Endocrine Disrupters and Thyroid Function

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Slide 1

I am Hisao Seo from the Research Institute of Environmental Medicine, Nagoya University. I am honored to chair this "Session, Thyroid". We have three guest speakers from abroad. Dr. Tsai, Dr. Samarut and Dr. Chen, all the speakers are the most famous scientists elucidating the action of thyroid hormone actions. Before their talk, I would like to introduce current knowledge about Endocrine disrupters and thyroid function.

Slide 2

Thyroid hormones, thyroxine, T4 and triidothyronine (T3) play important role on development and metabolism. Furthermore, some of the most important effects of TH occur during fetal development and in early childhood. Congenital hypothyroidism caused by impaired TH production is characterized by delayed growth and mental retardation. Severe cases with resistance to thyroid hormone caused by the mutation of thyroid hormone β receptor gene also manifest similar findings.

Slide 3

I would like to question whether environmental chemicals interfere with thyroid function. It has been shown that low-level perinatal exposure to dioxin and polychlorinated biphenyl (PCB) affect cognitive and motor development of children, suggesting that these chemicals impair thyroid function during the development of central nervous system.

Slide 4

Dioxin and polychorinated biphenyls (PCBs) have been drawing special attention because of their structural similarity with thyroid hormones.

Slide 5

Cheek et al. examined the interaction of some of the endocrine disrupters with thyroid hormone receptor and thyroid transport proteins in serum. As shown in the slide, week association of some of the PCBs with TR beta and with TBG was observed. More notably, some of the hydroxylated PCBs exhibited much higher affinity to transthyretin TTR) than the endogenous ligand, T4.

Slide 6

It is thus possible that hydroxylated PCBs could suppress thyroid function by binding to TTR especially in animals such as rodents and amphibians whose major T4-binding protein is TTR. Bindings of PCBs liberates free T4, accelerating its metabolism.

Slide 7

It is now well established that dioxins and PCBs interact with aromatic hydrocarbon receptor (AhR). The slide illustrates how AhR activates the transcription of target genes through complex formation with Arnt.

Slide 8

AhR mediated pathway is recently shown to increase biliary excretion of thyroid hormone. We have recently reported Dioxin induces L-amino acid transporter known as T4 transporter in hepatocytes. Also known is that dioxin and PCBs induces hepatic T4-UDPP-glucuronyl transferase. These effects of dioxin and PCBs should lead to enhanced uptake of T4, glucuronylation and its biliary excretion, thereby introducing hypothyroidism in the offspring of the mother exposed to the higher levels of the endocrine disrupters.

Slide 9

Indeed, suppression of thyroid function by postnatal exposure to chlorinated dioxins and related chemicals was reported in Japanese breast-fed infants. A higher intake of dioxins results in decreased serum levels of thyroxine and increased TSH concentrations.

Slide 10

PCBs also exert a thyroid hormone like effect through possible interaction with TRs. It has been shown that administration of PCBs to pregnant rats results in the upregulation of T3-responsive genes such as RC3/neurogranin of the offspring on P15 despite of the fact that maternal T4 levels were decreased to undetectable level.

Slide 11

With subsequent slides, I would like to introduce thyroid hormone receptors. This slide illustrates the functional domains of the TR. N-terminal domain called A/B domain plays a role in transactivation. C-region is a DNA binding domain, interacting with thyroid hormone response element of the target genes. D-region is called hinge region and contains nuclear localization signal and coreppressor interacting surface. C-terminal E-region is T3-binding domain which is also important in coactivator interaction and transactivation.

Slide 12

TRs are encoded by two different genes. Alpha gene on chromosome 17 encodes alpha 1 and alpha 2 isoforms. Beta gene on chromosome 3 encodes beta 1 and beta 2 isoforms. It should be noted that alpha 2 does not bind with T3, thereby does not function as the receptor. This isoform is likely to moderate the function of the other receptors. The expression of each isoform was regulated in temporal and spatial specific manner. Thus thyroid hormone exerts its effect at critical period in critical organs.

Slide 13

This slide illustrates the role of corepressors and coactivators in T3-mediated transcription which will be detailed by Dr. Tsai's lecture. Unliganded TR complexed with retinoid X receptor binds with corepressor and associates with histone deacetylase (HDAC) through Sin3. The HDAC then deacetylase histones, making chromatin structure unaccesible to general transcription factors. When the TR is bound with T3, it dissociates corepressor complex and recruits coactivator complexes such as SRC-1 CBP and P/CAF. These coactivators further associates with histone acetyl transferase. Acetylation of the histones remodels the chromatin structure accessible to GTFs, activating the transcription.

Slide 14

With subsequent few slides, I would like to introduce TR function in the development of frogs. *Xenopus laevis* like other vertebrate has two TR isoforms, TR α and TR β . TR α is distributed widely in

tissues even before the formation of thyroid gland. TR β , a TH response gene by itself increases along with the rise in endogenous TH during metamorphosis. During premetamorphosis the TH concentration and the TR β levels are very low when the early events of tadpole development such as limb growth and DNA replication in the brain occur. TR β and TH rise to a peak at the climax of metamorphosis when the final changes such as gill and tail resorption and intestinal remodeling occur. Thus, it is likely that TR is involved in the development of metamorphosis.

Slide 15

This slide illustrates the recent findings of Schreiber et al, demonstrating the inhibition of diverse developmental program of frog metamorphosis by a dominant negative thyroid hormone receptor. They made dominant negative TR alpha termed as TRDNalpha. This construct was driven by collagen promoter and linked with green fluorescent protein gene and dominant negative TR lucking C-terminal activation domain. As a control, GFP gene driven by collagen gene promoter was used. Expression of the transgene was ubiquitously observed and inhibited the development of metamorphosis.

Slide 16

Dramatic effect could be observed with TRDNalpha shown at the bottom. Treatment with T3 for 7 days results in resorption of tail and development of brain in Col:GFP control. However, TRDNalpha completely abrogated the development of metamorphosis.

Slide 17

Overexpression of TRs in X. laevis embryos by injecting in vitro-synthesized mRNA into fertilized eggs and the addition of TH to these embryos causes abnormal embryonic development that mimics retinoic acid-induced teratogenesis. It is thus speculated that alteration of thyroid function may results in teratogenesis in frogs.

Slide 18

This the last slide of my introduction. Incidence of cretinism is markedly increasing in Japan while the birthrate is steadily decreasing. Is this increase linked to the prevalence of Endocrine disrupters? Collaborative study with thyroid specialists and biologists studying frog development will give us the answer.

Slide 19

In conclusion, I would like to point out that endocrine disrupters affecting thyroid function may cause variable phenotypic expression including hypothyrodism, teratogenesis or cancer. Thank you very much for your attention.