Extragonadal Effects on Human Chorionic Gonadotrophins

Presented by Dr. Subhas Mukherjee at 59th Indian Science congress, 1972

Human chorionic gonadotrophins (HCG) is a biogenic protein hormone believed to be secreted by the trophoblastic tissues of the foetal placenta. However, inspite of a vast amount of work performed within the last four decades, the physiological role of HCG, either in the maintenance of pregnancy or in the maternal or foetal metabolism is not quite clear (Loraine and Schmidt Elmendorff. 1963; Stemm, 1962; Butt, 1967).

In clinical work and in biological research, with rare exceptions, only the gonad stimulating effects of HCG have been investigated. In clinical work except for the treatment of hypogonadism, anovulation and azoospermia HCG. although available in highly purified commercial preparations, has rarely been used. However, Kupperman (1964) pointed out the growth stimulating properties of HCG in human hypopituitary dwarfism when used along with anabolic steroids. It is known that the early foetus in utero as a whole and certain foetal organs like the adrenals in particular grow at a much higher rate during first trimester of human pregnancy - at a time when the HCG output is at its maximum. On such considerations it was thought desirable to examine the possible growth stimulating effects exogenously administered HCG in prepubertal male and female rats In order to avoid the effects of the enhanced steroid hormone output from gonads in response to administered HCG - it was thought advisable in all the experiments to conduct the investigations in gonadectomised animals. In this connection, it may be pointed out that certain effects of adenohypophyseal trophic hormone on the extra target organs have been shown with ACTH (Engel , 1956) and TSH (Engel and Lebouits, 1964).

Discussions

The results of the above pilot experiments (Chakravorty and Mukerji 1971) show it clearly that total protein, alkaline phosphatase, acid phosphatase, inorganic phosphorus and glycogen content of a majority of the tissues are significantly higher in HCG treated gonadectomised animals when compared to non-gonadectomised controls. The mean organ weight and the mean growth rate by body weight measurement is also higher in HCG treated gonadectomised animals. The RNA content of the liver tissue is significantly higher in HCG treated gonadectomised animals when compared to gonadectomised controls. These effects appear to be either directly due to HCG or through some other extra gonadal target organ specifically responsive to exogenously administered HCG.

It may be noted that some of these parameters for growth response used in the experiment were those used in the classical experiments of Li and Evans (1948) to establish the protein anabolic response of pituitary somatotrophin. The increase in total body substance associated with growth necessarily involves an accumulation of protein. Li and Evans (1948) summarised these effects as follows. The growth hormone causes

(a) Nitrogen retention
(b) Lowering of blood amino acids
(c) Increase of protein content and a decrease of fat content in the carcase.
(d) Increase in alkaline phosphatase and inorganic phosphorus
(e) enlargement of liver and thymus and
(f) slight increase in the ribonucleic acid content of the liver.

It seems therefore that in experimental animals used in our study the results of growth hormone

administration and HCG administration are quite comparable.

It is possible that the anabolic response to HCG administration may be mediated through the adrenal androgens. The available literature regarding any possible specific adrenocorticotrophic effect of HCG either in the experimental animals or in the human is controversial. In the experimental animals Velarado (1959) observed a statistically, significant adrenal response, whereas Diczfalusy and associates (1950) failed to notice this effect In the human subjects the work of Plato (1952), Borell (1954) Decio (1955), Birke et al (1954), Hibbitt et al (1958) and Eiknes et al (1959) observed a significant adrenotrophic effect charactorized by stimulation of adrenal androgens secretion rather than the glucocorticoid output. However, in the human subjects Borth and his co-workers (1953) failed to notice such changes. In this connection it may be worthwhile noting that the human foetal adrenals during the first trimester is characterized by disproportionately increased weight and high androgenic - Low glucocorticoid steroid synthesis (Block et al 1956). Villec et al 1961, (Volee and Viles, 1965) a condition, very much, comparable to the adrenotrophic effects of exogenously administered HCG reported by majority of the observers just reviewed. The direct correlations between HCG and adrenal becomes more suggestive when one considers the rapid remarkable change of the foetal adrenal from "Large adrenal high androgens - Low glucocortiocoid" to "Small adrenal - Low androgens - high glucocorticoid" state, during later periods of pregnancy at a time coinciding with the period of rapid decline in the HCG titre.

A few observations have been made regarding the possibility of a hypophysiotrophic effect of HCG (GuyeWot; 1946: Lajas et al 1959; Siegrand 1932). However, these findings envisage the existence of a possible gonadotrophic stimulating rather than a somatotrophin stimulating properties.

The thyrotropic effect of HCG observed in our experiment seems to be quite interesting. The available information regarding the functioning of the foetal thyroid is confusing particularly in view of Usorio and Myant s fInding (1960) that maternal TSH does not reach the foetus through the Placental barrier. If we are to explain the observed facts in connection with the functioning of the thyroid in anencephalic foetus it seems that some yet unidentified thyroid stimulating mechanism other than maternal and foetal TSH is likely to be involved.

Within recent times certain general metabolic effects of HCG have been shown in experimental animals. Kato and associates (1970) on the basis of the previous works of Pitengill and Fishman (1962 a,b) Freiden and associates (1964), Ide and Fishman (1969) and their own recent experiment in mice showed markedly increased de novo synthesis of renal F3-glucoronidase activity in response to exogenously administered HCG In this experiment a time dependent increase, first involving the microsomal ii-Glucoronidase then the lysosomal .3 -glucoronidase was shown.

It seems therefore, that HCG although specifically classified as a gonadotrophin possess many other remarkable biological properties - some of which closely resemble the actions of other pituitary hormones The extent to which these extra gonadal properties are due to possible contamination remains to be investigated.

However, the preliminary work regarding the therapeutic response to commercially available HCG in hypopituitary dwarfism has been found to be comparable to that of human somatotrophin (Mukerji, et al 1971).

We would like to extend this pilot work to include a wider species of animals (guinea pigs, rabbit and Monkey) and also to study the metabolic effects of HCG administration in intact human subjects.