Steroids after birth-puberty

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Summary

The production of gonadal steroids in the perinatal period may have an important influence on the later development of the hypothalamo-pituitary-gonadal axis. In the prepubertal period there is an increased output of gonadal steroids and of androgens from the adrenal cortex, with a further increase as the secondary sex characters develop. The precise role of individual steroids in the maturation of the reproductive system and of the neuroendocrine regulating mechanisms will probably remain unclear unless conclusions are based on longitudinal studies in which hormone production is related precisely to different parameters of sexual development and somatic growth.

Introduction

This paper is concerned with the role of steroids in the postnatal growth and development of children. Before puberty, steroids probably do not play an important specific role in growth although, of course, some are necessary for life. The output of C_{21} -steroids increases gradually with age but more or less in proportion to the increasing size of the child and they probably have only a permissive role in normal growth and development. Our concern, therefore, is essentially with androgens and oestrogens.

Sex steroids in the perinatal period

From the endocrine point of view, puberty, defined as the maturation of the gonads and the development of the secondary sex characters, is only the final stage in a long process of maturation. The early stages of this process take place before birth and are outside the scope of this paper. However, the production of hormones during the perinatal period by both the hypophysis and the gonads may have an important impact on the later development of the central nervous system and its regulation of endocrine function.

At birth, in normal and healthy boys, the concentration of testosterone in the blood of the umbili-

cal cord is significantly higher than in girls. This is true also of the peripheral blood (Forest *et al.*, 1974). In boys, the level falls during the first 5 or 6 days of life but it later rises dramatically to reach a new maximum in the region of 200 ng/100 ml at 1-3 months. The maximal levels attained at this stage vary considerably from one child to another but are similar to those found when the changes of puberty are well advanced. In infancy, however, the level begins to fall almost as soon as it has reached its maximum and is very low (about 7 ng/100 ml) by the age of about 7 months. The elevation in early childhood of the total testosterone corresponds to a genuine, although less dramatic, rise in the free, physiologically active, fraction of the blood testosterone. In girls, the picture is quite different. Levels in the cord blood at birth vary within the range 15-50 ng/100 ml but fall to normal prepubertal levels, with a mean of 7 ng/100 ml, in the first 1 or 2 weeks and this level is maintained throughout the first year of life.

Oestrone and oestradiol levels are elevated equally in the blood of both sexes at birth but fall rapidly within a few hours, after which there is a more gradual decline (Kenny *et al.*, 1973). During the second week of life, the girl's plasma oestradiol rises again to levels similar to those found when the changes of puberty are well advanced. The corresponding rise in boys is probably less great although there is a wide variation between individuals. Oestradiol levels apparently remain high throughout the second month and the fall to normal prepubertal levels is not completed until about the sixth month (Bidlemaier, Versmold and Knorr, 1974, cited by Forest *et al.*, 1975).

The interaction during early childhood of gonadotrophins and gonadal steroids, each regulating the output of the other, may play a part in setting the future pattern of hypothalamic activity which will regulate the endocrine system during puberty and adult life. However, there is insufficient evidence to raise this suggestion beyond the status of conjecture. An indication that the production of androgens and oestrogens in infancy is regulated by the central nervous system comes from the fact that plasma levels

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of gonadotrophin rise during the first 2 years of life. There is a significant sex difference, the FSH (follicle-stimulating hormone) levels being higher in girls than in boys, while during the first year, the boys have greater LH (luteinizing hormone) concentrations (Forest *et al.*, 1974). When the subjects were selected from the 0–2 year age range, both FSH and LH were higher in girls than in boys (Faiman and Winter, 1971). This observation was confirmed by Penny, Olambiwonnu and Frasier (1974) whose data suggest that the sex difference has disappeared in the 2–4 year age group. In boys, the concentrations of both FSH and LH rose significantly between the ages of 2 and 4 years while no significant change was observed in girls. The level of gonadotrophin is reduced by androgen while the testes secrete androgen in response to injections of chorionic gonadotrophin (Forest *et al.*, 1975).

Gonadal steroids in the prepubertal period and puberty

A satisfactory interpretation of the role of steroids in puberty would require data from longitudinal studies, i.e. repeated measurements of these hormones or their metabolites in the blood or urine of a single group of children. Detailed records of each child's height, bone age, and sexual development, when each sample of blood or urine was collected would also be necessary. Unfortunately, few longitudinal studies have been reported up to the present time and the information that they give about the relationship between steroid production and sexual development is not entirely satisfactory.

Endocrine studies, whose results are reported only in relation to age, are of limited value in this context because children vary widely in the ages at which they experience puberty. In some girls, the breasts begin to develop before the ninth birthday, but others have infantile breasts until they are in their fifteenth year. Pubic hair appears, on the average, about 6 months later than breast development begins, but in some children, pubic hair growth is well advanced before the breasts show any evidence of stimulation by oestrogens. The development of the breasts may be completed at any age between about 12 and 19 (Marshall and Tanner, 1969). The age at menarche (the beginning of the first menstrual period) is similarly variable and a range of approximately 11 to 15 years would include about 95% of European girls. In boys, the secondary sex characters begin to develop slightly later on average than in girls, but the range of variation is similar.

Clearly then, a child's age is not a satisfactory guide to his or her sexual development. For example, in a representative sample of 13-year-old girls, we should have a small percentage in whom the changes of puberty had not yet begun and another small percentage whose sexual maturation was complete.

The remainder of the sample would be at various stages between these two extremes.

Until recently, it was widely believed that the problem of varying maturation in children of any given age could be largely overcome by substituting bone age for chronological age, on the assumption that children with the same bone age would also be at the same stage of sexual development. However, Marshall (1974) has shown that this assumption is unjustified because the bone ages of children at most stages of sexual development are as variable as their chronological ages. Only at menarche did Marshall find that the bone age was significantly less variable than the chronological age. About 95% of girls experience menarche when their bone ages are between 13 and 14 years.

A further difficulty in interpreting the role of steroids in puberty arises from the limitations of the techniques available for their estimation. Reliable methods for estimating the amounts of most hormones in the blood have been developed only recently and the estimation of actual secretion rates from the endocrine organs is still largely impossible. We must also recognize the fact that biochemical assays of hormones in the blood or other fluids do not necessarily measure the amount of biological activity which is present. Ideally, chemical assays should be validated against bioassays but this is not always technically possible.

Testosterone

The amount of testosterone secreted in the urine increases gradually in the years before puberty, with little difference between the two sexes until the age of about 11 years. After this, boys exhibit a much greater increase than girls. In a longitudinal study, Faiman and Winter (1974) found that there was little rise in plasma testosterone levels until the secondary sex characters had begun to develop and then there was a steep rise which continued beyond the time at which the genitalia reached maturity. The high levels attained in the final stages of this rise may be necessary for the development of the moustache and beard which does not usually occur until after genitalia are mature.

In prepubertal girls, Faiman and Winter found mean levels similar to those in boys. There was a slight rise in early puberty and eventually levels in the region of 10% of those found in mature males were achieved by post-menarcheal girls. The levels in mature females are about the same as those in boys during the early stages of puberty.

It is interesting that an adult growth of pubic hair is maintained in women with testosterone levels which, in boys, are associated with only the early stages of hair growth. However, post-menarcheal girls have been exposed to slightly raised levels of

testosterone for a much longer time than have boys in early puberty. It is possible, therefore, that the same concentration of steroid as in girls would produce comparable hair growth in boys if they were exposed to it for a similar length of time. Androgens other than testosterone may play a greater part in hair growth in the female or, alternatively, female skin may be more sensitive to testosterone than that of males.

About 60% of the testosterone in female blood is believed to come from peripheral conversion of androstenedione (Horton and Tait, 1966). In the male, on the other hand, less than 1% of the blood testosterone is derived from androstenedione and the reverse reaction is more prominent, i.e. about 36% of the plasma androstenedione is derived from testosterone.

In the course of its action, testosterone is reduced to dihydrotestosterone which is further metabolized to form androstanediol. This last conversion occurs at a higher rate in men than in women (Mahoudeau, Bardin and Lipsett, 1971) and the amount of androstanediol which can be detected in the plasma of the boys increases about thirteen times during the course of their sexual development. According to Gupta (1975) the ratio of androstanediol to testosterone increases in early puberty but has declined again to approximately its prepubertal level by the time sexual maturity is reached. The ratio of dihydrotestosterone to testosterone changes similarly. The increase in these ratios in early puberty suggests that there is a corresponding increase in the activity of 5 α -reductase on which the conversion of testosterone to dihydrotestosterone depends.

Oestrogen

In girls, the oestradiol levels rise as the changes of puberty advance and adult values are attained by, or soon after, the time of menarche (Faiman and Winter, 1974). At all stages of sexual development there is a wide variation between individuals and even from day to day in the same subjects. In the urine, the excretion of oestrone, oestradiol and oestriol increases as the changes of puberty progress. In boys, the plasma oestradiol rises in early puberty and reaches an adult level similar to that found in girls whose breasts are beginning to develop. The source of oestradiol in males is not known, but it is probably the adrenal.

Plasma oestrone levels are similar in the two sexes when they are at comparable stages of development. In both girls and boys aged 7–10 years the mean value for oestrone increases before there is any similar rise in oestradiol (Saez and Morera, 1973). Also, there is evidence that this oestrone comes from the adrenal, which implies an increase, or change,

in hormone production by the adrenal before a similar change has begun in the ovary and before there are any overt signs of puberty.

Relationship between testosterone and oestrogen

In boys, there is a significant correlation between the plasma levels of oestrogen and testosterone. Gupta (1975) interprets this relationship as evidence that a significant portion of the oestrogen in boys may be derived from circulating androgen and not directly from the gonads. Studies with labelled steroids indicate that the conversion of androstenedione to oestrogen is sufficient to account for a major part of oestrogen production in the male.

In girls, no correlation between oestrogen and androgen levels has been demonstrated. This is in keeping with the view that the levels of the two hormones are independent of each other and that they come largely from independent sources.

Adrenal androgens

At adolescence there is a dramatic increase in the production of androgens by the adrenal. In contrast, the cortisol production rate and the output of cortisol metabolites in the urine increase only in proportion to the growth in overall size of the body.

In blood from the adrenal veins, in both men and women, the principal androgens found are dehydroepiandrosterone (DHA) and its sulphate; 11 β -hydroxy-androstenedione and similar quantities of androstenedione. In mixed venous blood, DHA and its sulphate are the most prominent. Very little of either of these substances can be detected in the mixed venous blood of children under the age of about 7 years. After this there is a steady increase and, just before puberty, the level is equal to about one-third of that found in young adults.

It can be argued that the output of androgens and their metabolites in the urine, over a 24-hr period, is a better guide to androgen production by the adrenal than is given by isolated blood samples. The 17-oxosteroids found in urine may be divided into two subgroups: (a) the 11-deoxy-17-oxo-steroids, derived from the DHA and androstenedione; (b) the 11-oxy-17-oxo-steroids which include further metabolites of androstenedione and the metabolites of cortisol.

The latter substances do not give a useful measure of androgen production and only the 11-deoxy-17-oxo-steroids need be considered here. These give a reasonably accurate indication of adrenal androgen secretion in both boys and girls before puberty and in adult women. In the urine, the products actually found are DHA itself together with aetiocolanolane and androsterone which are derived from androstenedione. In adult men, testosterone also contributes to the 11-deoxy-17-oxo-steroids in the

urine, although they are largely derived from adrenal androgens.

The output of these substances increases from the age of about 7 years with a steeper increase occurring between the eleventh and eighteenth years. The increase in DHA is less than that of aetiocholanolane while androsterone, which has greater androgenic properties, has the greatest increase. The increase is much greater than is required to keep pace with the growth in body size which is also occurring during puberty.

According to Gupta and Marshall (1971) the output of androsterone increases slowly from the third birthday, with a more rapid increase about the age of 5 or 6 in some individuals. Thus, the increase is taking place long before puberty. In another longitudinal study, Tanner and Gupta (1968) found that there was a dramatic increase in androsterone secretion at ages which varied between 8 and 11 years.

Before the age of 11, there is little sex difference in DHA secretion but over the age of about 12 a difference does appear and at 14, the upper limit of the range of variation in girls is approximately equal to the lower limit of the range for boys.

The importance of the increasing output of androgens by the adrenal is not clear. It is generally assumed that it is related in some way to puberty and this view is supported by the fact that it occurs early in children with precocious puberty. However, we still lack longitudinal data in which the androgen output is clearly related to the sexual development of normal individuals. Adrenal androgens may be largely responsible for the adolescent growth spurt in girls. Studies in growth hormone deficient children (Tanner *et al.*, 1976), indicate that growth hormone, as well as androgen, is necessary to obtain maximal growth during the adolescent spurt.

The cause of the increased output of adrenal androgens before puberty is not clear. The LH content of the blood does not increase until after the secondary sex characters have begun to develop. It is therefore unlikely that LH is implicated. Also, early development of the pubic hair without breast development in girls (premature adrenarche) is not associated with a rise in LH whereas other conditions associated with high blood levels of LH are not necessarily accompanied by an increased output of adrenal androgen. The output of FSH increases earlier than that of LH but there is no evidence that this influences the adrenal.

It is possible that steroids from the gonads stimulate the production of androgens by the adrenal and there is some evidence that androgens and oestrogens inhibit the activity of the enzyme 3- β -hydroxy-dehydrogenase in the adrenal, so that the metabolic pathway leading to the formation of corticosteroids is inhibited to a greater extent than that leading to the

production of androgens. Further support comes from the fact that administration of testosterone to prepubertal boys leads to increased output of 11-deoxy-17-oxo-steroids but does not increase the output of cortisol metabolites (Teller, 1967). An action of androgen or oestrogen on the adrenals might also account for the fact that congenital adrenal hyperplasia occasionally presents at puberty.

Gonadotrophic and gonadal hormones may act synergistically to stimulate adrenal androgen production. However, again, we are faced with a problem which can only be solved in the light of longitudinal studies in which the relevant hormones and their metabolites are assayed repeatedly in the same subjects before, during and after puberty.

Conclusion

Changing blood levels of gonadotrophins in the perinatal period suggest that important developmental steps leading to the normal maturation of the relationship between the nervous and endocrine systems, in so far as this influences the activity of the gonads, may be taking place at this time.

The output of gonadal steroids, and of androgens from the adrenals, increases in the prepubertal period but does so more dramatically as the secondary sex characters develop.

The precise roles of the various steroids in sexual development is largely unclear and is likely to remain so until appropriate longitudinal studies relating hormone production to both sexual development and somatic growth have been carried out on a sufficiently large scale.

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