Xenotransplantation of cultured newborn pig thyroid tissue for the treatment of post-radioiodine hypothyroidism in rats

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Abstract

The aim of the present study was to develop a transplantation technique for restoration of thyroid function in rats with radioiodine-induced hypothyroidism. Each Wistar rat received the dose of 75.0 μCi of 131-iodine by intraperitoneal injection. The serum thyroxine and triiodothyronine values in all rats fell to low levels by 2.5 weeks after radioiodine administration. The xenotransplantation of 3-day-old newborn pig thyroid organ culture was performed on day 18 after radioactive ablation by injection into the fat tissue of anterior abdominal wall. Epithelial cell swarms with follicular formation manifested themselves among adipose tissue on day 7 as well as day 17 after xenotransplantation. The serum thyroxine and triiodothyronine values in the rats were generally within the euthyroid range by day 7–17 after xenotransplantation. The thyroid gland of rats reverted to the norm in morphofunctional appearance. These results indicated that the xenografted newborn pig thyroid organ culture allowed a restoration of thyroid function in Wistar rats with post-radioiodine hypothyroidism.

Abbreviations: T4, thyroxine; T3, triiodothyronine; XTP, xenotransplantation.

Introduction

Persistent hypothyroidism resulting from radioiodine or X-rays irradiation of thyroid gland requires additional treatment with L-thyroxine for a long period of time, and even for life (Shimizu et al., 1996).

Hormonal therapy using xenotransplantation (XTP) of thyroid tissue may deliver such patients from pharmacotherapy. Porcine tissue is considered as one of the most suitable donor material, and preliminary organ culturing allows to significantly decrease the immunogenic properties of transplantation material (Lafferty et al., 1975).

The aim of the present study was to develop a transplantation technique for restoration of thyroid function in Wistar rats with post-radioiodine hypothyroidism.

Materials and methods

Transplantation of cultured newborn pig thyroid tissue

Each male Wistar rat (weight of rats: 100–150 g) received the dose of 75.0 μCi of 131-iodine by intraperitoneal injection. Newborn pig thyroid organ culture was obtained as previously described (Pasteur et al., 1999). The XTP of 3-day-old thyroid organ culture was performed on day 18 after radioactive ablation by injection into the fat tissue of anterior abdominal wall. Serum T4 and T3 levels were determined by radioimmunoassay.

Microscopy of rat thyroid gland and grafted newborn pig thyroid tissue

For light microscopy, thyroid gland of Wistar rats and grafts of newborn pig thyroid tissue were stained with hematoxylin and eosin.

Figure 1. Changes of serum T4 and T3 levels in rats after radioiodine administration. Serum T4, ■; serum T3, ▲.

Figure 2. Thyroid follicle structure of non-irradiated (left) and irradiated (right) rat thyroid gland. Hematoxylin-eosin stain.

Statistical analysis

Results are given as mean $\pm$ SD. Statistical analysis

of experimental data was performed using Student's *t*-test, and $P < 0.05$ was taken as significant.

Table 1. Effect of xenotransplantation of newborn pig thyroid organ culture on the restoration of thyroid function in rats with radioiodine-induced hypothyroidism

Group	Serum TT4 (nmol l ⁻¹)	Serum TT3 (nmol l ⁻¹)
Control	56.00±3.10	1.72±0.17
Radioiodine	26.06±2.78 ^a	1.08±0.13 ^a
Xenotransplantation: 7th day	40.84±9.75 ^b	1.76±0.16 ^b
Xenotransplantation: 17th day	51.74±3.87 ^b	–

^a $P < 0.05$, compared to control group.

^b $P < 0.05$, compared to radioiodine group.

Figure 3. Thyroid graft (left) and thyroid gland (right) of irradiated rat after newborn pig thyroid organ culture xenotransplantation. Hematoxylin-eosin stain.

Results

Studies of rat thyroid system after radioiodine administration

The serum T4 and T3 values in all rats fell to low levels (26.06±2.78 and 1.08±0.13 nmol l⁻¹, respectively) by 2.5 weeks after radioiodine administration (control rats group: 56.00±3.10 and 1.72±0.17 nmol l⁻¹, respectively); they remained significantly ($P <$

0.05) hypothyroid with respect to T4 and T3 for the 3.5-week duration of the study (Figure 1).

Signs of hypertrophy and sharp vacuolization of thyrocytes expressed by the disintegration of epithelial layer in rat thyroid gland in 20 days following iodine-131 injection were revealed by histological examination. Spreading of connective tissue was noted (Figure 2). In 30 days the dystrophic changes develop, and sometimes the parenchymal part of the gland is represented by destructive zones.

Studies of rat thyroid system and newborn pig thyroid graft after xenotransplantation

The values of serum T4 in the rats were generally within the euthyroid range by day 17 after XTP (Table 1). The serum T3 values rose rapidly and reached normal levels by day 7 after XTP.

The epithelial cell swarms with follicular formation manifested themselves among adipose tissue on day 7 as well as day 17 after xenotransplantation (Figure 3, left). Follicles and follicle-like structures formed with impressed thyrocytes, are shown at deadline of the examination. Sometimes, rather numerous disquamative nuclei are observed in follicular cavity.

Morphological signs of increased functional activity of thyrocytes, what is evidence of possible reparative processes as a result of transplantation, are observed in thyroid gland of preliminary irradiated rats in the mentioned terms after newborn pig thyroid organ culture transplantation comparing to suitable control. So, prevalence of follicles with relatively small diameter and rather high epithelial layer (Figure 3, right) was noted in the gland parenchyma. Signs of follicle forming are determined.

Discussion

Thyroid transplantation requires a functioning thyroid follicle as a minimum unity ensuring thyroid function. For synthesis and secretion of hormones, thyroid tissue of a maximum size of pieces up to 1 mm³ is quite sufficient, and it guarantees good results in transplantation of thyroid tissue (Bauer and Herzog, 1988; Kitamura et al., 1994).

When using results of such investigations in transplantation, it should be taken into account that the degree of hormonal compensation of hypothyroidism and real amount of radioiodine absorbed by a thyroid graft depend on its functional activity at the moment of study, on the amount of transplanted tissue, and level of thyrotropic hormone which circulates in the blood of the recipient (Lafferty et al., 1975).

Though functioning of an additional source of thyroid hormones is recognized as the main mechanism of therapeutic effect of transplantation in case of hypothyroidism (Pushkar et al., 1984; Shimizu et al., 1996), one may not exclude a possible stimulat-

ing effect on recipient's thyroid gland (Pushkar et al., 1984).

Therefore, the newborn pig thyroid organ culture preserves its morphological and functional features for a long period of time, and it may be used in transplantation for the treatment of persistent hypothyroidism (Pasteur et al., 1999).

The major finding in this study was the effect of XTP on the restoration of thyroid function and morphological features of thyroid gland in rats with postradioiodine hypothyroidism. In recipients of newborn pig thyroid organ culture euthyroid levels of serum T4 and T3 were approached within 7–17 days. It should be noted that the thyroid gland of rats reverted to the norm in morphofunctional appearance, and resumed a normal thyroid system relationship after xenografting.

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