Brain development and thyroid deficiency

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Development of thyroid function and regulation in rat

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Taking the day that spermatozoa are found in the vaginal smear as day 1, rat pregnancy lasts 22 days. Starting on day 17.5 of pregnancy, $^{131}$I collection has been detected in the fetal thyroid (Jost and Picon, 1970). The first thyroid follicles containing colloid are found on day 18 (Maat, 1974), the same day that thyroxine has been detected in fetal blood (Jost et al., 1974). On day 19 TSH and TRF are found in the pituitary and hypothalamus respectively (Conklin et al., 1973). So three days before birth the various components of the thyroid system are present.

This hypothalamo-hypophyseal system seems to be essential for normal fetal thyroid function and development. After fetal decapitation little or no $T_4$ can be shown in the thyroid or blood, unless TSH is given. Also feedback effects on pituitary level are shown. After fetal thyroidectomy an increase in fetal pituitary gland size and acceleration of basophilic cell development is found. Injected thyroxine has the opposite effect (Jost, 1966).

Fetal thyroid function is largely independent of the hypothalamus. Feedback effects are effected mainly via the pituitary gland, as is shown by means of PTU treatment of the mother rat by the group of Jost. Thyroid hypertrophy and colloid disappearance is found in intact or encephalectomized fetuses and can be prevented by thyroxine injection into the fetus. These phenomena of thyroid hypertrophy and colloid disappearance by PTU are absent after fetal decapitation. Yet the hypothalamus must have some stimulatory action, since in encephalectomized fetuses a slightly smaller $^{131}$I-uptake after 24 hrs and a reduction in circulating thyroxine were shown (Jost et al., 1974).

Thyroid hormones may have an organizing effect on the hypothalamic-hypophyseal axis in the first postnatal weeks. After systemic injection of thyroid hormones or implantation into the arcuate nucleus of the hypothalamus of small
amounts of hormones in neonatal rats, these animals showed in adulthood reduced body- and thyroid weight and decreased function (Eayrs and Holmes, 1964; Bakke and Lawrence, 1966; Bakke et al., 1972; 1974). Opposite changes are reported after PTU treatment of pregnant dogs (Arosenius et al., 1962).

Fetal hypothalamo-hypophyseal structures are essential for normal fetal growth. The growth retardation that was found after fetal brain aspiration could not be prevented by TSH administration. These findings and literature data warrant the presumption that the thyroid does not stimulate intra-uterine growth (Swaab and Honnebier, 1974). This agrees with observations in the human (Greenberg 1974).

Discussion

Dobbing: We decapitated 30 to 35 rabbit fetuses at 5 days before term and delivered them at term by caesarian section. We found absolutely no difference in any organ weight, in any organ DNA content or anything else, between the decapitated ones and the litter mate controls in the same uterus. I just wondered therefore whether aspiration was producing a different answer for, e.g., the different amount of bleeding you produced.

Swaab: No; we think that it does not make an essential difference whether you decapitate or brain aspirate the animals. We have checked the possibility of the influence of bleeding. It does, however, not affect the result of growth retardation after brain aspiration. But there are several possibilities for differences between your results and ours. In the first place, you are referring now to rabbits: it is a different species, and you took a different point in the growth curve. In the second place, in the kind of experiment you are performing only a few fetuses are decapitated and the rest of the litter is left intact. Compounds may cross from intact fetuses to decapitates via the maternal circulation. That is why we perform always the same operation on the whole litter.

Van der Werff: Dr. Pelt has not been able to find support for Eayrs' work on the organizing effect of thyroid hormones.

Pelt: What I found, actually, was that when you give MTU to rats for the first two weeks of their lives, they start growing slowly but they catch up later and actually reach normal body weights and body lengths. This would not be very likely if there was some permanent damage to the pituitary-thyroid axis. At all ages the body size was normal for skeletal age.

Van der Werff: In addition, thyroid function was tested by exposing the animals to cold to see their response in terms of T4 serum levels. And they were completely normal.

Honnebier: Dr. Swaab's remark that in intrauterine life the pituitary is more important for thyroid function than the hypothalamus finds strong parallels in the human. In cases of anencephaly the thyroid is more or less normally developed, whereas in cases of congenital absence of the pituitary the thyroid is almost completely atrophied. For growth, the contrary seems to be true. In case of anencephaly intrauterine growth is retarded and in absence of the pituitary it is not.
Van der Werff: Are you talking about the weights or the lengths of the anencephalics?

Honnebier: I referred to body weight. In anencephalics it is rather difficult to measure length because the brain is absent and they generally have a lordosis of the spine. In addition, the body scheme is different from normal.

Van der Werff: Do they have the same sort of body fat layer as normal babies?

Honnebier: Anencephalics have more body fat, especially around the trunk and shoulders.

Querido: I vaguely remember, Dr. Pelt, that you also did some experiments with excess of T3, after birth?

Pelt: Yes, I did the same experiments with T3-administration (Pelt, 1972), giving a large dose during the first three days after birth, or a much lower dose during the first 14 days after birth, in order to test the difference between the effects of dosage or duration. Both groups grewed at a lower rate than the controls. An 'early effect' was observed during the T3-treatment, and a 'long-term effect' was found starting some weeks later. The early effect was larger in animals receiving a large dose of T3 during three days. The long-term effect was larger in animals receiving a small dose during 14 days. So the early effect of the dosage of T3 appears to be more important, and for the long-term effect the duration of T3-treatment is more important than the dosage. From these studies I concluded that there were two effects of T3: an immediate effect, that may be a toxic effect, and a long-term effect that can be explained by the effect on skeletal maturation.

Querido: And you could relate that to pituitary-thyroid axis in some way?

Pelt: No, for none of the three groups showed any significant difference in thyroid function at adult age.

Swaab: Did you check thyroid function only at adult age, or also during the course of development?

Van der Werff: No, we were only interested in permanent effects, so we only looked in adults. There are permanent effects indeed, but they are comparable to those which you find after undernutrition. And this is a problem in such experiments, that you do cause actual or functional undernutrition. For example the locomotor behavior was much greater, which is also true after undernutrition.

Pelt: The hypothyroid as well as the hyperthyroid animals had a very elevated locomotor activity at three months of age. And this presented a striking difference with the situation at four weeks, for then the hypothyroid animals had a lower activity than the controls. This can be explained in two ways: an after-effect of the treatment itself, which is perhaps not so likely two weeks later, or the simple fact that the animals are very much retarded, also in motoric development.