ROLE OF THE PLACENTA IN FETAL THYROID HOMEOSTASIS

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INTRODUCTION

The placenta is usually regarded as a conduit through which maternal nutrients pass to the fetus, or as a barrier that allows for fetal development in an insulated environment. Thus, with respect to thyroid function, it is well known that the placenta transfers iodide to, and excludes thyrotropin from, the fetal circulation. It is less recognized that the placenta is a metabolically active organ, and that this activity is important for the conversion of fetal substrates. In order to relate this aspect of placenta physiology to fetal thyroid homeostasis it is necessary to first review thyroid hormone profiles and pharmacokinetics in the fetus.

THYROID HORMONE PROFILES AND IODOTHYRONINE PHARMACOKINETICS IN THE FETUS.

There are important differences in the plasma thyroid hormone profiles of the fetus and the adult. Figure 1, which depicts the ontogenesis of plasma thyroid hormones in the guinea pig (Castro et al., 1986), illustrates this. Similar data have been reported in other species including man and the sheep (Fisher et al., 1973; Fisher et al., 1972; Dussault et al., 1972; Nwosu et al., 1978; El-Zaheri et al., 1981; Isaac et al., 1979; Chopra, Sack and Fisher, 1975; Fisher and Klein, 1981). Early in gestation fetal plasma thyroxine (T4) and 3,5,3'-triiodothyronine (T3) concentrations are very low. As the fetus develops, plasma T4 concentrations increase. In many species, including the guinea pig, the increase is such that, at term, total and free T4 concentrations are higher in fetal than in maternal plasma. In contrast to T4, total and free T3 concentrations are lower in fetal plasma than in maternal plasma throughout gestation. Finally, whereas 3,3'5'-triiodothyronine (reverse T3, rT3) is difficult to detect in maternal plasma, it is easily measurable in fetal plasma. For example, as shown in Figure 1, rT3 is detectable in fetal plasma as early as 45 days of gestation. By term, fetal plasma rT3 concentrations are strikingly elevated. These differences are initially related to an inability of the fetal thyroid to secrete iodothyronines. As fetal thyroid function matures, they become more a result of dissimilarities, between the fetus and the adult, in the peripheral conversion of T4, and in the clearance of T3 and rT3.

Chopra et al. (Chopra, Sack and Fisher, 1975) have studied the production rate and clearance of fetal iodothyronines. Their data are summarized in Tables 1 and 2. Table 1 demonstrates that by the third trimester thyroidal secretion of T3 is, relative to T4 secretion, only
slightly lower in fetal sheep than in adult sheep. In contrast, whereas the adult sheep produces similar amounts of T3 from peripheral conversion of T4 as it does from thyroidal secretion, the fetus produces almost no T3 from peripheral conversion. Consequently the net production rate of T3 in the fetus is lower than in the adult. Moreover, the metabolic clearance rate (MCR) of T3 in the fetus is about twice that of the adult. Therefore, the relatively low concentrations of T3 in the fetus are due to both diminished production and accelerated clearance. Table 2 shows data for rT3. It is apparent that the peripheral production rate of this iodothyronine is almost three times greater, and MCR is nearly fourfold lower, in the fetus than in the adult. Therefore, fetal plasma rT3 concentrations are high because of increased production and low clearance.

Studies of broken cell preparations of fetal tissues (Harris et al. 1978; Wu et al., 1978; Borges, Labourene and Ingbar, 1980) indicate that they contain relatively little type I iodothyronine 5'-deiodinase activity. This probably accounts for the low peripheral production and clearance in the fetus, of T3 and rT3 respectively. Immaturity of type I 5'-deiodinase systems does not, however, account for the increased clearance of T3 and increased production of rT3. In fact, this is probably not related to any organs of the fetus proper. Rather it may be due to the placenta, an organ which is part of the fetoplacental unit and shares in the fetal circulation. This concept is based on in vitro and in situ studies showing that the placenta is able to deiodinate, convert, and clear certain iodothyronines. These properties of the placenta conform, to a remarkable degree, with what is known about the pharmacokinetics of iodothyronines in the fetus.

IODOTHYRONINE DEIODINASE ACTIVITIES IN PLACENTA HOMOGENATES

Several years ago we demonstrated that T4 and T3 underwent deiodination when incubated with rat or human placenta homogenates (Roti et al., 1981; Roti et al., 1982a). In these studies, the analytic methods were such that at least 2 percent deiodination of the substrate was required in order to detect iodothyronine degradation. In addition, deiodination could not be