# DOWNLOAD PDF THYROID HORMONE RECEPTORS

## Chapter 1 : Thyroid hormone receptor - Wikipedia

*The thyroid hormone receptor (TR) is a type of nuclear receptor that is activated by binding thyroid hormone.*

Hepatocarcinoma SK-hep1 , breast cancer MDA Human No treatment vs methimazole-induced hypothyroidism Reduced tumor growth and proliferation, but enhanced invasiveness and metastasis in hypothyroid mice Martinez-Iglesias et al. In rats, hypothyroidism inhibited both local and metastatic growth of hepatomas and prolonged host survival. Rats, in which hypothyroidism was induced by either PTU or I treatment or thyroidectomy 2 weeks after hepatoma implantation Morris hepatoma 44 into the hind limbs, survived longer and developed smaller tumors than untreated controls Mishkin et al. The time of induction of hypothyroidism by I treatment influenced the outcome significantly: The effect of T4 treatment and I-induced hypothyroidism on tumor growth and metastasis formation was compared to that in control mice for two murine cancer models, sarcoma S1 and fibrosarcoma T Kumar et al. T4 treatment led to increased growth rate of tumor implants and rate of metastasis to the popliteal lymph nodes and thymus or lung. Strikingly, hypothyroidism appeared to reverse the effect of T4 with reduced tumor weight as well as reduced metastasis. For these experiments, hypo- and hyperthyroidism were documented by increased or undetectable serum T4 levels. These results were obtained in syngenic murine tumor systems. Similar effects could be observed in xenografts with human cancer cell lines. In a similar experiment, mice were inoculated with PC-3 cells or the poorly differentiated lung carcinoma cell line T Theodossiou et al. The mice were treated with PTU 3 weeks before inoculation and through the 42 days of the experiment or not treated with PTU. All animals developed tumors, but for both carcinoma cell lines, the tumors in PTU-treated mice were significantly smaller than in untreated mice, demonstrating again that tumor growth is diminished in hypothyroidism. Xenografts of the same cell line were implanted in nude mice and treatment with Tetrac resulted in significantly smaller tumor volumes and lower tumor weights as well as lower hemoglobin content as a measure of tumor vascularity Mousa et al. The antitumor effect of Tetrac has also been shown in other xenograft models, e. These observations are very promising because they go beyond merely describing an effect of TH and provide a potential treatment. As the stimulatory effect of TH on cell proliferation and angiogenesis could clearly be inhibited by Tetrac in vitro, it seems logical to assume that the same mechanisms apply in vivo. But a demonstration that a tumor-stimulating effect of TH effect observed in vivo, as described earlier, can be blocked by Tetrac treatment has yet to be provided. In a live tumor environment, more signals other than TH e. This mutant completely lost T3 binding ability, showed no transactivation activity, and exerted a strong dominant negative effect Kaneshige et al. The degree of PI3K activation therefore cannot be modified by T3 levels. These mutants arise de novo in carcinomas and often harbor more than one mutation. This mechanism may contribute to tumor progress, but the clinical relevance is still unclear. TH and success of tumor therapy As TH appear to promote tumor growth, metastasis, and survival in animal models, it seems possible that thyroid function could influence the outcome of tumor therapy, which is defined by exactly these parameters. With the idea that IGF1 inhibits the efficiency of tamoxifen and IGF1 levels are reduced in hypothyroidism, the patients were co-treated with a fixed PTU dose to induce hypothyroidism. Eleven of the 22 patients became hypothyroid. Surprisingly, median survival was significantly longer in the hypothyroid patients Fifty-nine patients developed hypothyroidism with increased TSH levels. Hypothyroidism was most likely a consequence of radiation, but the radiation dose was not different for hypothyroid and euthyroid patients 70 vs 69 Gy, NS. Of the 59 patients who became hypothyroid during the course of treatment and follow-up, 16 had a recurrence ten before or with diagnosis of hypothyroidism and six after , whereas recurrence was detected in 41 of 96 euthyroid patients. The risk for death or recurrence was significantly lower in hypothyroid patients HR 0. In contrast to the intended induction of hypothyroidism in the glioblastoma patients, the hypothyroid head and neck cancer patients were started on T4, but data on efficacy of T4 supplementation were not available. Hypothyroidism as a side effect of treatment and treatment outcome Development of autoimmune thyroid disease, mostly thyroiditis with hypothyroidism and more seldom autoimmune hyperthyroidism, is a known side effect of interleukin-2 IL2 treatment. A potential correlation between treatment outcome and

thyroid function was noted in the s, when in a small series of 13 patients with RCC or malignant melanoma 6 of 7 eu- or hyperthyroid patients died from progressive disease, but only one of five patients who developed hypothyroidism. Four hypothyroid patients were placed on T4 supplementation Reid et al. Similarly, of 15 cancer patients RCC, malignant melanoma treated with IL2 and lymphokine-activated killer cells, five of seven hypothyroid patients responded with partial or complete remission, but none of the euthyroid patients Weijl et al. Three of the seven hypothyroid patients received T4 substitution. In the context of thyroid function and cancer treatment outcome, studies with tyrosine kinase inhibitors TKIs such as sunitinib are extremely interesting because hypothyroidism is a common side effect of TKIs. In a recent study using a German pharmacy prescription claims database, of patients  How TKI induce hypothyroidism is not fully understood and several mechanisms have been proposed, for example, reduction of thyroid volume due to atrophy of follicles, degeneration of follicular epithelial cells Shinohara et al. Extrathyroidal mechanisms affecting TH metabolism must also be involved because patients with medullary thyroid cancer treated with imatinib, who underwent thyroidectomy and were on T4 replacement therapy, also developed hypothyroidism de Groot et al. As one possible explanation, sunitinib appears to increase deiodinase 3 activity Kappers et al. A positive correlation between sunitinib-induced hypothyroidism and progression-free PFS or overall survival OS of RCC patients was first reported in Wolter et al. Thirteen hypothyroid patients were supplemented with T4. In a prospective Italian study, 13 of 22 sunitinib-treated RCC patients  Two patients required T4 substitution. Again, the hypothyroid patients experienced a longer median PFS 8. In an Austrian study, RCC patients were treated with either sunitinib or sorafenib and subclinical hypothyroidism occurred in 30 patients  The rate of objective remission RECIST criteria was significantly higher in the hypothyroid patients than in euthyroid patients  T4 replacement was started in 16 patients but normalized TSH in only four, while the other 12 remained hypothyroid. On multivariate analysis, only elevated TSH was an independent predictor of survival. Development of hypothyroidism was again an independent prognostic parameter in another study of 66 patients with metastatic RCC and sunitinib or sorafenib treatment. Twenty-one patients developed hypothyroidism  Patients with overt hypothyroidism were placed on T4 and the association of hypothyroidism with PFS was not diminished by T4 replacement. Interestingly, a prospective study, for which the investigators chose to supplement all hypothyroid patients, overt and subclinical, found no association between survival and thyroid dysfunction Sabatier et al. Patients with elevated TSH were placed on T4 replacement. Mean PFS was not significantly different with  Similar effects as for sunitinib were observed for another TKI, cediranib: Hypothyroidism was reported in of  Conclusion and outlook Epidemiological data suggest a tumor-promoting effect of TH as the incidence of some tumors colon, breast, prostate, and lung cancer was found to be increased with increasing TH whereas other tumors, e. In tumor transplant rodent models, TH appear to stimulate tumor growth and metastasis, whereas hypothyroidism has opposite effects. Therefore, the results of clinical studies showing that treatment-induced hypothyroidism is associated with a favorable outcome in several cancer types, most prominently in RCC, are immediately comprehensible. In two prospective studies of RCC treated with sunitinib, development of hypothyroidism was an independent predictor of treatment success. Furthermore, in the only study replacing T4 in every RCC patient with elevated TSH and including only patients with normal TSH in the final analysis, no difference in treatment outcome between the patients that developed hypothyroidism and those that remained euthyroid was observed Sabatier et al. It is tempting to assume that induction of hypothyroidism is one of the mechanisms through which TKIs slow tumor growth and that correction of hypothyroidism eliminates the survival advantage. There is reasonable concern that substituting these cancer patients with T4 could deprive them of the potential beneficial effects of hypothyroidism Garfield et al. Yet, one must be cautious because it cannot be ruled out that hypothyroidism is only a surrogate marker of antitumor treatment efficacy due to higher drug levels or different drug metabolism or susceptibility of the immune system in a subset of patients and does not influence tumor growth on its own. There may also be a bias because cancer patients on successful, and therefore continued, treatment are exposed to higher cumulative doses and have more time to develop hypothyroidism than rapidly deteriorating patients. Additionally, a tumor-promoting effect of TH may only be found in certain types of cancer, such as glioblastoma and RCC, but not for others, e. Given the results of the

tumor implant animal models and the TKI trials in cancer patients, it is of great clinical importance to determine whether and in which types of cancer hypothyroidism can contribute to prolonged survival and should be tolerated or, more provocative, should even be induced. To address these questions, future cancer treatment studies, especially with substances that can induce hypothyroidism, should be designed in a way that allows for an analysis of thyroid function status and its contribution on treatment outcome. Declaration of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## Chapter 2 : Thyroid hormone receptors and resistance to thyroid hormone disorders

*Receptor Structure. Mammalian thyroid hormone receptors are encoded by two genes, designated alpha and beta. Further, the primary transcript for each gene can be alternatively spliced, generating different alpha and beta receptor isoforms. Currently, four different thyroid hormone receptors are recognized: alpha-1, alpha-2, beta-1 and beta*

Overview of thyroid hormone action Thyroid hormone is produced by the thyroid gland, which consists of follicles in which thyroid hormone is synthesized through iodination of tyrosine residues in the glycoprotein thyroglobulin 6 , 7. Thyroid stimulating hormone TSH , secreted by the anterior pituitary in response to feedback from circulating thyroid hormone, acts directly on the TSH receptor TSH-R expressed on the thyroid follicular cell basolateral membrane 8. Thyroid hormone is essential for normal development, growth, neural differentiation, and metabolic regulation in mammals 2 , 3 , 10 and is required for amphibian metamorphosis These actions are most apparent in conditions of thyroid hormone deficiency during development, such as maternal iodine deficiency or untreated congenital hypothyroidism, manifesting as profound neurologic deficits and growth retardation 6. More subtle and reversible defects are present when ligand deficiency occurs in the adult Human genetics, animal models, and the use of selective pharmacologic agonists have been informative about the role and specificity of the two major isoforms 2 , 14 , The selective actions of thyroid hormone receptors are influenced by local ligand availability 1 , 16 ; by transport of thyroid hormone into the cell by monocarboxylate transporter 8 MCT8 or other related transporters 17 ; by the relative expression and distribution of the TR isoforms 13 and nuclear receptor corepressors and coactivators 18 ; and, finally, by the sequence and location of the thyroid hormone response element TRE; refs. In addition, nongenomic actions of thyroid hormone, those actions not involving direct regulation of transcription by TR, have been increasingly recognized Several studies have identified direct actions of TR on signal transduction systems 2 , 24 , which may be especially significant in relation to actions in cell proliferation and cancer. Figure 1 Nuclear action of thyroid hormone. Shown are the key components required for thyroid hormone action, as demonstrated by a range of clinical observations. B The major thyroid hormone forms, T4, T3, and rT3. C Circulating T4 is converted locally in some tissues by membrane-bound D2 to the active form, T3. D3 converts T3 to the inactive rT3. T3 binding to the ligand-binding domain results in movement of the carboxyterminal helix 12, disruption of corepressor binding, and promotion of coactivator binding, which then leads to recruitment of polymerase III and initiation of gene transcription. The broad range of genes whose expression is modified by thyroid hormone status makes studying the effect of thyroid hormone action a daunting challenge Many of the actions of thyroid hormone are the result of potentiation or augmentation of other signal transduction pathways Table 2 and ref. In metabolic regulation, this includes potentiation of adrenergic signaling 26 â€” 29 as well as direct interaction with metabolic-sensing nuclear receptors 30 â€” Similar direct receptor-to-receptor interactions and competition for overlapping DNA response elements are seen in neural differentiation, as TR interacts with chicken ovalbumin upstream transcription factor 1 COUP-TF1 and retinoic acid receptor RAR 3 , Table 2 Thyroid signaling cross-talk with other pathways from in vitro and in vivo models and TR isoform preference TR isoforms differ in length at both amino and carboxy termini and are differentially expressed developmentally and spatially Figure 1. TR isoform selectivity for TRE sequences in genes that mediate thyroid hormone response have been seen in some studies, but not all. TRE sequences influence TR isoform interaction with ligand 36 and may influence coactivator recruitment TR interaction with TREs is not static; as has been reported with other nuclear receptors, there is variation in the pattern of binding that may be influenced by the TRE In vitro studies have shown some TR isoform preferences for specific TREs 38 , although the ability to translate these findings to in vivo observations are likely limited. Cell membrane thyroid hormone transport and local ligand availability Local activation of T3 from the prohormone T4 at the tissue level is increasingly recognized as an important mechanism of regulation of thyroid hormone action T4 deiodination by D2 results in exposed lysine residues in D2: The inactivation of T4 to form reverse T3 rT3 , mediated by type 3 5-deiodinase D3 , is also important in regulating tissues levels of T3, especially in thyroid axis regulation and sensory development 43 , Some â€” but not all â€” human

genetic linkage studies of polymorphisms in D2 have shown an association with obesity and diabetes 45 , The relationship between the level of serum T4 and serum TSH, termed the set point, is stable for an individual when repeatedly measured prospectively, but varies significantly between individuals This variability in set point in the population suggests that there is a genetic influence involving one or more genes in the thyroid hormone pathway D2 polymorphisms have been associated with an altered pituitary set point of TSH 49 and with a blunted increase in serum T4 after thyrotropin-releasing hormoneâ€"stimulated TRH-stimulated acute increase in serum TSH Specific D2 polymorphisms were linked to an improved response in hypothyroid patients to replacement with combined therapy of T4 and T3, rather than T4 alone These patients may have reduced conversion of T4 to T3 at the tissue level and benefit from replacement with T3. Selenium is required for the enzyme function of all three deiodinases. Individuals with abnormal thyroid hormone metabolism have been described with defects in the SECISBP2 gene, which is required for the synthesis of selenoproteins 52 , thus confirming the essential role of this mineral in thyroid metabolism Table 1. Thyroid hormone is hydrophobic and was long thought to enter into the cytoplasm by passive diffusion. Thyroid hormone transporters, such as the monocarboxylate MCT family and organic anion transporters OATPs , were identified based on measurable in vitro activity, but the physiologic significance of these transporters was not established early on MCT8 was identified as a specific transporter of thyroid hormone and was reported to be located on the X chromosome Individuals with a severe form of X-linked mental retardation, Allan-Herndon-Dudley syndrome, manifest with truncal hypotonia, poor head control, and later spasticity and were found to have abnormal thyroid function elevated serum T4 and rT3 and low T3. When MCT8 was sequenced in these patients, inactivating mutations were identified in some individuals 54 , More recently, a mouse model with MCT8 inactivation demonstrated that MCT8 is also important for secretion of thyroid hormone Oatp1c1 was shown in a mouse model to be important for thyroid transport across the choroid plexus and into the brain Thyroid transporters in the developing brain are expressed in specific temporal and spatial patterns 17 , Individuals with an MCT8 mutation have myelination delays, which are thought to be caused by impaired thyroid hormone action on oligodendrocytes MCT8 is expressed in the hypothalamus, a major site of integration of thyroid hormone feedback and gene regulation Exogenous T3, even in the presence of functional MCT8 transporters, does not act on fetal rat brain, due to the requirement for local production of T3 from T4 It is likely, however, that DITPA therapy will require treatment at an early stage of brain development to be effective. Thus, thyroid hormone action in the brain is modulated by both regional activation and selective uptake into cells, identifying multiple selective targets for therapeutic interventions. Expanded spectrum of resistance to thyroid hormone: Clinical features include goiter, elevated circulating thyroid hormone levels, nonsuppressed serum TSH level, clinical euthyroidism, and tachycardia; some individuals also demonstrate attention deficit disorder and deficits of linear growth, hearing, and bone formation Levels of free T4 and rT3 in these patients were in the low-normal range, and T3 in the high-normal range, with normal TSH. This may result in peripheral hypothyroidism, and also points to a potential benefit of levothyroxine therapy in these individuals. Role of TR interaction with cofactors The essential function of gene repression by transcription factor corepressors in development and homeostasis is being increasingly recognized 71 , Initial in vitro transfection studies with TR expression vectors showed that the unliganded receptor had a repressive effect on genes positively regulated by T3 and an activating effect on genes normally repressed by T3 The significance of this property has subsequently been demonstrated by several in vivo models. The repressive actions of the unliganded receptor, therefore, have a greater physiologic effect than having no receptor at all The interaction of TR with corepressors has been carefully mapped and tested 76 , The disruption of this interaction resulted in a blunted TSH response to thyroid hormone, but enhanced peripheral tissue sensitivity, as the animals were euthyroid despite lower circulating thyroid hormone levels. This indicates that constitutive TR interaction with a corepressor is an important mechanism for RTH. The interaction of NCoR with histone deacetylase 3 seems to be important for both T3-induced gene activation and repression Another approach to determine the importance of TR coactivator interactions is to determine the impact of coactivator knockouts on thyroid hormone action 82 , Mice deficient in the coactivator SRC1 showed increased resistance to the action of thyroid hormone TR isoforms and neural

development Highly selective TR isoform requirements have been shown most clearly in models of sensory development, with marked and selective defects of structure and function in the setting of TR isoform inactivation  These include development of the inner ear and the cone photoreceptors in the retina 87 , Another site with specific TR isoform function is bone, both developmentally and in the adult  The developmental importance of TR isoforms is coupled with a requirement for specific transporter expression, such as MCT8 expression in the mouse cochlea 58 , as well as a requirement for D2 expression to provide local T3, and for D3 to inactivate thyroid hormone and protect from excessive T3 action during sensitive periods 86 ,  Thyroid hormone interfaces with other signaling pathways in neural development Table 2. There is a close developmental link between retinoic acid action in early neurologic development and thyroid hormone action 3. In most model systems studied, retinoic acid acts first, followed by thyroid hormone action. The orphan nuclear receptor COUP-TF1 is expressed early in neurological development, when thyroid hormone is present, but before the brain is responsive to it  CamKIV is regulated directly by T3 in primary cultured neurons from fetal cortex and promotes the maturation and proliferation of GABAergic interneurons from their precursor cells  The timing of the transport of thyroid hormone is tied to RA based on the stimulation of MCT8 gene expression. TR isoforms and metabolic regulation Specific actions of TR isoforms have been demonstrated for metabolic regulation, including in white fat and brown adipose tissue BAT. In addition to these examples of thyroid hormone potentiation of peripheral adrenergic signaling, thyroid also influences adrenergic signaling centrally  However, in a recent study of RTH patients, increased resting energy expenditure was reported  Although these actions speak strongly for TR isoform specificity, a significant part of the specificity of action of these agents is much greater concentration of the selective agonist compound in the liver compared with the heart  Interestingly, providing hypothyroid human subjects with only T3 rather than T4, but keeping their TSH in the normal reference range, also results in reduced LDL cholesterol and slight weight loss  This modest local hepatic excess of T3 may be sufficient to lower cholesterol and produce weight loss, even when systemic levels are in the normal range. The thyroid hormone analog DIPTA was found to have some specificity for action on the heart and was studied in a prospective randomized control study in patients with severe heart failure  Although improvement in some cardiac parameters was seen, the metabolic effects of weight loss were profound, and the study stopped. The metabolic effects of DITPA â€" reduction in body weight and LDL cholesterol â€" provide encouragement for beneficial effects of this class of compound, although stimulation of bone turnover and bone loss by DITPA will limit its therapeutic use  The clinical utility of a TR antagonist has been considered primarily to antagonize the cardiac effects of thyroid hormone, such as ischemia and arrhythmias  The structure of the apo TR, without ligand, has not been solved, but important features have been identified from studies of the liganded receptor with agonists and antagonists 35 ,  Helix 12 is the carboxyterminal helix of TR, which folds in response to ligand and is essential for TR interaction with coactivators and corepressors  Association of thyroid hormone receptor mutations with cancer The viral oncogenes v-erbA and v-erbB are the mediators of avian erythroblastosis retrovirus AEV induction of erythroleukemias and fibrosarcomas in chickens, first recognized in â€"  The link between the origins of TR and oncogenes is consistent with the role of thyroid hormone signaling and mutant TRs in several forms of cancer. Expression of D3, which inactivates thyroid hormone, has been associated with proliferation of malignant keratinocytes in basal cell skin carcinomas  Summary The elements required for thyroid hormone action are well recognized, but the interaction among the various pathways has been challenging to understand. Thyroid hormone interacts with a wide variety of signaling pathways, and its action is modulated based on nutritional and iodine status. A range of conditions with disordered thyroid signaling has allowed us to identify key regulatory pathways that are potential therapeutic targets. The role of the pituitary in responding to a defect in a thyroid hormone action pathway is central to the resulting phenotype. These pathways, as well as the role of thyroid hormone in metabolism, cardiac function, and oncogenesis, are likely to be the focus in applying these findings.

## Chapter 3 : 1A. Thyroid hormone receptors | Nuclear hormone receptors | IUPHAR/BPS Guide to PHARMA

*Thyroid hormone receptor: A molecule that receives a thyroid hormone and permits it to dock on the nuclear membrane of a cell. The thyroid hormone receptors (THRs) belong to a family of nuclear receptors that function as hormone-activated transcription factors and act by modulating the expression of genes.*

They stated that the so-called placental thyroid hormone receptor encoded by human chromosome 3 is the prototype beta form; its gene is referred to as ERBA2 or THRB. Isoform beta-1 is found in liver, heart, and brain; isoform beta-2 is specific for pituitary in the mouse and rat. Alternative splicing of the gene transcript yields a species called alpha-2 or variant I, which is identical to alpha-1 for amino acids, including the DNA-binding domain, but then diverges completely. The mRNA for this form is particularly abundant in the brain. They noted that the receptor that is expressed in the mammalian central nervous system and in most other tissues except liver is encoded by a gene on chromosome 17 THRA; The receptor that is present in liver and some other tissues is encoded by a gene on chromosome 3 THRB. By Southern blot analysis of DNA from somatic cell hybrids and in situ hybridization using the same human genomic probe, Rider et al. Malignant lymphomas and salivary gland tumors consistent with chromosomal changes in that region have been observed. The assignment was done by study of somatic cell hybrids containing various translocations involving human chromosome 3. By both somatic cell hybridization and in situ hybridization, Drabkin et al. Thus, the putative suppressor gene involved in that neoplasm is probably located centromeric to ERBA2. By nonisotopic in situ hybridization to metaphase chromosomes, Albertson et al. THRB and 95 other loci on 3p were used by Tory et al. The ancestral genes were duplicated before the divergence of vertebrates, since at least the TRs and RARs are also duplicated in birds and amphibians. An additional truncated species was detected with the TR-alpha-2 primer set, consistent with the TR-alpha-3 splice variant described in the rat. All TR-alpha-derived transcripts were coordinately expressed and increased approximately 8-fold between 8. A more complex ontogenic pattern was observed for TR-beta-1, suggestive of a nadir between 8. The authors concluded that these findings point to an important role for the TR-alpha-1 isoform in mediating maternal thyroid hormone action during first-trimester fetal brain development. Most thyroid hormone receptor isoforms associate with coactivator proteins and mediate transcriptional activation only in the presence of thyroid hormone. The pituitary-specific THR-beta-2 isoform departs from this general rule and is able to interact with p coactivators, and to mediate transcriptional activation in both the absence and presence of hormone. Yang and Privalsky reported that this hormone-independent activation is mediated by contacts between the unique N terminus of THR-beta-2 and an internal interaction domain in the steroid receptor coactivator-1 SRC1; and glucocorticoid receptor-interacting protein-1 GRIP1;

## Chapter 4 : Mechanism of Action: Hormones with Intracellular Receptors

*The thyroid hormone receptors (TRs) are members of the nuclear receptor superfamily that exhibit a dual role as activators or repressors of gene transcription in response to thyroid hormone (T3) and provide a model system for investigating complex networks of cellular trafficking and gene expression.*

Let us make an in-depth study of the hormone receptors. After reading this article you will learn about 1. Meaning of Hormone Receptors and 2. Types of Hormone Receptors. Meaning of Hormone Receptors: A hormone receptor is a receptor protein on the surface of a cell or in its interior that binds to a specific hormone. The hormone causes many changes that take place in the cell. Binding of hormones to hormone receptors often trigger the start of a biophysical signal that can lead to further signal transduction pathways, or trigger the activation or inhibition of genes. Types of Hormone Receptors: Are often trans membrane proteins. They are also called G-protein- coupled receptors, sensory receptors or ionotropic receptors. Steroid Hormone Receptors and Related Receptors: Are generally soluble proteins that function through gene activation. Their response elements are DNA sequences promoters that are bound by the complex of the steroid bound to its receptor. The receptors themselves are zinc-finger proteins. These receptors include those for glucocorticoids, estrogens, androgens, thyroid hormone T3 , calcitriol the active form of vitamin D , and the retinoids vitamin A. Receptors for Peptide Hormones: With the exception of the thyroid hormone receptor, the receptors for amino acid derived and peptide hormones are located in the plasma membrane. Receptor structure is varied. Some receptors consist of a single polypeptide chain with a domain on either side of the membrane, connected by a membrane-spanning domain. Some receptors are comprised of a single polypeptide chain that is passed back and forth in serpentine fashion across the membrane, giving multiple intracellular, trans membrane, and extracellular domains. Other receptors are composed of multiple polypeptides. Subsequent to hormone binding, a signal is transduced to the interior of the cell, where second messengers and phosphorylated proteins generate appropriate metabolic responses. Additionally a series of membrane-associated and intracellular tyrosine kinases phosphorylate specific tyrosine residues on target enzymes and other regulatory proteins. The classic interactions between receptors, G-protein transducer, and membrane-localized adenylate cyclase are illustrated using the pancreatic hormone glucagon as an example. The Ga-GTP complex binds adenylate cyclase, activating the enzyme. Stimulatory G-proteins are designated Gs, inhibitory G-proteins are designated Gi. Hormone binding is followed by interaction with a stimulatory G-protein which is followed in turn by G-protein activation of membrane-localized phospholipase C-y, PLC-y. PLC-y hydrolyzes phosphatidylinositol bisphosphate to produce 2 messengers viz. IP3, which is soluble in the cytosol, and DAG, which remains in the membrane phase. There it activates numerous enzymes, many by activating their calmodulin or calmodulin-like subunits. Like PKA, PKC phosphorylates serine and threonine residues of many proteins, thus modulating their catalytic activity. Is a trans membrane receptor that is activated by insulin. It belongs to the large class of tyrosine kinase receptors. Two alpha subunits and two beta subunits make up the insulin receptor. The beta subunits pass through the cellular membrane and are linked by disulfide bonds. The alpha and beta subunits are encoded by a single gene INSR. Function of insulin receptor-effect of insulin on glucose uptake and metabolism: Insulin binds to its receptor which in turn starts many protein activation cascades. Translocation of Glut-4 transporter to the plasma membrane and influx of glucose ii. IRS-1 binding and phosphorylation eventually leads to an increase in the high affinity glucose transporter Glut4 molecules on the outer membrane of insulin-responsive tissues, including muscle cells and adipose tissue, and therefore to an increase in the uptake of glucose from blood into these tissues. Briefly, the glucose transporter Glut4 is transported from cellular vesicles to the cell surface, where it then can mediate the transport of glucose into the cell. Glycogen synthesis is also stimulated by the insulin receptor via IRS Pathology of insulin receptors: The main activity of activation of the insulin receptor is inducing glucose uptake. Patients with insulin resistance may display acanthosis nigricans. A few patients with homozygous mutations in the INSR gene have been described, which causes Donohue syndrome or Leprechauns. This autosomal recessive disorder results in a totally non-functional insulin receptor. These patients have low set,

often protruberant ears, flared nostrils, thickened lips, and severe growth retardation. In most cases, the outlook for these patients is extremely poor with death occurring within the first year of life. Both diseases present with fluctuations of the glucose levelâ€"after a meal the glucose is initially very high, and then falls rapidly to abnormally low levels. Degradation of insulin and its receptors: Once an insulin molecule has docked onto the receptor and effected its action, it may be released back into the extracellular environment or it may be degraded by the cell. Degradation normally involves endocytosis of the insulin-receptor complex followed by the action of insulin degrading enzyme. Most insulin molecules are degraded by liver cells. It has been estimated that a typical insulin molecule is finally degraded about 71 minutes after its initial release into circulation. It is a 62 kDa peptide that is activated by glucagon and is a member of the G- protein coupled family of receptors, coupled to Gs. Stimulation of the receptor results in activation of adenylate cyclase and increased levels of intracellular cAMP. Glucagon receptors are mainly expressed in liver and in kidney with lesser amounts found in heart, adipose tissue, spleen, thymus, adrenal glands, pancreas, cerebral cortex, and G. Are proteins that have a binding site for a particular steroid molecule. Their response elements are DNA sequences that are bound by the complex of the steroid bound to its receptor. The response element is part of the promoter of a gene. Binding by the receptor activates or represses, as the case may be, the gene controlled by that promoter. It is through this mechanism that steroid hormones turn genes on or off. The DNA sequence of the glucocorticoid a protein homodimer response element is: For a steroid hormone to turn gene transcription on, its receptor must: The zinc fingers for binding DNA. Mutations in any one region may upset the function of that region without necessarily interfering with other functions of the receptor. The zinc-finger proteins that serve as receptors for glucocorticoids and progesterone are members of a large family of similar proteins that serve as receptors for a variety of small, hydrophobic molecules. They got their name from their initial discovery as the receptors for drugs that increase the number and size of peroxisomes in cells. In every case, the receptors consists of at least three functional modules or domains from N-terminal to C-terminal, these are: A domain needed for the receptor to activate the promoters of the genes being controlled ii. The zinc-finger domain needed for DNA binding to the response element iii. The domain responsible for binding the particular hormone as well as the second unit of the dimer Receptors for Thyroid Hormones: Are members of a large family of nuclear receptors that include those of the steroid hormones. They function as hormone-activated transcription factors and thereby act by modulating gene expression. Thyroid hormone receptors bind DNA in absence of hormone: Usually leading to transcriptional repression. Hormone binding is associated with a conformational change in the receptor that causes it to function as a transcriptional activator. Mammalian thyroid hormone receptors are encoded by two genes, designated alpha and beta. Further, the primary transcript for each gene can be alternatively spliced, generating different alpha and beta receptor isoforms. Like other members of the nuclear receptor superfamily, thyroid hormone receptors encapsulate three functional domains: A transactivation domain at the amino terminus that interacts with other transcription factors to form complexes that repress or activate transcription. There is considerable divergence in sequence of the transactivation domains of alpha and beta isoforms and between the two beta isoforms of the receptor. A ligand-binding and dimerization domain at the carboxy-terminus. Disorders of thyroid hormone receptors: A number of humans with a syndrome of thyroid hormone resistance have been identified, and found to have mutations in the receptor beta gene which abolish ligand binding. Clinically, such individuals show a type of hypothyroidism characterized by goiter, elevated serum concentrations of T3 and thyroxine and normal or elevated serum concentrations of TSH. More than half of affected children show attention-deficit disorder, which is intriguing considering the role of thyroid hormones in brain development. In most affected families, this disorder is transmitted as a dominant trait, which suggests that the mutant receptors act in a dominant negative manner. Adrenergic Receptors or Adrenoceptors: Many cells possess these receptors, and the binding of an agonist will generally cause a sympathetic response i. There are several types of adrenergic receptors, but there are two main groups viz. Phenylephrine is a selective agonist of the a-receptor. These receptors are linked to Gs proteins, which in turn are linked to adenyl cyclase. Agonist binding thus causes a rise in the intracellular concentration of the second messenger cAMP. The result is that high levels of circulating epinephrine cause vasoconstriction. The mechanism of adrenergic receptors: This

triggers all other effects.

## Chapter 5 : Thyroid hormone receptor-Î± | 1A. Thyroid hormone receptors | IUPHAR/BPS Guide to PHARM

*Thyroid hormone receptors (TRs, nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors []) are nuclear hormone receptors of the NR1A family, with diverse roles regulating macronutrient metabolism, cognition and cardiovascular homeostasis.*

Resistance to thyroid hormone Resistance to thyroid hormone Resistance to thyroid hormone is a rare genetic condition where some body tissues do not respond normally to thyroid hormones produced by the thyroid gland. It may be associated with no symptoms or with features of both an overactive and underactive thyroid. It can be subdivided into different forms â€" either generalised resistance to thyroid hormone or pituitary central resistance to thyroid hormone. What is resistance to thyroid hormone? Blood levels of thyroid hormone are elevated because the pituitary gland which controls hormone production from the thyroid gland is not appropriately shut off by thyroid hormone. Thyroid hormone overproduction can lead to enlargement of the thyroid gland goitre. Peripheral tissues are either resistant or remain sensitive to high levels of thyroid hormones resulting in features of both an under- and over-active thyroid. What causes resistance to thyroid hormone? Usually thyroid hormones carry out their role by interacting with a receptor in the various target cells in the body. In resistance to thyroid hormone, these receptors are abnormal, meaning that the thyroid hormones cannot act normally on cells and bring about their usual effects. There are two types of thyroid hormone receptor: Tissues of the body contain differing proportions of alpha and beta receptors. Tissues in the body respond differently to high thyroid hormone levels depending on the relative amount of alpha versus beta receptor contained in that tissue. Thus tissues containing mainly normal alpha receptors can exhibit features of thyroid overactivity, whereas tissues with defective beta receptors are resistant to hormone action and can show features associated with thyroid underactivity. What are the signs and symptoms of resistance to thyroid hormone? Hence, some patients might have no symptoms if they have a milder, partial resistance because they can overcome this by increasing the amount of thyroid hormones they make. Some patients might have signs of an underactive thyroid if their receptors respond very little to thyroid hormones. These include raised cholesterol levels, feeling tired and a tendency to be overweight see the article on hypothyroidism for more information. However, there can also be some symptoms of an overactive thyroid , especially a fast heart rate see the article on hyperthyroidism for more information. This is because the heart has few beta receptors and more of the normal alpha receptors that respond normally to the increased levels of thyroid hormone. Most people with this condition develop an enlarged thyroid gland goitre. This occurs because of the need to make more thyroid hormones than normal. In children, there can be failure to grow, more frequent ear, nose and throat infections, attention deficit hyperactivity disorder ADHD , learning disability and hearing loss. How common is resistance to thyroid hormone? Resistance to thyroid hormone is rare, affecting around 1 in every 40,â€"50, people. It affects men and women equally. It may be diagnosed at any age although the blood test will be abnormal from birth. Is resistance to thyroid hormone inherited? How is resistance to thyroid hormone diagnosed? The first step is to do a simple blood test called a thyroid function test. This usually shows high levels of thyroid hormones thyroxine and triiodothyronine along with a normal or slightly high level of thyroid stimulating hormone. This abnormal test is also seen in those patients with thyroid hormone resistance and no symptoms. This pattern of results can also be seen in several other situations. The laboratory will check the test results carefully to exclude interference with measurement or a problem with circulating binding proteins. A test called a thyrotropin-releasing hormone test is also usually carried out to differentiate resistance to thyroid hormone from TSH-secreting pituitary adenoma. This is done in hospital but only takes a morning. It involves taking an initial blood sample followed by an injection of thyrotropin-releasing hormone, then further blood tests over an hour. Blood will also be taken to look for abnormalities of the thyroid hormone beta receptor by genetic testing. Family members may also be asked to have thyrotropin-releasing hormone checked. After these investigations, if the diagnosis is still not clear, a triiodothyronine suppression test may be required. This involves taking a high dose of the thyroid hormone triiodothyronine for eight to 10 days with blood tests to measure hormone levels before and afterwards. Genetic testing can provide a definitive

confirmation, though it is likely that not all variants are known. How is resistance to thyroid hormone treated? Many people with resistance to thyroid hormones have abnormal blood tests but no symptoms. They do not require any treatment. Children will need extra assessment to check they are growing and developing normally. Patients who have symptoms of hypothyroidism underactive thyroid are treated with levothyroxine tablets â€" a synthetic version of thyroxine given to replace the sub-optimal level of thyroid hormone. Once the levothyroxine is absorbed in the bloodstream, it is converted to triiodothyronine, which is the active hormone that the tissues and cells require. Combination treatment with levothyroxine and triiodothyronine is not recommended because there is no clear evidence in research studies that it is more beneficial than levothyroxine alone. The treatment needs to be monitored with regular blood tests. Drugs to slow the heart rate e. Are there any side-effects to the treatment? If high doses of thyroid hormones are required to compensate for the resistance, this can sometimes cause a fast heart rate requiring extra treatment with a beta-blocker. What are the longer-term implications of resistance to thyroid hormone? Rarely, the very high levels of thyroid hormones can cause growth and related problems in an unborn child and this requires careful monitoring. Women who have resistance to thyroid hormones should speak to their specialist before becoming pregnant. Resistance to thyroid hormone comes with an increased likelihood of thinning of the bones osteoporosis so monitoring of bone density is carried out in adult patients. There is no evidence that any specific dietary modification can help in resistance to thyroid hormone.

## Chapter 6 : Thyroid Hormone Receptors

*Thyroid hormones (THs) affect growth, development, and metabolism in almost all tissues. THs exert their actions by binding to thyroid hormone receptors (TRs). There are two major subtypes of TRs, TRÎ± and TRÎ², and several isoforms (e.g. TRÎ±1, TRÎ±2, TRÎ²1, and TRÎ²2).*

Thyroid hormone provides an example of how the endocrine system and the nervous system can functionally merge to achieve an objective. Thyroid hormone is crucial to growth, nutrient metabolism and in people heat generation. Among numerous other things, it supports neuron maturation in infants and assists pituitary growth hormone in regulation of long bone growth. On it lays the parathyroid gland. This photomicrograph shows a section of thyroid gland on the left and adjacent parathyroid gland on the right. Notice the structural difference in the two types of tissue. The center of each thyroid follicle is filled with a colloid material. In this section the thyroid cells are at the edges of the colloid. Thyroid hormone synthesis Follicle cells increase their synthesis of thyroid hormone in response to the blood presence of another hormone name Thyroid Stimulating Hormone TSH. TSH is secreted by the pituitary gland and binds to a plasma membrane receptor on thyroid follicle cells. This sets in motion cellular pathways for the synthesis of thyroid hormone. Thyroglobulin is transferred from the cell into the central colloid material by exocytosis. In the colloid of the follicle iodine is added to the thyroglobulin. Iodide Iâ€" is pumped into the follicle cells from the capillaries supplying the follicle cells. As the concentration of Iâ€" increases in the cell it is passively transported into the central colloid. Iâ€" in the colloid is oxidized by an enzyme reaction to iodine I0 , a highly reactive molecule. I0 combines with the many tyrosine residues of thyroglobulin. Iodinated thyroglobulin then reenters the follicle cell by endocytosis. Various cell enzymes that break apart proteins named proteases excise thyroxine T4 with four attached iodine and triiodothyronine T3 with three attached iodine. Cell membrane transporters then move T4 and T3 into blood capillaries. In the blood, these small molecules are bound to large globular plasma proteins. Thyroid hormone receptors For a target cell to respond to a hormone it must have a receptor, a cell protein that binds to the hormone. Thyroid hormone receptors reside in the cell nucleus. Because thyroid hormone is not lipid soluble, it enters the target cell with the help of membrane transporters located in the plasma membrane to reach its receptors. There are multiple types of thyroid hormone receptors. The number and type of thyroid receptor available varies by tissue. TRHA produces six isoforms. The purpose of the short protein isoforms in thyroid hormone function is unclear. Thyroid hormone receptor mechanism of action in cell nucleus, released to public domain by author Boghog2 via WikiMedia Thyroid hormone receptor may bind to DNA as a monomer one thyroid receptor , a homo-dimer two thyroid receptors bound together or a hetero-dimer one thyroid receptor plus a retinoid X receptor. The hetero-dimer with the retinoid X receptor is the major functional form of the thyroid hormone receptor. The active form of thyroid hormone at nuclear receptors is T3. Iodine must be removed from T4 converting it to T3 for receptor binding to occur. There are 3 forms of the de-iodination enzymes within thyroid hormone target cells. These enzymes, depending upon their location and activity, allow thyroid hormone function to be regulated deferentially throughout the body. Thyroid hormone regulation at the cellular level may take place at plasma membrane uptake, at enzymatic removal of iodine from T4 and T3, and in the nucleus depending upon the type of receptor available. Thyroid hormone negative feedback The hypothalamus-pituitary-thyroid feedback loop is a negative feedback process that regulates synthesis and release of thyroid hormone from the gland. The simplest view of thyroid hormone feedback is presented in this image. However, the system is more complex than it first appeared. Somatostatin and dopamine, brain neurotransmitters, and glucocorticoid from the adrenal gland inhibit synthesis and release of TSH. Also, several pituitary peptides affect TSH production and release. In fact, there is a daily rhythm of TSH in blood. Plasma TSH is low during the day and increases in early evening, peaking near the beginning of sleep. This hormonal rhythm is generated by the part of the hypothalamus known as the biologic clock of the brain. Neurons of the clock region synapse on the TRH neurons in another part of the hypothalamus. Multiple neuron pathways in the brain also connect to the thyroid gland indirectly through the autonomic nervous system. Fasting disconnects the basal negative feedback loop. One theory is that this is a way to

conserve energy when food is short. That is why I chose them for this and my last post. However, they do illustrate general features found in endocrinology. Here are the elements to look for when learning endocrinology. Cells with components necessary to synthesize and secrete hormone into blood Cells with protein receptors that bind a hormone found in blood Receptor binding that sets in motion particular cellular pathways Brain neurons that respond to hormone fluctuation in blood A negative feedback regulatory loop â€" positive feedback exists, but rarely.

## Chapter 7 : Thyroid hormone receptor beta - Wikipedia

*In resistance to thyroid hormone, these receptors are abnormal, meaning that the thyroid hormones cannot act normally on cells and bring about their usual effects. There are two types of thyroid hormone receptor: alpha and beta.*

Let me break it down for you: Some hormones can go easily into cells to find receptors. For example, fat based steroid hormones like estrogen, progestins, etc. As a result they can pass easily through the cell membrane, but they need proteins to help them through the watery bloodstream these are the binding globulins that you may have heard of. Receptors for these steroid hormones are found in several different places: Other hormones stay outside the cell and attach to receptors found in the outer membrane. This keeps these peptide hormones outside the cell where they only bind with receptors found there. Thyroid Hormone Is Unique Thyroid hormones, which are derived from amino acids, behave more like steroids than its peptide cousins and can actually bind to receptors both inside and outside the cell. Which means they are very adaptable and flexible and it can also mean that they are able to bind to other things as well, like food, chemicals and minerals. Many Drugs and Supplements Bind to Thyroid Hormone Many commonly used medications or supplements like iron, calcium, estrogen, proton pump inhibitors, and statins can cause affect thyroid hormone absorption or binding to plasma proteins. Sometimes, if the doctor is paying attention, this may require making changes in dosage of levothyroxine. If you have been prescribed any of these drugs with your thyroid medication, you need to be aware of this. Alcohol Alcohol can disrupt thyroid function in a number of different ways. There are some indications that it may lower peripheral T4 and T3 levels. In addition, it has a toxic effect on thyroid cells and ethanol is actually used to treat thyroid nodules in some cases. It can also, potentially, reduce the risk of certain types of thyroid cancer. On the flip side, alcohol is very hard on the digestive tract and can also lead to destruction of the gut lining and make leaky gut worse. I generally recommend avoiding alcohol, especially if you are trying to heal the gut. Coffee and Tea Coffee also impacts the absorption of levothyroxine; this is why thyroid patients need to take their hormone replacement pill at least an hour before drinking coffee. Caffeine found in coffee can also increase blood sugar levels. This is especially bad for people with hypoglycemia or low sugar levels because it can lead to complications. For example, blood sugar fluctuations can cause cortisol spikes, which not only exhaust the adrenals, but also can wreak havoc on the immune system. I recommend avoiding coffee if you have adrenal issues or hypoglycemia. Black and green tea also has caffeine though in lesser amounts than coffee , and it contains tannins which can hamper iron absorption and many teas also contain fluoride which blocks iodine absorption and may hamper thyroid function. Green and Black tea are also Th2 stimulants. Drinking it in moderation may be ok for some and not good for others. If you drink a lot of tea, you may want to eliminate it for a period of time to see if it has an impact on your symptoms. High doses of green tea have also been found to cause a significant decrease in serum T3 and T4 and increase in TSH levels has been reported along with decreased TPO and deiodinase activity in response to dietary green tea extract in rats. Gluten There is ample evidence that gluten can lead to poor absorption of thyroid hormone. For an in depth look at this read this post. Dairy Lactose has also been found to hamper thyroid hormone absorption. And casein, a protein found in milk is similar in protein structure to gluten and can also cause gluten like problems. Grass fed butter is one possible exception For an in depth look at this read this post. Soy Soy is rich in phytoestrogens and affect levels of thyroid binding globulin creating more of it. It can also hamper thyroid hormone absorption. Soy can also be goitrogenic in large quantities. I generally recommend avoiding soy with the occasional exception of miso and fermented soy products like tempeh. Sugar As mentioned above, the adrenals release cortisol to compensate for low blood sugar levels. This can lead to low T3 levels. In addition, elevated cortisol will cause thyroid hormone receptor insensitivity meaning that even if T3 levels are high enough, they may not be able to bind normally to receptor sites. Cortisol will also increase the production of reverse T3 rT3 which is inactive. Cortisol can also lower the levels of protein that binds to thyroid hormone so it can circulate in a stable structure. And finally, elevated cortisol will slow TSH production by messing with hypothalamic-pituitary feedback leading to lower TSH production. Sugar should be treated as the addictive drug that it is. Use with

extreme caution. Processed Foods Processed foods tend to be high in both sodium, sugar and saturated fat. High sodium levels have been linked to autoimmunity and to thyroid disease. Sodium is important for getting iodide into thyroid cells. Excess amounts of sodium can lead to higher amounts of iodine in the thyroid which can lead to a more aggressive autoimmune attack. We have already discussed problems caused by low sugar. High blood sugar levels can lead to insulin resistance. This can also cause a reduced conversion of T4 to T3 hormones. Eat real whole food. Processed food has little or no nutritional benefit. Fat Diets high in polyunsaturated fat caused significant thyroid dysfunction in rats. Goitrogens Naturally Found in found in legumes, plants, amiodarone, lithium, as well as cabbage, cauliflower, broccoli, turnip, forms of root cassava. Generally, I think these foods have so many health benefits that they should be eaten. Goitrin is an active goitrogen present in plants of Rutabaga, turnip and Brassicae seeds. Steam or blanch the vegetables as cooking destroys the enzyme responsible for activation of progoitrin to goitrin thus negating its anti-thyroid effects. Normal moderate amounts are fine, in my opinion. Millet This common gluten free ingredient contains C-glycosylflavones which may inhibit TPO activity. Be cautious with millet. In moderate amounts it is probably ok. Environmental Toxins Pesticides can lead to decreased half life of T4. BPA bisphenol-A has been found to be an endocrine disruptor and may have direct action on thyroid receptors. Percolates found in rocket fuel, thiocyanates and nitrates interfere with iodine uptake. A study in California on pregnant women found a strong association between urinary percolate levels and decreased total and free T4 and increased TSH. Heavy metals like cadmium and lead are also known to affect thyroid function. In a study on pregnant women, those from lead exposed town had lower mean free thyroxine FT4 , higher mean TPO antibodies along with higher lead concentration suggesting stimulation of auto-immunity by prolonged lead exposure. As you can see, there are many things that can bind to thyroid hormone both natural and chemical. All must be considered when deciding on dosage and when trying to improve thyroid hormone function in the body.

## Chapter 8 : JCI - Mechanisms of thyroid hormone action

*VK Selective Thyroid Receptor-Î² Agonist Liver Disorders. Overview & Profile. We are developing a unique series of selective thyroid hormone receptor beta (TRÎ²) agonists for lipid disorders.*

They function as hormone-activated transcription factors and thereby act by modulating gene expression. In contrast to steroid hormone receptors, thyroid hormone receptors bind DNA in the absence of hormone, usually leading to transcriptional repression. Hormone binding is associated with a conformational change in the receptor that causes it to function as a transcriptional activator. Receptor Structure Mammalian thyroid hormone receptors are encoded by two genes, designated alpha and beta. Further, the primary transcript for each gene can be alternatively spliced, generating different alpha and beta receptor isoforms. Currently, four different thyroid hormone receptors are recognized: Like other members of the nuclear receptor superfamily, thyroid hormone receptors encapsulate three functional domains: A transactivation domain at the amino terminus that interacts with other transcription factors to form complexes that repress or activate transcription. There is considerable divergence in sequence of the transactivation domains of alpha and beta isoforms and between the two beta isoforms of the receptor. A ligand-binding and dimerization domain at the carboxy-terminus. As depicted in the figure below, the DNA-binding domains of the different receptor isoforms are very similar, but there is considerable divergence among transactivation and ligand-binding domains. Most notably, the alpha-2 isoform has a unique carboxy-terminus and does not bind triiodothyronine T3. The different forms of thyroid receptors have patterns of expression that vary by tissue and by developmental stage. For example, almost all tissues express the alpha-1, alpha-2 and beta-1 isoforms, but beta-2 is synthesized almost exclusively in hypothalamus, anterior pituitary and developing ear. Receptor alpha-1 is the first isoform expressed in the conceptus, and there is a profound increase in expression of beta receptors in brain shortly after birth. Interestingly, the beta receptor preferentially activates expression from several genes known to be important in brain development e. The presence of multiple forms of the thyroid hormone receptor, with tissue and stage-dependent differences in their expression, suggests an extraordinary level of complexity in the physiologic effects of thyroid hormone. The half sites of a TRE can be arranged as direct repeats, pallindromes or inverted repeats. The DNA-binding domain of the receptor contains two sets of four cysteine residues, and each set chelates a zinc ion, forming loops known as "zinc fingers". A part of the first zinc finger interacts directly with nucleotides in the major groove of TRE DNA, while residues in the second finger interact with nucleotides in the minor groove of the TRE. Thus, the zinc fingers mediate specificity in binding to TREs. Thyroid hormone receptors can bind to a TRE as monomers, as homodimers or as heterodimers with the retinoid X receptor RXR , another member of the nuclear receptor superfamily that binds 9-cis retinoic acid. The heterodimer affords the highest affinity binding, and is thought to represent the major functional form of the receptor. However, the biological effects of TRE binding by the unoccupied versus the occupied receptor are dramatically different. In general, binding of thyroid hormone receptor alone to DNA leads to repression of transcription, whereas binding of the thyroid hormone-receptor complex activates transcription. The transactivation domain of the T3-free receptor, as a heterodimer with RXR, assumes a conformation that promotes interaction with a group of transcriptional corepressor molecules. A part of this corepressor complex has histone deacetylase activity HDA , which is associated with formation of a compact, "turned-off" conformation of chromatin. The net effect of recruiting these types of transcription factors is to repress transcription from affected genes. Binding of T3 to its receptor induces a conformational change in the receptor that makes it incompetent to bind the corepressor complex, but competent to bind a group of coactivator proteins. The coactivator complex contains histone transacetylase HAT activity, which imposes an open configuration on adjacent chromatin. The coactivator complex associated with the T3-bound receptor functions to activate transcription from linked genes. A growing number of specific proteins have been identified as members of the corepressor and coactivator complexes described. It should also be mentioned that there are several exceptions to the scheme described above. As mentioned, the alpha-2 receptor is unable to bind T3 and acts as similarly to a dominant-negative mutant of the receptor, but its

carboxy-terminus can be differentially phosphorylated, which affects DNA binding and dimerization. Also, the beta-2 isoform apparently fails to function as a repressor in the absence of T3. Disorders of Thyroid Hormone Receptors A number of humans with a syndrome of thyroid hormone resistance have been identified, and found to have mutations in the receptor beta gene which abolish ligand binding. Clinically, such individuals show a type of hypothyroidism characterized by goiter, elevated serum concentrations of T3 and thyroxine and normal or elevated serum concentrations of TSH. More than half of affected children show attention-deficit disorder, which is intriguing considering the role of thyroid hormones in brain development. In most affected families, this disorder is transmitted as a dominant trait, which suggests that the mutant receptors act in a dominant negative manner. Mice with targeted deletions in thyroid receptor genes have provided additional understanding of the possible roles of different forms of thyroid hormone receptors. Knockout mice that are unable to produce the alpha-1 receptor showed subnormal body temperature and mild abnormalities in cardiac function. Other mice which lacked expression of both alpha isoforms were severely hypothyroid and died within the first few weeks of life. Mice with disruptions of the entire beta gene exhibited elevated TSH levels and deafness, while mice with mutations that disrupted only beta-2 expression had elevated TSH, but normal hearing. Such experiments are beginning to allow determination of which functions of the different receptor isoforms are redundant and which are not. Inactivating mutations in thyroid hormone receptors do not produce a syndrome analogous to the lack of thyroid hormones. This is the case even in mice with targeted deletions in both alpha and beta receptor genes. The most likely explanation for the relative mild effects of receptor deficiency is that responsive genes are left in a "neutral" state, rather than being chronically suppressed as happens with hormone deficiency. References and Reviews Brent GA: The molecular basis of thyroid hormone action. New Eng J Med  Annu Rev Biochem  Zhang J, Lazer MA: The mechanism of action of thyroid hormones. Annu Rev Physiol

## Chapter 9 : Resistance to Thyroid Hormone: Laboratory Support of Diagnosis and Management

*With the exception of the thyroid hormone receptor, the receptors for amino acid derived and peptide hormones are located in the plasma membrane. Receptor structure is varied. Some receptors consist of a single polypeptide chain with a domain on either side of the membrane, connected by a membrane-spanning domain.*

Hormones with Intracellular Receptors Receptors for steroid and thyroid hormones are located inside target cells, in the cytoplasm or nucleus, and function as ligand-dependent transcription factors. That is to say, the hormone-receptor complex binds to promoter regions of responsive genes and stimulate or sometimes inhibit transcription from those genes. Thus, the mechanism of action of steroid hormones is to modulate gene expression in target cells. By selectively affecting transcription from a battery of genes, the concentration of those respective proteins are altered, which clearly can change the phenotype of the cell. Structure of Intracellular Receptors Steroid and thyroid hormone receptors are members of a large group "superfamily" of transcription factors. In some cases, multiple forms of a given receptor are expressed in cells, adding to the complexity of the response. All of these receptors are composed of a single polypeptide chain that has, in the simplist analysis, three distinct domains: In most cases, this region is involved in activating or stimulating transcription by interacting with other components of the transcriptional machinery. The sequence is highly variable among different receptors. Amino acids in this region are responsible for binding of the receptor to specific sequences of DNA. The carboxy-terminus or ligand-binding domain: This is the region that binds hormone. In addition to these three core domains, two other important regions of the receptor protein are a nuclear localization sequence, which targets the the protein to nucleus, and a dimerization domain, which is responsible for latching two receptors together in a form capable of binding DNA. Hormone-Receptor Binding and Interactions with DNA Being lipids, steroid hormones enter the cell by simple diffusion across the plasma membrane. Thyroid hormones enter the cell by facilitated diffusion. The receptors exist either in the cytoplasm or nucleus, which is where they meet the hormone. When hormone binds to receptor, a characteristic series of events occurs: Receptor activation is the term used to describe conformational changes in the receptor induced by binding hormone. The major consequence of activation is that the receptor becomes competent to bind DNA. Activated receptors bind to "hormone response elements", which are short specific sequences of DNA which are located in promoters of hormone-responsive genes. In most cases, hormone-receptor complexes bind DNA in pairs, as shown in the figure below. Transcription from those genes to which the receptor is bound is affected. Most commonly, receptor binding stimulates transcription. The hormone-receptor complex thus functions as a transcription factor. As might be expected, there are a number of variations on the themes described above, depending on the specific receptor in question. For example, in the absense of hormone, some intracellular receptors do bind their hormone response elements loosely and silence transcription, but, when complexed to hormone, become activated and strongly stimulate transcription. Some receptors bind DNA not with another of their kind, but with different intracellular receptor. As a specific example, consider glucocorticoids , a type of steroid hormone that probably affects the physiology of all cells in the body. The image to the right depicts a pair of glucocorticoid receptors blue and green on the top bound to their DNA hormone response element bottom. The two steroid hormones are not visible in this depiction.