a

lower excretion of androgens and estrogens than white men (12,13). Additionally in these men excretion of androgens is modified by socioeconomic status (14) and diet (15). Thus steroid hormone metabolism is different in the black SA men who are at low risk for prostatic cancer. While such differnces are not necessarily associated with prevention of this disease, changes in steroid hormone excretion are known to be associated with remission and relapse (16,17). Furthermore exercabation of androgen changes in black SA men with prostatic cancer fed a western diet has been reported (18). It is of interest therefore to find when during life the pattern of steroid hormone metabolism is established in black SA men.

A considerable amount of data is available on the changes in plasma steroid hormones during puberty (19,20) and a number of studies have addressed the hormone control of maturation of the hypothalamic-pituitary-gonadal axis (21,22). However, the CNS mechanism initiating puberty remains unknown. Similarly environmental factors initiating earlier maturation as in immigrants to Western Societies or when socioeconomic status is increased (23,24), remains unclear. It is therefore suggested that dietary factors modifying gut and CNS peptide hormones modify the hypothalamic-pituitary-gonadal axis altering the timing of maturation.

PROCEDURES

To determine, in non-western versus western societies, whether hormonal differences occur during puberty a comparison was made between urban black and white NA boys and rural black SA boys between 11 and 18 years of age. Black and white NA boys were recruited from schools in suburban New York where their dietary habits were determined using a modified health and nutrition examination survey (25). In rural black SA boys, dietary records are more easily quantified since the number of food items is limited and the meal pattern constant.

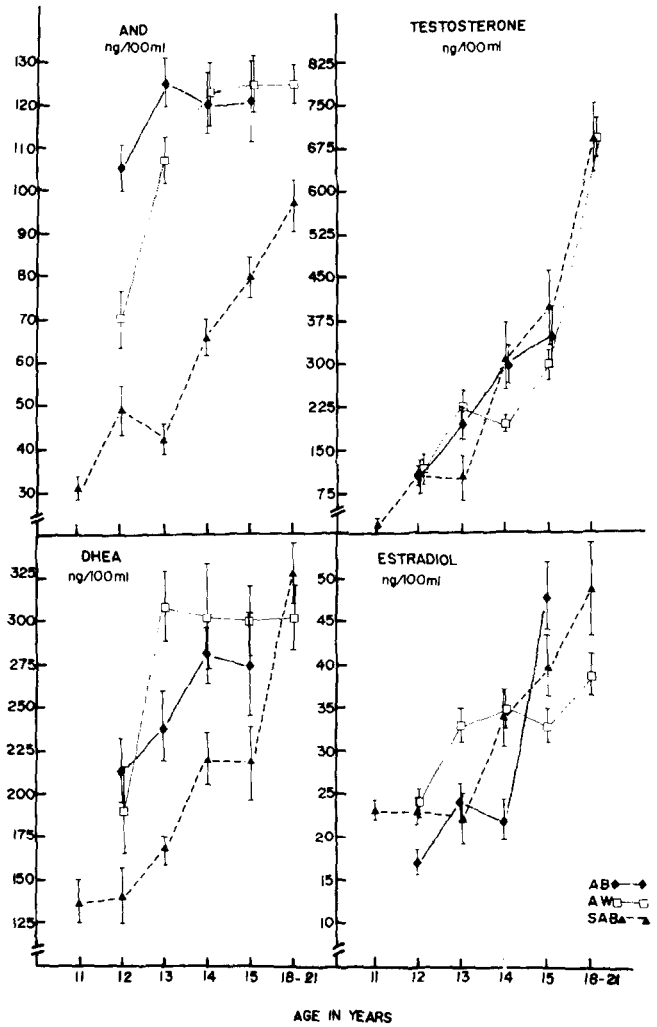
To ascertain plasma hormone concentrations in these boys,blood was drawn under standard conditions and steroid hormones and gonadotrophins determined by radio-immunoassay as described previously (26). The sensitivity, inter and intra assay variation of these methods are given below.

SENSITIVITY AND VARIATION IN ASSAYS OF PLASMA HORMONES

Hormone	Sensitivity	Intra assay variation(%)	Inter assay variation(%)
LH	2.5 mIU/ml	5	7
FSH	2.5 mIU/ml	5	7
Estradiol	2.5 pg/ml	8	10
Testosterone	0.1 ng/ml	5	10
DHEA	25 pg/ml	5	9
Androstenedione	10 pg/ml	9	10

RESULTS AND DISCUSSION

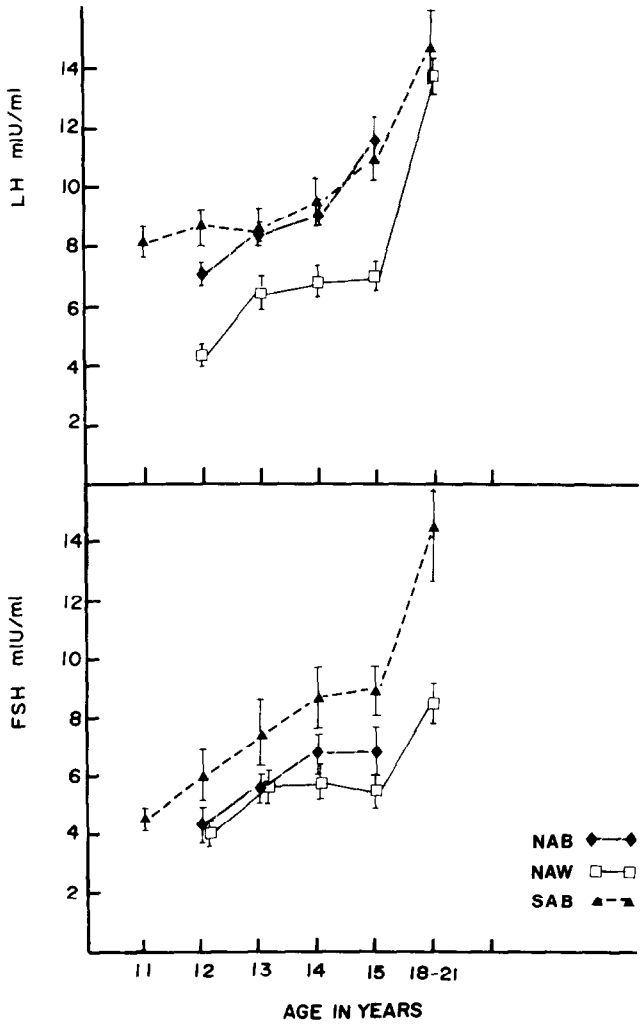
During puberty in white boys, androstenedione (19) and DHEA (27) have been reported to increase between 11 to 15 years before the increase in testosterone while LH increases prior to the increase in test osterone. In this study plasma testosterone at 12 years of age was comparable in the three groups of boys and increased progressively until 18-21 years.



Blood was drawn between 9 - 10 am using heparinized vacutainer. After centrifugation, plasma was stored at -80°C until analyzed. Each point represents a minimum of 15 boys. Results given as Mean ± SE.

Estradiol showed an earlier increase in white NA boys, being significantly higher at 13 years ($t=3.29, p \leq 0.01$). However, by 15 and 18 years, estradiol levels were significantly higher in black SA boys ($t=2.06$, $p \leq 0.01$; $t=2.08, p \leq 0.05$, respectively). Higher levels of estradiol have been reported in adult black SA versus white NA men (28). Interestingly DHEA and androstenedione were significantly lower in black SA boys ($F=16.4, p \leq 0.01$; $F=22.8, p \leq 0.01$ respectively. One way analysis of variance) while little increase in these androgens occurred earlier in white NA boys.

However, gonadotrophin concentrations were lower in white NA boys than black SA boys up to 15 years of age (LH: $F=23.6, p \leq 0.01$; FSH: $F=37.7$, $p \leq 0.01$ - one way analysis of variance).



Each point represents a minimum of 15 boys. Results given as mean±SE.

Thus the pattern of steroid hormones and gonadotrophins during puberty in white boys is similar to previously reported studies, while in black SA boys the sequence and timing of hormonal changes differs markedly.

As shown in Table I, black SA boys maintain a lower weight and shorter stature throughout puberty; rural black SA men being shorter than white.

TABLE I

WEIGHT AND HEIGHT OF SOUTH AFRICAN (SA) BLACK, NORTH AMERICAN (NA) BLACK AND WHITE BOYS

AGE	SAB(n=90)		NAW(n=100)		NAB(n=80)	
YEARS	WEIGHT	HEIGHT	WEIGHT	HEIGHT	WEIGHT	HEIGHT
12	32.1±0.9(a)**	142±0.9**	45.9±1.6	151±1.3	47.7±2.4	157±1.5
13	35.2±1.0**	146±1.0**	50.8±1.5	159±1.5	50.0±2.1	160±2.0
14	40.9±1.0**	151±1.1**	56.7±1.7	169±2.0	56.2±1.9	168±2.0
15	46.1±1.0**	159±1.1**	61.7±2.4	172±1.8	60.8±3.1	169±2.0
18-21	52.5±1.0**	168±0.9**	74.2±1.3	177±1.1	73.0±2.0	175±1.8

(a) Mean±SE **$p \leqslant 0.01$ Significantly lower in SA black boys

In regard to maturation, the increase in stature in Polish (23) and Japanese boys (29) and the comparable age of maturation of urban 'well to do' black SA and white children (24) implies environmental factors modify growth. As dietary factors, overall calorie intake and physical activity modify steroid and peptide hormone metabolism, life-style early in life appears to be crucial in the timing and outcome of maturation. Until recently little data associating diet and/or exercise to CNS activity has been reported. Evidence now associates CNS peptide hormones with the control of food intake (30,31) and the control of basal and episodic release of gonadotrophins (32,33). Many peptide hormones are present in the CNS and gut (34,35); their release from the gut being dependent on food intake (30,36,37). Consequently the gut-CNS peptide hormone profile depends on the fat, protein and carbohydrate content of the diet and therefore the nutritional status of the individual.

In obese women higher levels of plasma β-endorphins have been reported (38) while naloxone administration, an opioid antagonist, decreases food intake in obese women (39). Interestingly obesity initiates earlier pubertal development and concomitantly increases plasma DHEA (40). As β-endorphin suppresses the release of LH (41),elevated levels of β-endorphins could lead to a generalized hypothalamic-pituitary dysfunction which frequently occurs in obese women (42,43).

If in adult men, pulsatile release of LH is essential for testicular activity and spermatogenesis, changes in the episodic release of β-endorphin (44) will modify LH release. As high levels of plasma LH

cause testicular densitisation (45), this could occur during puberty in black SA boys as a result of low levels of β-endorphins. Low CNS β-endorphin levels may occur on a vegetarian diet or a diet associated with a low calorie intake, prior to puberty. While the relation of specific dietary components to CNS peptide hormones remains unclear, evidence indicates that diet modifies the episodic release of LH (46) and the LH release following LH.RH administration in women (47) and LH release in men (48).

Furthermore, since Wildt et al (49) reported the initiation of ovulatory cycles in prepubertal Rhesus monkeys with pulses of Gn.RH, it is apparent that the mechanisms controlling puberty may reside in the CNS.Subsequent use of an opiate antagonist, naloxone (50), or a super-active met-enkephalin analogue (FK 32,824) (51) and comparison of LH release after naloxone administration in early prepubertal boys and adult men (52) also indicate changes in CNS-opioid peptides occur during maturation.

Consequently as earlier maturation is associated with nutrition (23,24,29), diet must act on the higher CNS-centres and/or the feeding satiety control in the hypothalamus. In view of the numbers of CNS-peptide hormones and their different receptors involved in food selection and caloric intake (30) and the involvement of catecholamines and serotonin in gonadotrophin release, dietary components, fat, protein and carbohydrate may each act at more than one site.

Since ACTH and β-endorphin arise from a common precursor in the pituitary gland (53), concomitant changes in response to diet or exercise in the hypothalamic-pituitary axis and the adrenals may frequently occur. Recently Quigley et al (54) reported that a single meal caused a simultaneous increase in prolactin and cortisol. However, during maturation adrenache precedes gonadarche. Adrenache is associated with growth of the zona reticularis of the adrenals (55) and a possible increased response to ACTH (56) and is perhaps controlled by a CNS-peptide other than ACTH (57).

Whatever the mechanism an increase in plasma DHEA precedes the increase in plasma LH in Caucasian children. In black SA boys versus white boys, in this study high LH levels are associated with low DHEA and androstenedione levels. Interestingly, Parra et al (58) reported higher plasma levels of LH in underpriviledged Mexican boys up to 13 years of age who concomitantly had a two year delay in puberty when compared with 'well to do' Mexican boys. Thus in less socioeconomically advanced societies late maturation in children may be associated not only with an altered CNS-hypothalamic maturation but also delayed adrenal stimulation.

While prostatic cancer is a hormone dependent disease, specific hormonal changes associated with the development of this cancer are unknown. Despite this, in rural black SA men it is apparent that the interaction of environmental factors and hormone metabolism is associated with a low incidence of this disease.

It is therefore of interest that the rural black SA boys have a different sequence of hormonal changes during puberty than found in the white boys.

CONCLUSIONS

Consequently it is suggested that the vegetarian diet eaten by black SA boys and their fathers, maintains a gut-CNS peptide hormone profile which modifies the hypothalamic testicular axis maintaining plasma testosterone and sexuality until late in life.

While much is known of the feeding and satiety centres of the hypothalamus, little as yet is known of the gut-CNS peptide hormone balance which could modulate their maturation.

Study of the peptide hormones in early and late maturing populations would give leads on the relationship of diet to maturation and a hormone profile associated with a low risk of prostatic cancer.

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