Thyroid hormones and thermogenesis

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An extensive review article on thyroid hormone published nearly 40 years ago (Barker, 1951) might have led one to suppose that little could be added to the subject of thyroid hormones and thermogenesis. However, a large number of new ideas have since emerged with respect to the mechanisms of action of thyroid hormones, although there is still considerable uncertainty as to how they function at the cellular level to increase metabolic rate. In addition, major advances have been made with respect to the extent that environmental factors such as temperature and nutrition can influence thyroid hormone metabolism.

The present paper does not aim to give an extensive review on all the actions of thyroid hormones but rather to consider specific areas related to cold-induced and diet-induced thermogenesis. Emphasis will be on studies in large mammals in which, unlike rodents, brown adipose tissue does not appear to play a major role in non-shivering thermogenesis. First, the role of thyroid hormones in clinical and pharmacological situations will be considered. Second, their mechanism of action in elevating resting metabolic rate (RMR) will be discussed. Third, evidence concerning the influence of environmental factors on thyroid hormone metabolism will be examined. Finally, the extent to which any environmentally-induced changes in thyroid hormones may affect RMR will be investigated.

THYROID HORMONE INFLUENCES ON METABOLIC RATE IN CLINICAL AND PHARMACOLOGICAL STATES

Thyroid hormones have long been known to influence oxygen consumption ($\dot{V}_{O_2}$). Magnus-Levy (1895) deduced that the excessive weight loss in clinical hyperthyroidism was due to accelerated catabolism of food and an elevated metabolic rate. The time-course of changes in tissue metabolism of thyroidectomized rats following a single injection of 6·12 mg DL-thyroxine (T_4)/kg body-weight is correlated with changes in whole-body metabolic rate (Barker & Klitgaard, 1952). By 12 h after injection, $\dot{V}_{O_2}$ is elevated in heart, muscle, liver, kidney and gastric mucosa and reaches a peak after 4–6 d. There are only a few non-responsive tissues such as lungs, spleen and adult brain. A refinement in technique was associated with studies in which measurements were made in anaesthetized animals kept at thermal neutrality (Denckla & Marcum, 1973). These showed a highly specific relation between minimal $\dot{V}_{O_2}$ and thyroid hormones.

The extent and nature of the response to thyroid hormones is dependent not only on dose (Tata, 1974) but also on the thyroid status of the individual. There is an enhanced sensitivity to 3,5,3′-triiodothyronine (T_3) in hypothyroid compared with euthyroid rats, since only the hypothyroid show an increase in $\dot{V}_{O_2}$ 12–48 h after injection of 6 nmol T_3/kg (Wimpfheimer *et al.* 1979). Such a finding could be related to differences in the number of nuclear T_3 receptors. However, although pituitary growth hormone (GH) cells in vitro

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show an increase in receptors with low T_3 and vice versa (Samuels, 1983), no relation between receptors and thyroid status has been found in the liver of hypo-, eu- and hyperthyroid rats (Spindler *et al.* 1975; DeGroot *et al.* 1976). Nevertheless, recent studies have shown an elevated number of T_3 receptors in skeletal muscle from hypothyroid pigs on the same energy intake as euthyroid controls (Morovat & Dauncey, 1990) and such a finding is consistent with reported differences in tissue responsiveness.

A major factor which needs consideration is the energy intake of subjects of different thyroid status. Thus, *ad lib.* food intake is reduced in hypothyroid pigs (Macari, 1984) and as will be discussed later, this reduction in energy intake could itself significantly influence metabolic rate.

MECHANISMS BY WHICH THYROID HORMONES MAY INFLUENCE RMR

There is an extensive literature on the possible mode of action of thyroid hormones in relation to thermogenesis (e.g. Hoch, 1974; Rall, 1978; Guernsey & Edelman, 1983; Danforth & Burger, 1984; Oppenheimer *et al.* 1987; Samuels *et al.* 1988). This section, therefore, aims simply to consider a few areas in which there is currently particular interest or controversy.

Evidence obtained during the last 10 years suggests that thyroid hormones exert many of their effects by regulating gene expression. They can, thus, enhance or diminish the accumulation of mRNAs which code for specific proteins. For example, thyroid hormones control key enzymes which ultimately increase the supply of reducing equivalents to the mitochondrial matrix (Oppenheimer *et al.* 1977; Samuels *et al.* 1989). The activity of α-glycerophosphate dehydrogenase (α-GPD) increases in hyperthyroid and decreases in hypothyroid rats and there is a close correlation between α-GPD activity and $\dot{V}_{O_2}$ of specific tissues (Ruegammer *et al.* 1965). The extent to which any such changes contribute to the overall change in RMR remains to be established. Apart from their effects on substrate supply, regulation of energy metabolism by thyroid hormones can also be considered at the levels of: (1) oxidative phosphorylation, and (2) ATP hydrolysis.

Oxidative phosphorylation. Most studies carried out in this field, as in others on the mode of action of thyroid hormones, have been in small mammals such as rats and mice. Animals have often been kept below thermal neutrality and food intake has not been controlled. The extent to which these factors could significantly influence the results and their extrapolation to large mammals is not known. Nevertheless, the results need detailed consideration.

In the 1950s it was postulated that thyroid hormones act by uncoupling oxidative phosphorylation, since the P:O ratio (the amount of ATP formed per oxygen atom consumed) was reportedly lower in hyperthyroid than in euthyroid animals. However, doubt was later cast on this hypothesis for several reasons, one of the most valid being that the uncoupling observed could have represented a pharmacological rather than a physiological effect. Doses of T_4 100–10 000 times greater than the daily endogenous output had been used.

Recent studies on mitochondrial structure and function in animals of different thyroid status have provided renewed interest in the control of mitochondrial respiration by thyroid hormones (Brand & Murphy, 1987). For example, thyroid hormones can affect mitochondria directly and effects have been reported over periods of weeks, days and

even hours. Thus, the long-term mechanism involves increases in the area of mitochondrial inner membrane, increased amounts of respiratory chain proteins and possibly changes in membrane lipids. Some studies have focused on possible influences of thyroid hormones on increased permeability of the mitochondrial inner membrane to protons (lcak) and decreased H^+:O ratio (number of protons released to the external bulk phase per oxygen atom reduced) of the respiratory chain (slip). The relation between respiration rate and proton motive force (Δp) has been examined in non-phosphorylating hepatic mitochondria in rats of different thyroid status (Hafner *et al.* 1988). Relative to mitochondria from euthyroid controls, the membrane potential ($\Delta\psi$) and hence Δp of mitochondria from hypothyroid rats is substantially elevated, indicating decreased leak/slip. In addition, mitochondria from hyperthyroid rats have increased leak/slip as indicated by a lower $\Delta\psi$ at any given respiration rate. This result was not reversed by the addition of serum albumin to the buffer, suggesting that the increased leak/slip was not an artefact resulting from an uncoupling action of T_3 but rather a physiological change in the properties of the mitochondrial inner membrane. These thyroid-related changes in efficiency of energy transduction could, thus, be a significant component of the thyroid-induced increase in RMR.

ATP hydrolysis. The suggestion in the 1960s that ATP formation remains normally coupled to $\dot{V}_{O_2}$ in hyperthyroidism led to a search for sites of increased ATP utilization.

Evidence in favour of thyroid thermogenesis being linked to the action of the sodium pump (Na^+,K^+-ATPase; *EC* 3.6.1.3) in the plasma membrane has been reviewed by Guernsey & Edelman (1983). Thyroid hormones are the major endocrine influence on this ATPase, with the number of Na-pump sites being increased in hyperthyroidism and decreased in hypothyroidism (Kjeldsen *et al.* 1984). A substantial proportion of the elevated $\dot{V}_{O_2}$ in the hyperthyroid state has been attributed to the action of the Na-pump (Ismail-Beigi & Edelman, 1970). However, Biron *et al.* (1979) concluded that despite parallel changes in heat production and ouabain-sensitive components of heat production and potassium influx with thyroid status, active Na^+,K^+-transport could not be considered a primary effector of thyroid thermogenesis in intact mammalian skeletal muscle.

Results for the relation between the Na-pump and RMR are contradictory. Thus, in hyperthyroidism there is an increase in both the number of Na-pump sites and RMR, whereas the increase in Na^+,K^+-ATPase in muscle of dystrophic hamsters is not associated with an increase in RMR (Sulakhe *et al.* 1971; Himms-Hagen, 1976). A recent finding in skeletal muscle of young pigs living at 35 or 10° on a high or low energy intake also demonstrated this inverse relation (Dauncey & Burton, 1989): animals at 10° on a low intake have the highest number of Na-pump sites (Fig. 1) but the lowest RMR at thermal neutrality (Macari *et al.* 1983*b*). Estimates of the contribution of Na^+,K^+-ATPase to whole-body metabolic rate vary widely in different species (Clausen & Hansen, 1982; Milligan & McBride, 1985; Herpin *et al.* 1987) and its role in non-shivering thermogenesis remains controversial.

Other investigations have been concerned with the significance of calcium ion homeostasis to thyroid hormone-induced thermogenesis (van Hardeveld & Clausen, 1986). Thyroid hormones stimulate the proliferation of sarcoplasmic reticulum (SR) in skeletal muscle, increase the amount of SR Ca^{2+}-ATPase and probably increase Ca^{2+} availability in the cytoplasm by enhancing its mobilization from the SR. Dantrolene (an inhibitor of Ca^{2+} release from the SR) inhibits the resting $\dot{V}o_2$ significantly in perfused

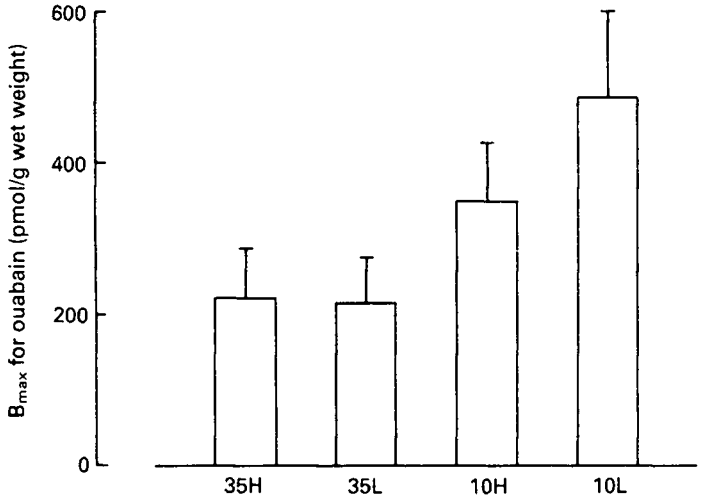

Fig. 1. Maximal binding capacity (B_{max}) of [^{3}H]ouabain in *longissimus dorsi* muscle taken 20–24 h after the last meal from 8-week-old pigs which had been living at 35 or 10° on a high (H) or low (L) level of energy intake (H = 2L) for 4 weeks. There was a significant influence of temperature (10°>35°; $P<0{\cdot}001$) and energy intake (L>H; $P<0{\cdot}04$) with an interaction between the two variables ($P<0{\cdot}02$). Mean values with their standard errors represented by vertical bars for six pigs for each group. (From Dauncey & Burton, 1989.)

skeletal muscle of euthyroid and particularly hyperthyroid rats, but has no effect in hypothyroid animals (van Hardeveld & Kassenaar, 1980). The suggestion that Ca^{2+}-cycling in liver mitochondria might also be increased by thyroid hormones (van Hardeveld & Clausen, 1986) indicates that the effect of thyroid hormones on Ca^{2+} homeostasis is not tissue specific and the role of Ca^{2+}-cycling in non-shivering thermogenesis remains to be established.

ENVIRONMENTAL INFLUENCES ON THYROID HORMONE METABOLISM

Influence of temperature. A low environmental temperature has classically been associated with an increase in thyroid hormone metabolism. For example, Starr & Roskelly (1940) found the height of secretory epithelium in the thyroid gland to be increased in rats exposed to the cold. A relation between temperature and the thyroid has also been found in man (Eastman *et al.* 1974) and the pig (Ingram & Slebodzinski, 1968). The immediate response to cold exposure involves secretion of thyroid-stimulating hormone (TSH) from the pituitary (Reichlin *et al.* 1972). This in turn may involve thyroid-releasing hormone (TRH) since local cooling of the hypothalamus leads to increased secretion from the thyroid gland (Andersson *et al.* 1962; Evans & Ingram, 1974). However, the extent to which this may be part of the physiological response to a reduction in ambient temperature is unknown since on initial exposure to cold, body temperature does not fall and indeed it may even increase. Only in very severe cold exposure, when thermoregulatory mechanisms fail, is there likely to be hypothermia.

The short-term effect of reducing air temperature from 32 to 8° for the young pig is an increase in output of T_4 from the thyroid and a rise in plasma T_4. However, the increases are not maintained if there is no increase in food intake (Evans & Ingram, 1977).

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Similarly, the fractional rate at which ^{125}I-labelled T_4 disappears from the blood (fractional disappearance rate; K) increases only if the animals are allowed to feed *ad lib.* in the cold. Thus, although the thyroid–pituitary axis appears to respond in the short-term to cold exposure, it is probable that low temperature alone cannot maintain the elevated thyroid activity. More recently, it has been found that in young pigs living at 12–13° compared with 30° there is a peak in nuclear T_3 receptors of skeletal muscle after 3–8 d in the cold (Dauncey & Morovat, 1989). This increase cannot be maintained in the long-term if there is no increase in energy intake and the extent of the decline may depend on the level of energy intake and its latency on the animal's energy reserves.

Examination of many studies on thyroid metabolism and cold exposure reveals that subjects have eaten *ad lib.* Since food intake increases in the cold (Hamilton, 1976; Peeters *et al.* 1989) comparisons have, therefore, involved subjects in the warm on a low energy intake with those in the cold on a high intake. A review on the interacting effects of temperature and nutrition on thyroid metabolism has been published recently (Ingram & Dauncey, 1990).

Influence of nutrition. The extent to which thyroid hormone metabolism can be influenced by the quantity and composition of food eaten has received considerable attention in recent years. Changes occur both in the short-term, over several hours, and in the long-term, after several weeks of altered energy intake.

Fig. 2 shows that plasma T_3 increases in the young pig within an hour of eating a meal and that the rise is directly related to energy intake (Dauncey *et al.* 1983). There is also a rise in T_4, although it is much slower and not detected in animals on a low energy intake. The composition of the meal also has a significant effect, with glucose and sucrose being particularly potent stimulators of plasma T_3, although intravenous infusion of glucose has no measurable effect. Recent results have also shown that both total and free T_3 and T_4 are influenced by a single meal and that a large meal with negligible digestible energy content is without effect (M. J. Dauncey and D. L. Ingram, unpublished results). A meal also significantly influences the fractional disappearance and catabolic rates of thyroid hormones (Dauncey & Ingram, 1986). For example, the K value of T_3 in the young pig is significantly greater 1–3 h after a meal than at 22–24 h. The origin of thyroid hormones after a meal remains to be established, although the possibility is that the rise in plasma T_3 is related to increased peripheral conversion of T_4 to T_3 via increased monodeiodinase activity.

There are also longer-term influences of level of energy intake on thyroid hormone metabolism. In adult man, plasma T_3 increases during overfeeding (Utiger, 1982), while fasting or underfeeding are associated with reduced TSH and T_3 (Palmblad *et al.* 1977; Beer *et al.* 1989; Matzen & Kvetny, 1989). There is reduced 5′-deiodination of T_4 in liver and kidney during underfeeding (van der Heyden *et al.* 1986), while results for plasma T_4 vary, with reduced levels being reported in only some studies. The influence of level of energy intake on the K value of T_4 in the young pig at 26° changes with time (Griggio & Ingram, 1985). During the first 1–4 weeks, K is greater on a high than a low intake, whereas after 5 weeks there is no effect of diet.

The metabolic response to T_3 depends not only on the concentration of hormone but also on the number of hormone receptors. The maximal binding capacity (B_{max}) of nuclear T_3 receptors in skeletal muscle taken 24 h after feeding from young pigs at 26° is significantly greater on a high compared with a low energy intake, even after only 3 d of

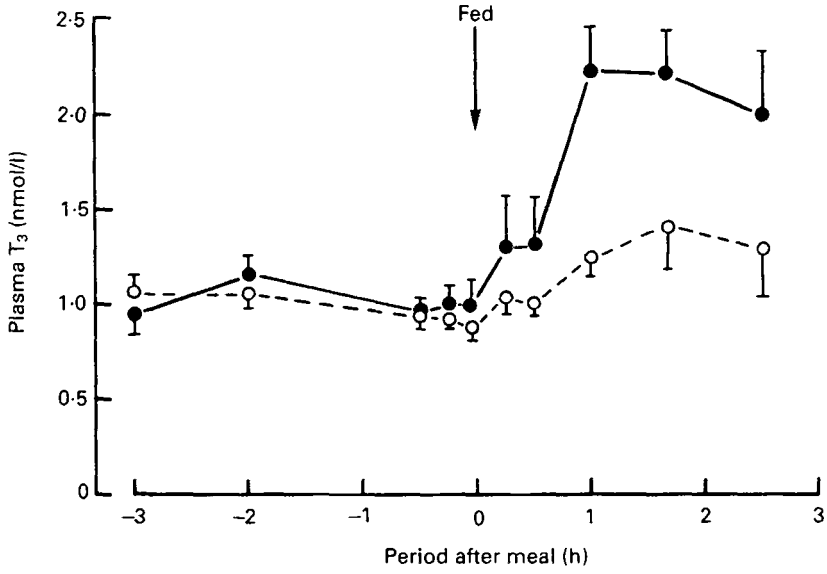

Fig. 2. Influence of a meal on plasma concentration of 3,5,3′-triiodothyronine (T_3) and its dependence on level of energy intake. Results are from two groups of young pigs at 26° given a meal of 600 g = 9·48 MJ (●) or 300 g = 4·74 MJ (○) standard feed. Mean values with their standard errors represented by vertical bars for six pigs for each group. (From Dauncey *et al.* 1983.)

treatment (Geers *et al.* 1988). By contrast, in rats a fall in liver T_3 receptor numbers is observed only after total starvation for several days (DeGroot *et al.* 1977). These changes may be mediated by plasma glucagon which is likely to increase on a low energy intake and is known to decrease T_3 receptor numbers (Dillmann *et al.* 1978).

Interaction between temperature and food intake. The interacting effects of temperature and energy intake on thyroid metabolism have been investigated in young pigs living for several weeks at 35 or 10° on a high (H) or low (L) energy intake (where H=2L). In the experimental design there are, thus, four treatment groups: 35H, 35L, 10H and 10L (Ingram & Dauncey, 1986). Under these conditions it was found that only energy intake had a significant influence on the thyroid gland, with the height of the secretory epithelium being greater in those on the H than the L intake, whereas there was no effect of environmental temperature (Dauncey *et al.* 1984). Plasma concentrations of T_4 and T_3 24 h after feeding were also significantly greater on the H than the L intake and again there was no effect on temperature (Fig. 3). By contrast, Fig. 4 shows that the *K* values for T_3 and T_4 were not influenced by level of energy intake but were greater in the cold than the warm (Macari *et al.* 1983*a*).

Fig. 5 shows that the greatest number of nuclear T_3 receptors in skeletal muscle occurred in the 35H group, the least in the 10L, with the values for 35L and 10H being intermediate and similar to each other (Dauncey *et al.* 1988). This suggests that, contrary to expectation, a cold environment reduces tissue responsiveness to T_3. The possibility is that energy intake in relation to energy requirement is an important factor in determining the number of T_3 receptors. Thus, cold increases the energy demand for thermoregulation and the same absolute intake would be smaller in relation to energy demand in those at 10° compared with 35°.

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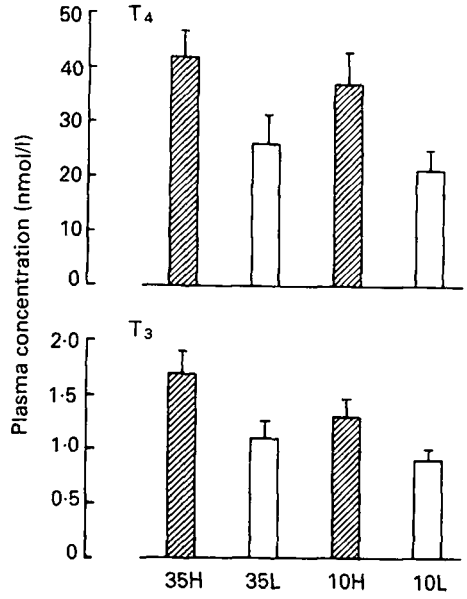

Fig. 3. Plasma concentrations of thyroxine (T_4) and 3,5,3'-triiodothyronine (T_3) measured 16–21 h after the last meal in 10-week-old pigs which had been living at 35 or 10° on a high (H) or low (L) level of energy intake (H=2L) for 6 weeks. There was a significant influence of energy intake (H, ▨ > L, □; $P<0{\cdot}02$ for T_4 and T_3) but no significant influence of temperature. Mean values with their standard errors represented by vertical bars for eight pigs for each group. (From Macari *et al.* 1983*a*.)

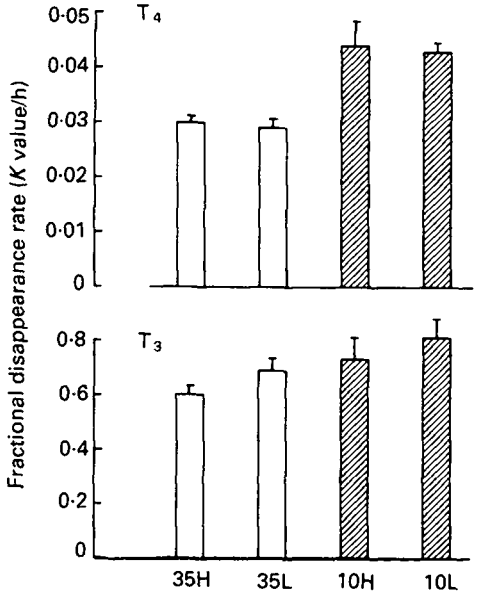

Fig. 4. Fractional disappearance rates (K) of thyroxine (T_4) and 3,5,3,'-triiodothyronine (T_3) measured 16–21 h after the last meal in 10-week-old pigs which had been living at 35 or 10° on a high (H) or low (L) level of energy intake (H=2L) for 6 weeks. There was a significant influence of temperature (10°, ▨ > 35°, □; $P<0{\cdot}01$ for T_4 and T_3) but no significant influence of energy intake. Mean values with their standard errors represented by vertical bars for eight pigs for each group. (From Macari *et al.* 1983*a*.)

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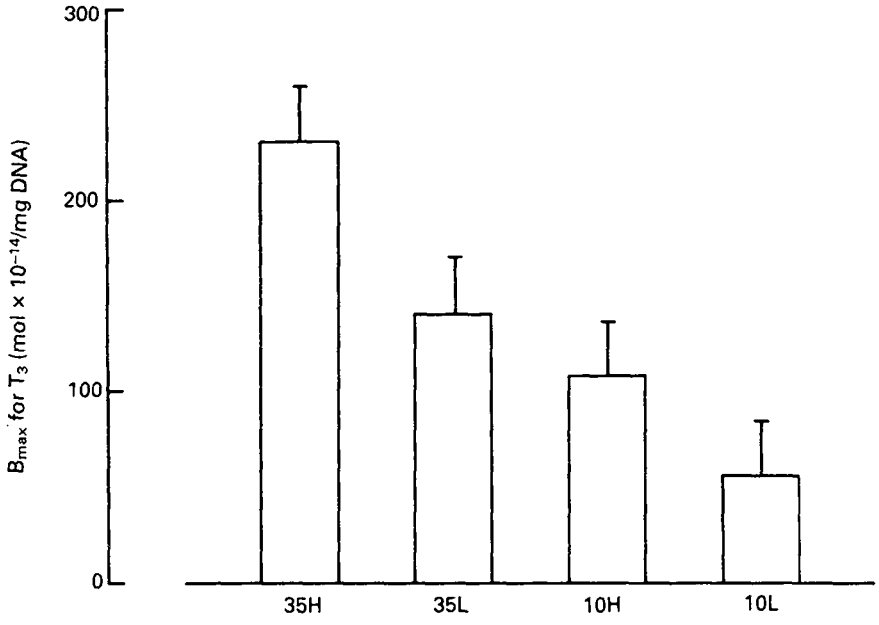

Fig. 5. Maximal binding capacity (B_{max}) of 3,5,3′-triiodothyronine (T_3) in nuclei of *longissimus dorsi* muscle taken 20–24 h after the last meal from 8-week-old pigs which had been living at 35 or 10° on a high (H) or low (L) level of energy intake (H=2L) for 4 weeks. There was a significant influence of temperature (35°>10°; $P<0{\cdot}01$) and energy intake (H>L; $P<0{\cdot}05$) with no significant interaction between the two variables. Mean values with their standard errors represented by vertical bars for four pigs for each group. (From Dauncey *et al.* 1988.)

ROLE OF THYROID HORMONES IN COLD-INDUCED AND DIET-INDUCED THERMOGENESIS

Changes in RMR induced by environment. Of particular interest is the extent to which the differences in thyroid metabolism induced by environment are reflected in changes in metabolic rate. $\dot{V}_{O_2}$ increases in man as in other mammals during initial exposure to both mild and severe cold (Chaffee & Roberts, 1971; Close *et al.* 1980; Dauncey, 1981). However, in many studies on the longer-term effects of cold, food intake has not been controlled and the possibility is that this itself could have affected RMR. Thus, RMR is influenced by level of energy intake both in the period immediately after a meal and during the subsequent 24 h. This has been documented for periods of altered energy intake which extend from days to weeks, in many species including man (Apfelbaum *et al.* 1971; Dauncey, 1980), sheep (Graham *et al.* 1959), pig (Close *et al.* 1971; Dauncey & Ingram, 1979; Ingram & Dauncey, 1980) and rat (Rothwell & Stock, 1979). The interaction between temperature and energy intake on metabolic rate 24 h after feeding has been examined in the model of the young pig mentioned earlier (Macari *et al.* 1983*b*). At each of a series of test temperatures there was a significant effect on $\dot{V}_{O_2}$ related to energy intake (H>L) but not to the temperature at which the animal had been living. There was also a significant interaction between living temperature and level of energy intake on the RMR at thermal neutrality such that the effect of diet was greater in those living at 10° than at 35°.

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These changes in $\dot{V}_{O_2}$ associated with temperature and nutrition are directly correlated with many of the changes in thyroid hormone metabolism mentioned previously. Mechanisms by which the changes in RMR take place are highly dependent on species. On initial exposure to cold, shivering and behavioural changes are important in both large and small mammals. In the long-term, changes in insulation may considerably reduce or even eliminate the effect of cold. In the longer-term, non-shivering heat production in brown adipose tissue also plays a vital role in replacing much of the shivering thermogenesis of small mammals (Himms-Hagen, 1989). Brown adipose tissue may also be involved in diet-induced thermogenesis of rodents (Rothwell & Stock, 1979; Nicholls & Locke, 1984). However, apart from its contribution in the newborn of some species, the extent to which brown adipose tissue contributes to the energy expenditure of large mammals is unknown (Trayhurn, 1989). Both adult man and the young pig have relatively little brown fat (Heaton, 1972; Dauncey *et al.* 1981) and the increase in metabolic rate in response to noradrenaline is small compared with that in rodents (LeBlanc & Mount, 1968; Jung *et al.* 1979; Heath & Ingram, 1983).

Physiological changes in thyroid hormones and RMR. In view of the effects of thyroid hormones on RMR, the possibility is that at least part of the enhanced rate of metabolism associated with a large meal is related to the plasma concentration of T_3. Recent evidence using physiological rather than pharmacological doses of T_3 does not, however, lend support to this idea (Kamada *et al.* 1987; Dauncey & Kamada, 1990). In young pigs, doses of 10, 20 or 40 nmol T_3/kg body-weight were infused intravenously and RMR was measured over the following 20 h. The marked increases in plasma T_3 were much higher than those recorded after either feeding or short-term cold exposure. However, there was a significant 12% increase in RMR only after the highest dose of T_3. In addition, the injection of 6 nmol T_3/kg into 72 h fasted rats does not affect metabolic rate whereas re-feeding does (Rothwell *et al.* 1982).

The extent to which the reduction in RMR during underfeeding may be related to thyroid hormones has been examined in man (Acheson & Burger, 1980). No evidence was found to support this hypothesis since a decrease in plasma T_3 after treatment with iopanoic acid, which blocks deiodination of T_4, failed to influence RMR. By contrast a mild T_3 toxicosis over a 2-week period was associated with a 6% increase in RMR (Acheson *et al.* 1984). There was, however, evidence of a slight hyperthyroidism because of T_4 injection which was intended only to block endogenous T_4 secretion. Whether any part of the rise in RMR after overfeeding is associated with thyroid hormones, therefore, needs further investigation.

There is, thus, as yet no clear-cut evidence which links the elevation in thyroid hormone metabolism on short-term cold exposure or a high energy intake to the changes in RMR. Undoubtedly, further investigations are needed to elucidate the possible role of thyroid hormones in cold-induced and diet-induced thermogenesis. Thyroid hormones interact with a number of other endocrine factors, including catecholamines, and although space precludes discussion of these interactions, their importance should not be underestimated. In addition, more needs to be known about: (1) the extent to which changes in plasma T_3 due to administered hormone can mimic changes which occur when T_3 is produced within the cell; and (2) the detailed nature and function of T_3 receptors, especially in relation to changes in B_{max} and receptor occupancy induced by environmental temperature and nutrition.

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