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Original article

Peroral administration of triiodothyronine (T_3) affects absorption of immunolactoglobulins in calves

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Summary — On the basis of our studies which demonstrated that T_3 is a natural milk-borne component of cow mammary secretions, this study investigated the influence of T_3 (and thyroxine, T_4) on the serum Ig level (used here as an indicator of intestinal absorption). Forty healthy calves were given a single dose of either T_3 or T_4 with the first colostrum meal 6 h following birth. Blood samples were taken before and 42–50 h after hormone administration. The T_4 treatment resulted in metabolic changes that were reflected by an increase in blood glucose, triglycerides (TG), non-esterified fatty acids (NEFA), and a decrease in total serum proteins (TP). Ig levels were reduced from 27.5 g/l (controls) to 20.6 g/l. The T_3 treatment caused an increase in serum TG and FFA ($p < 0.01$), and, in contrast to T_4, an increase in TP and Ig ($p < 0.001$). These results indicated that peroral administration of T_3, but not T_4, could exert a positive effect on the transfer of immunolactoglobulins in the neonatal calf intestine. The contrasting hormonal effects are likely attributable to different responses of intestinal cells to T_3 and T_4.

triiodothyronine / thyroxine / neonatal calf / immunolactoglobulin absorption

Résumé — L'administration orale de triiodothyronine (T_3) influence l'absorption des immunolactoglobulines chez le veau. *Basée sur nos travaux antérieurs montrant que la triiodothyronine (T3) est un composant naturel des sécrétions lactées de la vache, la présente étude a pour objectif de rechercher l'influence de T3 (et de la thyroxine, T4) sur le taux sérique des Ig, utilisé ici comme un indicateur de l'absorption intestinale. Quarante veaux en bonne santé ont reçu une dose unique de T3 ou de T4 avec le premier repas de colostrum 6 h après la naissance. Des échantillons de sang furent prélevés avant et 42–50 h après l'administration de l'hormone. Le traitement T4 a conduit à des modifications métaboliques traduites par des augmentations des taux sanguins de glucose, de triglycérides (TG) et des acides gras non estérifiés (NEFA) et par une baisse des protéines totales sériques (TP). Les taux d'Ig étaient diminués de 27,5 g/l (témoins) à 20,6 g/l. La T3 a provoqué une augmentation des taux*

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sériques de TG et de FFA (p < 0,01) et, contrairement à T4, à une augmentation de TP et Ig (p < 0,001). Ces résultats montrent que l'administration orale de T3, mais pas de T4, peut exercer un effet positif sur le transfert des immunolactoglobulines dans l'intestin du veau nouveau-né. Les effets divergents des 2 hormones pourraient être attribués à une action différente de T3 et de T4 directement sur les cellules intestinales.

triiodothyronine / thyroxine / veau nouveau-né / absorption / immunolactoglobuline

INTRODUCTION

Calf immunolactoglobulins (Ig), mainly IgG, are absorbed intact by the process of pinocytosis within the period of non-selective intestinal permeability to macromolecules which lasts, on average, 24 h after birth (Stott *et al,* 1979) but ranges from 12 to 48 h (McCoy *et al,* 1970; Weaver, 1992). A failure in colostral Ig uptake frequently results in diarrhea, septicemia and an increasing incidence of morbidity and mortality.

In spite of the importance of postnatal macromolecular absorption for adaptation and neonatal survival there are few studies on the mechanism responsible for duration of the period of macromolecule transfer. The following are the most important factors affecting the intestinal closure time to macromolecules: epithelial cell replacement; meconium discharge; the presence and multiplication of bacteria; and a change in gastric acidity (for review see Roy, 1990). However the exact mechanisms regulating the time and cessation of absorption remain unknown.

It is well documented that hormones are natural trophic constituents of colostrum and milk, which assist perinatal adaptation. When ingested they may exert local or systemic effects in the neonate (Pearlman, 1991). Little is known, however, about their effect on the acceleration of epithelial differentiation, enzymic maturation or protective-activity within the alimentary tract. Steroid and thyroid hormones are implicated in the maturation process of the fetus and the newborn, and so their possible role as factors influencing Ig absorption has long been studied. Deutsch and Smith (1957) unsuccessfully attempted to maintain the permeability of calf gut beyond 24 h postpartum, using diethylstilbestrol, progesterone, cortisol and ACTH given parenterally. In other studies, the concentration of cortisol at birth appeared to have no effect, but injections of ACTH have tended to increase serum Ig at 48 h (Stott and Reinhard, 1978; Johnston and Oxender, 1979). A positive correlation between corticosteroid concentration and labelled globulin absorption was noted by James *et al* (1981).

Conflicting results were published in relation to the possible effects of thyroxine (T_4). Boyd and Hogg (1981) failed to find a correlation between serum T_4 and Ig concentrations in the calf. However, Cabello and Levieux (1978, 1980) studied calves with thyroxinemia at birth or a hyperthyroid state during fetal development, and found that the negative influence of T_4 on the absorption of Ig was observed in procedures which detected significant influence of the absorption period of Ig for maximal Ig concentrations.

On the basis of our studies, which demonstrated that triiodothyronine (T_3), but not T_4, is an easily measurable component of cow milk (Ślebodziński and Brzezińska-Ślebodzińska, 1991), the influence of T_3 on the serum Ig level (used here as an indicator of intestinal absorption) was investigated. Contrary to previous studies, the thyroid hormones were given orally to ensure their local and direct action on the epithelial cells of the intestine. Some indirect metabolic, effects of the administered hormones were quantified and the results were related to immunolactoglobulin transfer.

MATERIALS AND METHODS

The investigation involved newborn calves (Polish Lowland Black and White dairy cattle) studied over a 2-year period on 1 farm in a condition unmodified by the experimental procedures. The animals selected were of comparable body weight at birth, after the rejection of large or dystocial calves, and weighed 31.2 ± 0.57 kg (mean ± SEM). Calves were given the colostrum of their dams from a bucket *ad libitum*. The first feeding was 5–6 h after birth. The initial feeding was followed by 3 more at 3.5 h intervals, and the last after 8 h. This feeding regime ensured an intake of about 6 h colostrum per calf per day. Forty healthy calves were administered a single dose of either 1 mg of T_4 ($n = 20$) or 10 mg of T_4 ($n = 20$) with the first colostrum. An equal number of randomly selected control calves (n = 20 and 20) received colostrum that was not supplemented with hormones.

The thyroid hormones T_4, T_3 and rT_3 were measured in the serum by radioimmunoassay (Ślebodziński *et al*, 1982). The metabolic effects of administered T_4 and T_3 were traced by means of changes in the total serum proteins (TP), nonesterified fatty acids (NEFA), triglycerides (TG), serum glucose and cholesterol. These were determined according to Lowry's method (TP) modified by Hartree (1972), Duncombe's method (NEFA), the TG-test (Lachema NP, Brno), Glucose Test (Cormany GS, Lublin) and Liebermann-Burchard reaction (cholesterol).

The level of the serum immunolactoglobulin complex was determined by the polyethyleneglycol immunoglobulin precipitation test (Brzezińska-Ślebodzińska and Ślebodziński, 1982).

Statistical analysis

Significant differences between mean values, experimental *vs* control, were evaluated by the Student's unpaired *t*-test.

RESULTS

The thyroxine treatment resulted in a significant rise in serum T_4, which was sustained 40 h after the peroral administration of the hormone. In consequence, significant changes in the absolute concentrations and in the relative proportions of the serum thyroid hormones occurred. These were mainly increases in the T_3 and reverse T_3 levels and the T_3/T_4 ratio (figs 1 and 2).

The metabolic effects of ingested T_4 (fig 3) included (controls *vs* experimental) an increase in blood glucose (96.2 ± 4.07 *vs* 120.0 ± 4.54 mg/dl; $p < 0.001$), TG (293.3 ± 35.80 *vs* 450.3 ± 46.79 µmol/l ; $p < 0.02$) and NEFA (184.3 ± 14.81 *vs* 259.4 ± 7.75 µmol/l; $p < 0.01$), and a decrease in TP (67.4 ± 2.22 *vs* 61.2 ± 1.82; $p < 0.05$).

The Ig levels were reduced from 27.5 ± 2.83 g/l in the controls to 20.6 ± 1.92 g/l in the T_4-treated animals; the statistical significance was approximately $p = 0.05$.

Triiodothyronine treatment resulted in both increased serum T_3 (fig 1) and T_3/T_4 ratio (fig 4). The T_3/rT_3 ratio, however, remained unchanged after the T_3 and T_4 treatments (figs 2 and 4).

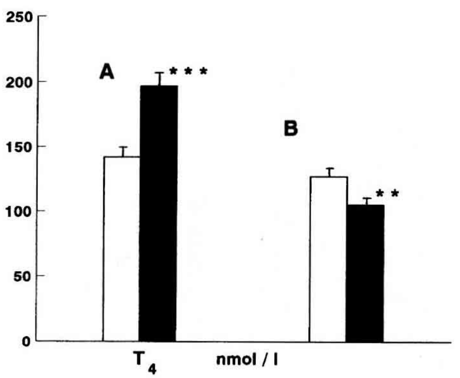

Fig 1. Serum thyroxine concentrations (mean values ± SEM; $n = 20$ in each group) in calves after peroral administration of T_4 **(A)** or T_3 **(B)**. Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. ❑ : control; ■ experimental.

The metabolic effects of ingested T_3 (fig 5) included (controls *vs* experimental) increased TP (71.4 ± 1.61 *vs* 84.6 ± 2.28 g/l; $p < 0.01$), TG (270.4 ± 44.74 *vs* 391.1 ± 39.07 µmol/l; $p < 0.05$), and NEFA (226.5 ± 18.46 *vs* 488.7 ± 23.80 µmol/l; $p < 0.01$), while the glucose concentration was unchanged. The serum cholesterol level was unaffected by either treatment.

In contrast to T_4, triiodothyronine caused an increase in serum Ig (23.0 ± 2.18 *vs* 40.4 ± 2.28 g/l; $p < 0.01$).

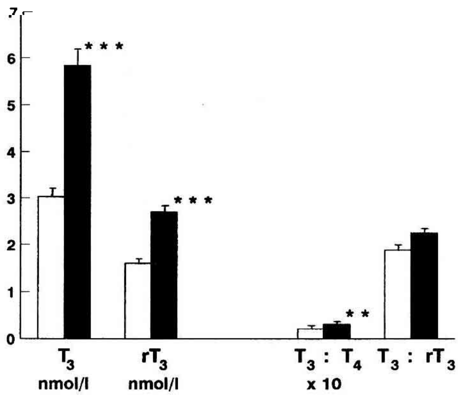

Fig 2. Thyroid hormones status after peroral T_4 administration with the first colostrum. Hormone concentrations; mean values ± SEM; $n = 20$ in each group. Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. ❑ : control; ■ experimental.

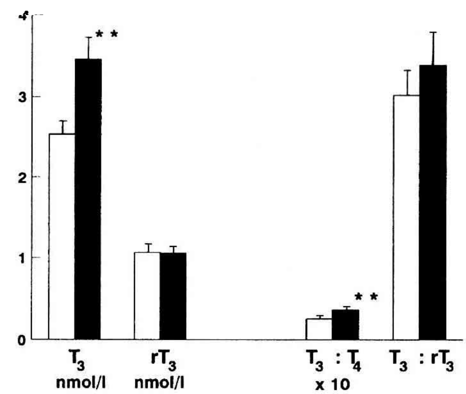

Fig 4. Thyroid hormone status after peroral T_3 administration with the first colostrum. Hormone concentrations, mean values ± SEM; $n = 20$ in each group. Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. ❑ : control; ■ experimental.

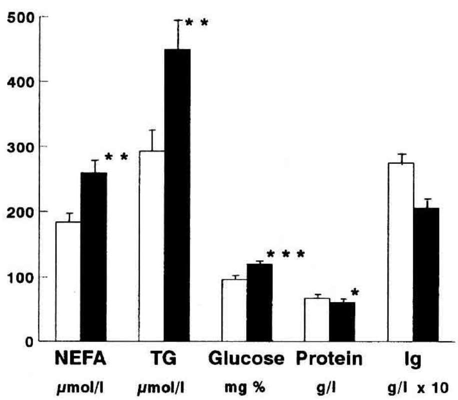

Fig 3. Metabolic effects after peroral T_4 administration with the first colostrum. Note that the protein and Ig concentrations tended to be reduced. Mean concentrations ± SEM; $n = 20$ in each group. Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. ❑ : control; ■ experimental.

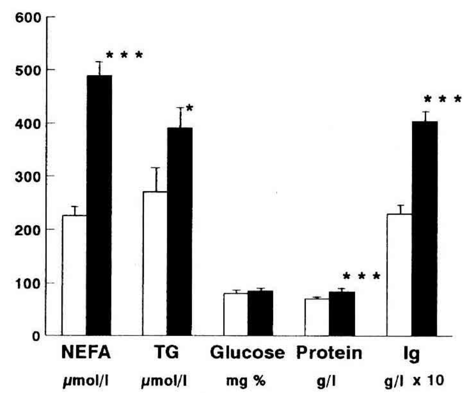

Fig 5. Metabolic effects after peroral T_3 administration with the first colostrum. Note the increase in protein and Ig concentrations. Mean concentrations ± SEM; $n = 20$ in each group. Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. ❑ : control; ■ experimental.

DISCUSSION

The calves used in this study were fed in a way that ensured a high colostrum and Ig intake. As established in some previous studies, the intestinal permeability for Ig in calves is maximal during the first 4–13 h, the mean absorption period being 30 h; (Marx and Stott, 1979). The first feeding by bucket 4–6 h after birth, followed by an additional feeding at 8–12 h, was considered sufficient to produce an Ig concentration that would ensure an optimal Ig level in 95% of the calves (Fallon, 1978). The amount of T_4 given orally (3.2 mg T_4 per 10 kg body weight) was comparable to the total dose (3 mg T_4/10 kg bwt, im) used by Cabello and Levieux (1980) in their study of the effects of T_4 on Ig absorption.

The results showed that a peroral administration of thyroxine with the first colostrum, brought about strong metabolic effects. There were reflected by changes in blood constituents and inhibited rather than enhanced Ig transfer. This finding seems to be in agreement with the results obtained by Cabello and Levieux (1978, 1980), suggesting that thyroxinemia at birth is negatively correlated with the absorption of IgG in calves, and that the parenteral T_4 administration tends to reduce the IgG absorption period in newborn kids and lambs (Cabello *et al*, 1980; Cabello and Levieux, 1981).

The present work further revealed that, in contrast to T_4, triiodothyronine exerted a positive influence on the Ig transfer although it brought about similar metabolic effects. Both the total proteins and Ig were found to be higher in the T_3-treated calves than in controls (fig 5).

We found recently (Ślebodziński and Brzezińska-Ślebodzińska, 1991) that T_3, but not T_4, is an easily measured component of cow mammary secretions. T_3 is locally generated in the gland by an enzymic mechanism that converts T_4 to T_3. This process of iodothyronine conversion lowered the concentration of T_4 and increased that of T_3. In consequence, the calf receives predominantly T_3 with the colostrum, and it thus appeared to be the principal thyroid hormone capable of influencing the process of Ig absorption under natural conditions.

Although the observed contrasting response to T_3 and T_4 in calves is difficult to explain, it is well documented that hormones play a significant role in the process of intraluminal digestion and absorption in rats and in the maturation of their enzyme systems (Koldovsky *et al,* 1974, 1980). In suckling rats, the period of immunoglobulin transfer ends between 18–21 d postpartum and the period of decreasing absorption coincides well with marked enzymic changes (Halliday, 1956; Clark, 1959). Premature cessation of macromolecular absorption has been induced by the injection of pharmacological doses of cortisone (Halliday, 1959; Morris and Morris, 1976) as well as by thyroxine (Chan *et al,* 1973; Jones, 1982). Some other studies seem to indicate that exogenous thyroxine induces a reduction rather than an increase in pancreatic or intestinal enzyme activities (Deschodt-Lanckman *et al,* 1974; Hewitt and Smith, 1984; Britton and Koldovsky, 1988). The effect of T_3 administration on macromolecular transmission has not been studied as yet.

Large doses of thyroid hormones affect carbohydrate metabolism by increasing glycolysis, glycogenolysis and gluconeogenesis. They increase lipolysis in adipose tissue, depress the synthesis of lipids, accelerate the oxidation of fatty acids and suppress protein synthesis (for references, see Hoch, 1974). The results of this study showed that thyroid hormones already appeared to exert control over those metabolic systems in newborn calves.

The direction of metabolic effects and the magnitude of changes in the level of various metabolites were similar, irrespective of the hormone administered (with the exception of NEFA which was greater in the T_3-treated group). The similarity of the metabolic effects might have been related to an increased conversion of T_4 to T_3 in peripheral tissues, resulting in a high production of metabolically active T_3 during the first 2 d of life. This view was supported by the higher T_3 plasma level in the T_4-treated calves as compared to those treated with T_3 (figs 2 and 4). In the T_4-treated animals, the metabolic response might have appeared after a latency period. This was different from direct T_3 action upon intestinal cells following the first colostrum feeding.

The positive effect of peroral administration of T_3 on the transfer of immunolactoglobulins observed in the present study may not therefore occur, contradictory to the observed effects of thyroxine. Whereas the inhibitory influence of pharmacological doses of T_4 appeared to be more systemic, the stimulatory effect of T_3 seemed to be more direct (local within the intestinal tract) than systemic.

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