Nutrition–hormone receptor–gene interactions: implications for development and disease

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Nutrition profoundly alters the phenotypic expression of a given genotype, particularly during fetal and postnatal development. Many hormones act as nutritional signals and their receptors play a key role in mediating the effects of nutrition on numerous genes involved in differentiation, growth and metabolism. Polypeptide hormones act on membrane-bound receptors to trigger gene transcription via complex intracellular signalling pathways. By contrast, nuclear receptors for lipid-soluble molecules such as glucocorticoids (GC) and thyroid hormones (TH) directly regulate transcription via DNA binding and chromatin remodelling. Nuclear hormone receptors are members of a large superfamily of transcriptional regulators with the ability to activate or repress many genes involved in development and disease. Nutrition influences not only hormone synthesis and metabolism but also hormone receptors, and regulation is mediated either by specific nutrients or by energy status. Recent studies on the role of early environment on development have implicated GC and their receptors in the programming of adult disease. Intrauterine growth restriction and postnatal undernutrition also induce striking differences in TH-receptor isoforms in functionally-distinct muscles, with critical implications for gene transcription of myosin isoforms, glucose transporters, uncoupling proteins and cation pumps. Such findings highlight a mechanism by which nutritional status can influence normal development, and modify nutrient utilization, thermogenesis, peripheral sensitivity to insulin and optimal cardiac function. Diet and stage of development will also influence the transcriptional activity of drugs acting as ligands for nuclear receptors. Potential interactions between nuclear receptors, including those for retinoic acid and vitamin D, should not be overlooked in intervention programmes using I or vitamin A supplementation of young and adult human populations.

Abbreviations: GC, glucocorticoid; GH, growth hormone; GR, glucocorticoid receptor; IGF, insulin-like growth factor; RXR, retinoid X receptor; TH, thyroid hormone; TR, thyroid hormone receptor

Development: Hormones: Intrauterine growth restriction: Nuclear receptors: Nutrition

Nutritional status can profoundly alter the phenotypic expression of a given genotype, and hormone receptors play a key role in mediating the effects of nutrition on numerous genes involved in development. Whereas polypeptide hormones act on membrane-bound receptors, receptors for lipophilic hormones act directly within the nucleus to regulate transcription. Nutrition influences not only hormone synthesis and metabolism but also hormone receptors, and regulation is mediated either by specific nutrients or by energy status.

The present review briefly mentions some of the many hormones involved in development, and then illustrates the complexity of nutrition–hormone receptor–gene interactions by focusing on nuclear hormone receptors. As paradigms for nuclear hormone action, the receptors for glucocorticoids (GC; GR) and especially those for thyroid hormones (TH; TR) are considered. These hormones have long been recognized to play crucial roles in regulating differentiation, growth and metabolism. Advances in molecular cloning and structural analysis, combined with sophisticated gene-targeting studies, have revealed new insights into the developmental functions of these hormone systems. Recent findings on tissue-specific and developmental-stage-specific regulation of nuclear TR isoforms, and their modulation by intrauterine growth restriction and postnatal undernutrition, are particularly relevant to the understanding of development and disease. They highlight a mechanism by which nutritional status can influence normal development and modify nutrient utilization, thermogenesis, insulin resistance and optimal cardiac function. Interactions

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between diet and stage of development in influencing the transcriptional activity of drugs acting as ligands for nuclear receptors is mentioned. Finally, the potential significance of interactions between members of the superfamily of nuclear receptors in nutrient-intervention programmes is discussed.

**Hormone receptors and gene transcription**

All stages of development involve complex and coordinated patterns of signalling at the intracellular, cell–cell and cell–environment levels. Numerous hormones are involved in this communication network and, in relation to the external environment, they act as especially powerful nutritional signals and are themselves subject to modification by nutritional status. Specific receptors and receptor isoforms enable a given circulating level of hormone to have both tissue-specific and developmental-stage-specific effects. The polypeptide hormones such as growth hormone (GH), insulin-like growth factors (IGF) and insulin act on membrane-bound receptors to trigger gene transcription via complex intracellular signalling pathways (Argentsinger & Carter-Su, 1996; Czech & Corvera, 1999). By contrast, nuclear receptors for lipid-soluble molecules such as GC and TH act predominantly by directly regulating transcription via DNA binding and chromatin remodelling (Collingwood et al. 1999; McNally et al. 2000).

**Superfamily of nuclear receptors**

The nuclear hormone receptors are members of a large superfamily of transcriptional regulators with the ability to activate or repress numerous genes. The superfamily of nuclear receptors includes not only GR and TR, but also those for retinoids, vitamin D and the sex steroids (Lazar, 1993; Kumar & Thompson, 1999). Knowledge of nuclear receptors has increased considerably during the last decade, with identification of a group termed orphan receptors, i.e. receptors originally identified without knowledge of their specific ligand, such as peroxisome proliferator-activated receptors and farnesoid X receptors, the functions of which are currently being elucidated (Desvergne & Wahli, 1999; Gustafsson, 1999). Nuclear receptors are of particular interest in the present context, because the cognate ligand for each receptor is usually dependent on the supply of a specific dietary component for its synthesis, e.g. I and tyrosine for TH, cholesterol for vitamin D and GC, vitamin A as the ligand for all-trans-retinoic acid receptors, and fatty acids for peroxisome proliferator-activated receptors.

**Mechanism of action of nuclear hormone receptors**

Nuclear receptors usually act by remodelling of chromatin, and this process is dependent on their common structure which has several specific functional domains (Fig. 1). The highly-conserved DNA-binding domain binds to specific response elements in the promoter region of the target gene. The carboxy-terminal region contains a hormone- or ligand-binding region and sites necessary for dimerization and for recruitment of coactivators and corepressors (Collingwood et al. 1999). Transcription of target genes involves receptor binding to DNA together with hormone binding to the receptor. This process results in recruitment of coactivator proteins, an open chromatin structure is formed and gene expression is initiated. The precise modes of action of the various nuclear hormone receptors differ. To illustrate the complexity of nuclear receptor action and indicate the many functional aspects that may be subject to nutritional modulation, the specific mechanisms by which GC and TH act at the molecular level will be outlined.

In the absence of ligand, GR is located in the cytoplasm where it exists in the inactive state bound to heat-shock proteins. Binding of GC releases these proteins and the receptor is then translocated to the nucleus where it regulates transcription by binding as a GR–GR homodimer to specific DNA response elements. In addition to direct DNA recognition, GR can also act as a monomer to modulate transcriptional activation via protein–protein interactions (Tronche et al. 1998).

The major actions of TH are exerted at the genomic level via a group of receptors which regulate the expression of numerous target genes, usually by remodelling of chromatin structure (Wu & Koenig, 2000). Unliganded TR are located in the nucleus and can interact directly with chromatin to modulate gene transcription either in the presence or absence of TH (Fig 2). Binding to specific TH response elements is usually by heterodimerization with retinoid X receptors (RXR). In the presence of TR (Fig. 2(b)), the TR–RXR heterodimer recruits a coactivator protein complex with histone acetyl transferase activity. Acetylation of histones results in a relaxed open chromatin structure, enabling access of basal transcription factors and RNA polymerase to DNA, hence activating gene transcription. In the absence of TH (Fig. 2(c)), the TR–RXR heterodimer binds to a group of corepressor proteins, leading to recruitment of histone deacetylase, a closed form of chromatin and silencing of transcription.

TR add a further level of complexity to transcriptional regulation because they occur as a series of isoforms encoded by two distinct proto-oncogenes, c-erbA-α, and c-erbA-β, each of which regulates a specific set of target genes. Alternative splicing of the TRα mRNA transcript produces two carboxy-terminal variants (TRα1 and TRα2) and the TRβ gene produces two amino-terminal variants, TRβ1 and TRβ2. Whereas TRα1, TRβ1 and TRβ2 can bind TH and transactivate TH response elements, the TRα2
variant cannot bind TH and hence is not strictly a receptor for TH. Structural changes in the TRα2 hormone-binding domain and lack of AF-2 transactivation function prevent TH binding and transactivation (Lazar, 1993; Tagami et al. 1998). The precise functions of TRα2 are unknown, but it is thought to compete with the TH-binding TR isoforms for specific DNA response elements and thus inhibit transcription. Recent findings outlined in the section on developmental actions of TH and TR (pp. 66–67) lend support to this hypothesis.

**Hormones, nuclear receptors and development**

Hormones and their receptors exert marked tissue-specific and age-specific effects on development (Dauncey, 1995). During fetal development, the coordinated actions of IGF, insulin, TH and GC play central roles in the control of differentiation, growth and maturation (Fowden, 1995). By contrast with its essential role postnatally, pituitary GH does not appear to have a major role in controlling fetal growth; hepatic GH receptor expression is either absent or extremely low and the GH–IGF axis does not mature until around birth. However, GH receptor expression is high in fetal skeletal muscle, suggesting direct actions of prenatal GH in muscle differentiation and metabolism (Duchamp et al. 1996). Interactions between hormones also occur. For example, TH exert a striking tissue-specific influence on prenatal GH receptor gene expression: hypothyroidism induces down regulation in liver but a marked up regulation in muscle.

The following sections discuss the widespread developmental actions of GC, TH and their receptors, and focus especially on regulation of gene expression in brain and functionally-distinct muscles. This discussion emphasises the potentially significant role of nutrition in modulating neurodevelopment, cardiac function, and the numerous actions of skeletal muscles. Not only is muscle essential for locomotion, postural maintenance, breathing and thermogenesis, but it plays a key role in determining nutrient oxidation rates and is the main peripheral site of insulin action.

**Developmental actions of glucocorticoids and glucocorticoid receptors**

The main effects of GC (predominantly cortisol or corticosterone, depending on the species) before birth are on tissue differentiation and maturation (Fowden et al. 1998). They act directly to alter gene transcription or post-translational processing of gene products, and may also initiate the
transition from fetal to adult mode of growth regulation by inducing the switch from hepatic IGF-II to IGF-I. The prepartum surge in GC appears to have an important maturation role in initiating the perinatal switch from the fetal to adult mode of somatotrophic regulation; during late gestation GC regulate hepatic GH receptors and IGF-I gene expression, and preferentially increase the class 2 transcript of the IGF-I gene (Li et al. 1996, 1998b). During infancy and later life GC have a wide range of functions in many tissues and play a key role in homeostasis. They are important regulators of glucose, fat and protein metabolism and, by contrast with their prenatal role, act as growth inhibitors. GC also have marked influences on cognitive function (McEwen & Sapolsky, 1995) and affect neuronal activity at several levels including membrane polarity, neurotransmitter release and neuronal survival.

Gene-targeting studies have revealed important insights into the developmental role of GR (Tronche et al. 1998). The majority of GRnull mutants, i.e. mice with complete inactivation of the GR gene, die a few minutes after birth because of lung atelectasis (incomplete expansion of the lungs at birth), and there are defects in the function of many other tissues including liver and adrenal gland. Conditional mutations of the GR gene using the Cre/loxP system circumvents the problem of early death by generating tissue-specific mutations. Absence of GR in the nervous system is not lethal, demonstrating that the lung atelectasis in GRnull mutants is not neuronal in origin. By contrast, absence of GR feedback regulation in the hypothalamus of mice with the nervous-system-specific mutation profoundly alters the equilibrium of the hypothalamic–pituitary–adrenal axis; secretion of corticotrophin-releasing hormone increases, leading in turn to elevated circulating GC levels. Mutants not only exhibit growth retardation and redistribution of adipose tissue but they are less anxious, suggesting direct involvement of GR in emotional behaviour. These findings highlight the importance of GR to development of the nervous system, and are directly relevant to an understanding of mechanisms by which nutrition modulates neurodevelopment and cognitive function (Dauncey & Bicknell, 1999).

**Developmental actions of thyroid hormones and thyroid hormone receptors**

The widespread actions of hormones during development are exemplified by the striking effects of TH (thyroxine and 3,5,3'-triiodothyronine) on differentiation, growth and metabolism of many tissues and cell types (Fisher et al. 1977; Dauncey, 1990; Fowden, 1995). Particularly well recognised are the effects of TH on myelination and development of the central nervous system, and TH deficiency during the perinatal period results in severe mental and physical retardation (Oppenheimer & Schwartz, 1997; Chan & Kilby, 2000). Since I is essential for TH synthesis, I deficiency during fetal and early postnatal life can also result in brain damage and mental retardation (Delange, 2000). Moreover, Se has essential roles in TH metabolism, and has the potential to play a major part in the outcome of I deficiency (Arthur, 1999).

The differential temporal and spatial distributions of TRα and TRβ, together with coexpression at comparable levels in some brain regions, suggest different roles for TR isoforms during brain development and in the mature animal (Mellstrom et al. 1991). However, the target genes of TH that play crucial roles in brain development are as yet unclear, and the rat cerebellum is currently proving useful as a model system for studying TH action in brain development (Koibuchi & Chin, 2000).

TH have direct actions on protein turnover, affecting both protein synthesis and protein breakdown, and they are essential for muscle development (Muscat et al. 1995; Dauncey & Gilmour, 1996). Recent studies also suggest that the relative distribution of TRα1 and TRα2 isoforms plays a pivotal role in regulating the phenotypic and functional differences between the wide diversity of muscle types (White & Dauncey, 1999). Prenatally, TH act via muscle-specific regulatory factors to induce myoblasts to exit from the cell cycle and differentiate to form myotubes and mature myofibres. Perinatal sequential transitions from embryonic to fetal adult myosin heavy-chain isoforms are followed by switching between mature myosins. In skeletal muscle TH induce type I slow fibres to become type II fast fibres, and similarly in cardiac muscle they induce switching from β-myosin to α-myosin. Other genes specifically regulated by TH include glucose transporters, cation pumps and uncoupling proteins (Castello et al. 1994; Dauncey & Harrison, 1996; Gong et al. 1997). These diverse actions enable TH to exert a powerful influence on many aspects of muscle function including contractility, nutrient utilization and metabolic activity.

Gene-inactivation studies have shown that the four TR isoforms probably regulate individual tissue-specific functions and common functions in vivo (Forrest & Vennstrom, 2000). Table 1 describes some of the major phenotypes of targeted TR inactivation, and highlights the widespread influences of these receptors during development. Disruption of either TRα1 or TRα2 alone does not produce a lethal phenotype, but reveals that TRα1 plays a pivotal role in determining basal heart rate, irrespective of TH status (Wikstrom et al. 1998). However, simultaneous disruption of both TRα isoforms results in a lethal phenotype postnatally (Fraichard et al. 1997). Deletion of both TRβ isoforms results in relatively mild effects on phenotype, similar to those associated with TH resistance in humans (Chatterjee, 1997). Overall, the effects of TR deletion are not always as profound as those occurring in response to hypothyroidism and a reduction in circulating TH levels. This situation is probably because TR deletion simply results in basal levels of transcription, whereas TR in the absence of TH represses basal transcription (see Fig. 2). Thus, although the transgenic approach is of considerable value, it does not necessarily lead to a complete understanding of hormone receptor action.

Major differences occur with respect to the relative abundance of the TR isoforms in functionally distinct muscles (White & Dauncey, 1999). In fast muscles TRα1 predominates and TRα1:TRα2 is high, whereas in slow muscles, the non-TH-binding TRα2 predominates (Fig. 3). These differences have important functional consequences;
Viability Reference

Phenotype

TRα1 + TRβ2 Death at 4–5 weeks Growth arrest at 2 weeks Progressive hypoiodyroidism Small intestine: delayed maturation Bone: delayed development Post-weaning lethality (rescued by 1 week with T3 treatment) Fraihard et al. (1997)

TRα1 Viable Growth rate normal Mild hypoiodyroidism Heart rate ↓ (no response to T3 treatment) Body temperature ↓ (restored by T3 treatment) Skeletal muscle: slow myosin ↑, fast myosin ↓, Ca2+-ATPase ↓, longer contraction and relaxation times Wikstrom et al. (1998), Johansson et al. (2000), Yu et al. (2000)

TRβ1 + TRβ2 Viable Growth rate normal Plasma TH levels elevated; goitre Heart rate ↑ (no response to T3 treatment) Auditory function defective Skeletal muscle: slow and fast myosins not affected, less fatigue-resistant Forrest et al. (1996), Weiss et al. (1998), Johansson et al. (1999, 2000), Yu et al. (2000)

TRβ2 Viable Plasma TH levels elevated Auditory function normal Basal GH gene expression slightly decreased Response to T3 blunted Abel et al. (1999)

TRα1 + TRβ1 Viable Growth rate reduced; lower body weight all ages Plasma TH levels grossly elevated; very large goitre Bone: delayed development Heart rate ↓ (no response to T3 treatment) Body temperature ↓ Skeletal muscle: slow myosin ↑, fast myosin ↓ GH gene expression profoundly down regulated Gothe et al. (1999), Johansson et al. (1999), Yu et al. (2000)

TRα1 + TRβ1 Death at 4–5 weeks Growth arrest at 2 weeks Plasma TH levels elevated (more than in TRβ1null); goitre Ileum: pronounced malformation Bone: delayed development Post-weaning lethality Gauthier et al. (1999)

T3, 3,5,3′-triiodothyronine; ↓, decrease; ↑, increase; GH, growth hormone.

*Disruption of TRβ2 results in viability; its other effects and those of TRβ1 disruption have not yet been described. Severity of phenotype in response to disruption of TRα gene alone or TRα plus TRβ1 genes may result from an artefact; it has been suggested that expression of partial TRα products may be causing the lethality (Forrest & Vennstrom, 2000).

preponderance of TRα1 in longissimus will result in a high proportion of type II fast myosin for rapid movement, while high levels of TRα2 in cardiac muscle will enhance slow sustained contractility. Recent findings on the ontogeny of porcine TR expression also indicate that the relative levels of TRα1 and TRα2 are important in regulating TH action (P White, K A Burton, A L Fowden and M J Dauncey, unpublished results). During cardiac development TRα2 expression is two to four times greater than that of TRα1, and as development progresses the TRα isoforms decrease gradually to reach low levels at 7 weeks postnatally. This developmental expression pattern is strikingly different from that in the fast-twitch skeletal muscle longissimus. Taken together, these novel findings highlight a key role for TR isoforms in regulating tissue-specific TH sensitivity and muscle phenotype during development. Moreover, nutritional modulation of specific TR isoforms will have a marked effect on optimal physiological function of cardiac and skeletal muscles.

**Nutritional regulation of hormones and hormone receptors**

Numerous investigations have shown that nutrition markedly influences the synthesis and metabolism of many hormones involved in development, growth and metabolism (Dauncey, 1995; Brameld, 1997; Holness, 1999). Effects are exerted both by specific nutrients and by changes in overall food intake, as occurs during undernutrition or intrauterine growth restriction. A further mechanism by which nutrition modulates hormone action is by regulation of hormone receptors. Particularly important is the finding that the response to nutrition can be tissue-specific, because this factor enables highly specific and diverse functional responses to a given circulating hormone level. Postnatal undernutrition down regulates GH receptor gene expression in liver, whereas it is up regulated in muscle (Dauncey et al. 1994; Weller et al. 1994). This situation will affect the GH–IGF-I axis and limit growth by reducing hepatic IGF-I synthesis, while simultaneously enhancing the anti-

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**Table 1.** Major phenotypic effects of disrupting genes for the thyroid hormone (TH) receptor (TR) isoforms

<table>
<thead>
<tr>
<th>Gene disrupted*</th>
<th>Viability</th>
<th>Phenotype</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>TRα1 + TRβ2</td>
<td>Death at 4–5 weeks</td>
<td>Growth arrest at 2 weeks, Progressive hypoiodyroidism, Small intestine: delayed maturation, Bone: delayed development, Post-weaning lethality (rescued by 1 week with T3 treatment)</td>
<td>Fraihard et al. (1997)</td>
</tr>
<tr>
<td>TRα1</td>
<td>Viable</td>
<td>Growth rate normal, Mild hypoiodyroidism, Heart rate ↓ (no response to T3 treatment), Body temperature ↓ (restored by T3 treatment), Skeletal muscle: slow myosin ↑, fast myosin ↓, Ca2+-ATPase ↓, longer contraction and relaxation times</td>
<td>Wikstrom et al. (1998), Johansson et al. (2000), Yu et al. (2000)</td>
</tr>
<tr>
<td>TRβ1 + TRβ2</td>
<td>Viable</td>
<td>Growth rate normal, Plasma TH levels elevated; goitre, Heart rate ↑ (no response to T3 treatment), Auditory function defective, Skeletal muscle: slow and fast myosins not affected, less fatigue-resistant</td>
<td>Forrest et al. (1996), Weiss et al. (1998), Johansson et al. (1999, 2000), Yu et al. (2000)</td>
</tr>
<tr>
<td>TRβ2</td>
<td>Viable</td>
<td>Plasma TH levels elevated, Auditory function normal, Basal GH gene expression slightly decreased, Response to T3 blunted</td>
<td>Abel et al. (1999)</td>
</tr>
<tr>
<td>TRα1 + TRβ1</td>
<td>Viable</td>
<td>Growth rate reduced; lower body weight all ages, Plasma TH levels grossly elevated; very large goitre, Bone: delayed development, Heart rate ↓ (no response to T3 treatment), Body temperature ↓, Skeletal muscle: slow myosin ↑, fast myosin ↓, GH gene expression profoundly down regulated</td>
<td>Gothe et al. (1999), Johansson et al. (1999), Yu et al. (2000)</td>
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lipogenic, lipolytic and diabetogenic actions of GH in muscle. There are also striking muscle-specific differences both in postnatal GH receptor gene expression, and in its regulation by nutritional status, that are related to the metabolic, contractile and functional properties of different muscles (Katsumata et al. 2000). Recent findings on nutritional regulation of nuclear receptors are described later (pp. 68–69). They highlight mechanisms by which early nutrition may exert permanent or long-term effects on optimal development. The probability is that the diverse actions of hormone receptors on cellular development persist long after subsequent optimization of nutrition has restored hormone receptor expression to its appropriate level.

**Glucocorticoid receptors and nutrition**

Energy restriction may exert many of its effects on modulating disease and longevity via the hypothalamic–pituitary–adrenal axis (Duffy et al. 1997). A reduction in food intake alters the patterns of pulsatile, circadian and ultradian GC release and increases plasma GC levels (Vance & Thorner, 1989), whereas overfeeding reduces GC levels (Lewis et al. 1992). There is a fine balance between the beneficial and harmful effects of GC, which is related in part to the stage of development, and the magnitude and duration of any changes (Fowden et al. 1998). Intrauterine programming of the hypothalamic–pituitary–adrenal axis has been implicated in the link between low birth weight and later disease (Nyirenda et al. 1998; Phillips et al. 1998), and elevated basal GC levels may cause hippocampal damage and hippocampus-dependent learning and memory deficits in later life (Lupien et al. 1998).

Investigations on the nutritional regulation of GR are limited. Nevertheless, altered regulation of developmental GR expression may affect the later incidence of many diseases, including hypertension and the insulin resistance syndrome. Maternal low-protein diet in the rat results in persistent up regulation of GR expression in central and peripheral tissues (Bertram et al. 1999). Moreover, GR expression is differentially regulated in skeletal myocytes from men with contrasting levels of insulin resistance and obesity (Donovan & Whorwood, 1999). GR are present in several brain areas, and are most abundant in the hippocampus where they play an essential role in GC feedback inhibition (Dauncey & Bicknell, 1999). Their precise role in neurodevelopment and long-term health or disease has yet to be established. An important area for future investigation is to determine the extent to which diet can influence tissue-specific GR expression during prenatal, postnatal and adult life.

**Thyroid hormone receptors and nutrition**

Nutrition has a major influence both on the hypothalamic–pituitary–thyroid axis and on nuclear TH binding in peripheral tissues. A low energy intake reduces thyroid gland activity, plasma TH levels and total TR numbers, and the decrease in nuclear TH binding is even greater when metabolic demand is increased by lowering the environmental temperature (Dauncey, 1990; Swoap et al. 1994; Morovat & Dauncey, 1995). Intrauterine growth restriction also down regulates TR (Dauncey, 1995). Thus, when energy is restricted, because of either a low intake or a high expenditure, the reduction in TR will limit responsiveness to TH and result in reduced growth and metabolism.
Ligand-binding studies provide no information on the expression of specific receptor isoforms, and this factor is especially important in the case of TR, in which the TRα2 variant does not bind TH. Investigations on the role of energy status in regulating porcine TR isoform expression have revealed new insights into mechanisms by which nutrition can influence gene expression (White & Dauncey, 1998; P White, KA Burton and MJ Dauncey, unpublished results). Studies on intrauterine growth restriction and postnatal undernutrition indicate that responses are markedly dependent on stage of development and muscle type. Particularly significant are results for cardiac muscle; intrauterine growth restriction down regulated TRα1 by 50 %, whereas postnatal undernutrition induced a striking 140 % increase in TRα2 (Fig. 3). These nutritionally-induced changes in cardiac TRα isoforms may profoundly affect myocardial function; either a low level of the TH-binding TRα1 or a high level of the non-TH-binding TRα2 isoform, combined with a reduction in plasma TH levels, would reduce cardiac α- myosin transcription, leading in turn to a lower intrinsic contractile ability and operational heart rate. Undernutrition also induces marked changes in TR in skeletal muscle. Expression of TRα2 in longissimus of small-for-gestational-age piglets is more than two-fold greater than that in controls, and TRα2/TRα1 increases. This preferential up regulation of TRα2 expression would reduce TH binding and decrease transcription of target genes, resulting in reduced growth and metabolism, energy conservation and impairment of muscle phenotype and function (White et al. 2000).

Potential significance of nutrition–nuclear receptor interactions

Not only are interactions between nutrition and hormone receptors critical for optimal development, but there is currently considerable interest in specific targeting of nuclear receptors by novel pharmaceutical agents. The therapeutic action of thiazolidinediones in decreasing insulin resistance and blood glucose levels is probably mediated by their action as ligands for peroxisome proliferator-activated receptor-γ (Barroso et al. 1999). Interactions between different hormones and their receptors illustrate the complexity of mechanisms involved in nutritional regulation of gene expression. For example, GC increase RXRα expression and enhance TH action in primary-cultured rat hepatocytes (Yamaguchi et al. 1999). Moreover, up regulation of the insulin-dependent glucose transporter in selected muscles by postnatal undernutrition is probably induced by the concomitant increase in GC levels and not to changes in TH status (Li et al. 1998a; Katsumata et al. 1999).

The importance of nutrition–hormone–drug interactions should not be underestimated. Interactions between dietary I, TR and amiodarone, for example, have major consequences for TH metabolism and optimal cardiac function. Amiodarone is a powerful anti-arrhythmic drug that probably exerts its major effect by antagonism with TH at the receptor level (Drvota et al. 1995). It acts on cardiomyocytes to block ion channels and adrenergic receptors, and hence prolongs action potential and refractory period and reduces heart rate. This drug contains 370 mg I/g and a major side effect is induction of thyroid dysfunction; hypothyroidism is frequently encountered in I-sufficient geographical regions, whereas thyrotoxicosis is more common in I-deficient areas (Loh, 2000). This finding may be explained by an excess of I preventing thyroidal I uptake, by blocking the I pump. Moreover, the presenting clinical features are age-dependent, and probably reflect changes in peripheral responsiveness to TH. The additional finding that some types of amiodarone-induced thyrotoxicosis benefit from treatment with GC further highlights the complexity of the interactions between nutrition and nuclear receptors.

Nutrient–nuclear hormone receptor interactions

Precise interactions between members of the nuclear receptor superfamily and their diverse range of ligands remain to be established. The heterodimerization properties of some of the receptors ensure a complexity of transcriptional responses to nutritional and hormonal stimuli (Glass, 1996). RXR are receptors for the vitamin A metabolite 9-cis-retinoic acid and are also cofactors which heterodimerize with many members of the nuclear receptor superfamily, including those for all-trans-retinoic acid, TH, vitamin D and peroxisome proliferator-activated receptors (Rowe, 1997). The vitamin D receptor is thought to heterodimerize with RXR but not with TR, and distinct repressive actions of TR on vitamin D receptor-mediated signalling have been demonstrated; a TH-independent action, presumably via direct competition with TR–RXR for DNA binding, and a TH-dependent repression, probably by diversion of RXR from vitamin D receptor–RXR heterodimers to TR–RXR heterodimers (Thompson et al. 1999). These interactions may provide a partial explanation for the observed association between hyperthyroidism and bone demineralization or osteoporosis. Moreover, the finding that vitamin D interferes with transactivation of the GH gene by TR and retinoic acid further highlights the potential significance of interactions between nutrients and hormones during development (Garcia-Villalba et al. 1996).

During early development both TR and retinoic acid receptors are expressed. Although this stage of development is predominantly sensitive to retinoic acid rather than to TH, unliganded TRα1 in mouse embryonic stem cells inhibits retinoic acid responsiveness and retinoic acid-stimulated neural differentiation (Lee et al. 1994). Moreover, vitamin A may suppress the thyroid-stimulating hormone β-subunit transcription directly, via a retinoic acid receptor–RXR-mediated mechanism (Breen et al. 1995). Important interactions between TR, GR and retinoid acid receptors are also suggested by studies on TH, I and vitamin A status (Garcin et al. 1984; Filteau et al. 1994; Coustaut et al. 1996). Potential interactions between members of the superfamily of nuclear receptors, and their cognate ligands, should not be ignored in intervention programmes using I or vitamin A supplementation of young and adult human populations.

Concluding remarks

Considerable advances in understanding of the molecular structure and function of hormone receptors have occurred...
during the last decade. Advances have been dependent on new techniques of molecular and structural analysis combined with sophisticated gene-targeting studies. Less clear-cut is our understanding of the mechanisms by which nutritional status regulates phenotypic expression via genetic and epigenetic events involved in hormone receptor action. The next decade should see significant advances in knowledge of the precise mechanisms by which nutrition modulates hormone receptor function throughout fetal, infant and adult life. Insight should also be gained into the relative contributions of nutrition and genotype to optimal development. Studies should focus not only on specific nutrients but also on energy status and overall food intake. It is well recognized that intrauterine growth restriction and postnatal undernutrition can impair both immediate and long-term development, with profound consequences for optimal health and disease (Lucas, 1994; Barker, 1995; Dauncey, 1997; Desai & Hales, 1997). Detailed understanding of nutrition–hormone receptor–gene interactions will lead to improvements in preventative and therapeutic strategies, from the nutritional to the molecular level.

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