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Maternofetal Thyroid Action and Brain Development

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Editorials and Commentary

Thyroid hormones (THs) are a key regulatory factor of the developmental program and maternal-fetal communication network. The cellular basis for these effects lies in the organizational role of TH in neuronal migration, synaptogenesis and differentiation of multiple cell types. Thus, any vigorous changes in the THs levels during the development may cause a patho-physiological states and serious damage to the structural development and organization of the brain. It can be hypothesized that the disturbance in the maternofetal THs due to antithyroid drugs, Levo-thyroxine or environmental disruptors may lead, in turn, to the biochemical dysfunctions, morphofunctional alterations, developmental abnormalities and brain damage if not corrected prior/after the birth. Thus, further studies need to be done to emphasize this concept.

Keyword: Thyroid hormones; deiodinases; transporters; mothers; fetus.

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I- Normal state

Due to TH action can be controlled in individual cells through selective TH uptake and intracellular TH metabolism, the placenta is an important axis in the maternal-fetal communication system for THs which are vital for the normal development and differentiation of the fetus (Ahmed et al., 2008; Scapin et al., 2010; Ahmed, 2012a; Forhead and Fowden, 2014; Micke et al., 2015). In general, intracellular activation or inactivation of L-thyroxine (T4) and 3,5,3'-triiodothyronine (T3) in turn is determined by three types of iodothyronine deiodinases (Ds), namely D1, D2, and D3 (Incerpi et al., 2005; Gereben et al., 2008; Horn and Heuer, 2010; Van Herck et al., 2012; Chung, 2014; Guzmán-Gutiérrez et al., 2014; Sánchez-Huerta et al., 2015). I reported that the placenta transports and metabolizes maternal THs, and mainly expresses D3, which inactivates T4 and other iodothyronines and thus limits the transport of maternal active THs to the fetus in the late pregnancy (Ahmed, 2012b). D2 is also dynamic in the placenta and locally provides active T3 from the maternal T4 for placental metabolic functions (Ahmed et al., 2008; Ahmed, 2012a). The placental expression of D1, which also activates T4 to T3, is still controversial. Additionally, the ability to transport THs in and out of cells has been described in members of different transmembrane TH-transporters (THTs) including the monocarboxylate transporters (MCT), L-type amino acid transporters (LAT), Na+/Taurocholate cotransporting polypeptide (NTCP) and organic anion transporting polypeptides (OATP) (Yen, 2001; Incerpi et al., 2002; Suzuki and Abe, 2008; Visser et al., 2008; Loubiére et al., 2010; Guzmán-Gutiérrez et al., 2014). To date six different THTs are recognized to be present in the placenta: MCT8, MCT10, LAT1, LAT2, OATP1A2 and OATP4A1 but their relative contributions to placental TH transport are unknown (Patel et al., 2003). There is elevation in the MCT8 mRNA expression with the gestation progress (Chan et al., 2006) but there is limited information regarding the ontogeny of the other THTs. Moreover, placental membranes are also concerned in 4'-OH-sulfation reactions of iodothyronines (Köhrle, 1997). Sulfation plays a role in TH metabolism by cooperating between the deiodination and sulfation pathways of TH (Kilby et al., 2005).

The cellular action of THs is frequently classified as genomic (nuclear) and non-genomic (initiated either at cytoplasm or at membrane TH receptors) (Incerpi, 2011; Ahmed et al., 2013). Because integrin αvß3 contains a cell surface receptor for TH but also is a co-receptor for insulin-like growth factor type 1 (IGF1) (Clemmons and Maile, 2003), we postulated that TH might modulate IGF-I actions (Incerpi et al., 2014). The proliferative actions of T4 initiated at integrin αvβ3 are MAPK dependent; T4 is anti-apoptotic and pro-angiogenic (Lin et al., 2013; Davis et al., 2014). TH also modulates the actions of interferon-γ (Lin et al., 1996), adiponectin (Wang et al., 2008, Ahmed, 2013 & 2014), leptin (Ahmed, 2013 & 2014), tumor necrosis factor-α (TNF-α) (Ahmed, 2013; Ahmed et al., 2013), brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3, NT-4/5, inositol trisphosphate (IP) 3 receptor, retinoic acid receptor (ROR) α, myelin basic protein (MBP) (Yu et al., 2015), and growth factors, such as epidermal growth factor (EGF), transforming growth factor-α (TGF-α) (Shih et al., 2004), vascular growth factors (Davis et al., 2004; Mousa et al., 2006) and nerve growth factor (Yu et al., 2015) by non-genomic mechanisms. An alternative clarification of my recent work is that the leptin, adiponectin, and TNF-α are concerned in the modulation of thyroid function and insulin sensitivity, and they may interrelate with thyroid stimulating hormone (TSH), growth hormone (GH), and GH/IGF axis (Ahmed, 2013). It can be deduced that the steady increase in the concentrations of these markers is synergistic and intimately interconnected with the action of the hypothalamic–pituitary–thyroid axis (HPTA) and GH/IGF1 axis during the development. Furthermore, binding of T3 to its nuclear thyroid receptors (TRs) directly influences transcription of numerous genes that are significant in development (Harvey CB, Williams, 2002). There are growing data that T4 could affect nuclear T3 action by causing alteration of TH nuclear receptors through acetylation (Hung-Yun et al., 2005) and phosphorylation (Davis et al., 2000; Babu et al., 2011). Notably, placental cells express high affinity, stereo-specific, energy-dependent uptake systems for T4 and T3.

II- Abnormal state

Gestation is accompanied by deep alterations in the thyroidal economy (hypo- or hyper-thyroidism), resulting from a complex combination of factors specific to the pregnant case, which together agree to stimulate the maternal thyroid axis (Ahmed et al., 2008; Ahmed, 2011). The low maternal levels of T4 seen in gestation period may be compensated by higher placental availability of THs via elevation in the activity of placental TH transport and metabolism (Guzmán-Gutiérrez et al., 2014). High maternal free T4 levels during the first half of gestation were related to lower birth weight and increased risk of small gestational age newborns, suggesting that maternal thyroid function may influence the fetal growth, even within the normal range (León et al., 2015). Moreover, clinical studies demonstrated that maternal TH deficit during the first trimester of pregnancy can influence the result of human neurodevelopment (Pop et al., 1999 & 2003). Experiments in rats proved that early maternal TH deficiency affects neuronal migration in the cortex (Lavado-Autric et al., 2003), while maternal hyperthyroidism too can disturb the fetal developing brain (Evans et al., 2002). In chick, we reported that the maternal transport of methimazole (MMI) and its metabolites to the embryo can be injurious for embryonic development, in particular, for the brain, by a combination of anti-thyroidal and probably local cytotoxic effects, an observation that may also be of significance to the human condition (Van Herck et al., 2013). These alterations may be either directly or indirectly linked to TH action. As well, the clinical epidemiological and basic observations obviously demonstrate that maintaining normal TH regulation from the starting of gestation is significant to diminish the risk of obstetric complications and to ensure optimal neurodevelopment of the offspring (Ahmed, 2012a). Thus, the suggestion that neurodevelopmental deviations might be associated to the THs is reasonable. More importantly, the THs disorders due to antithyroid drugs (MMI or propylthiouracil (PTU)), and polychlorinated biphenyls (PCBs) or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) during the development may lead to deformations rather than coordinated shifts in the relative development of numerous central biological organizations that guides to a multitude of irreversible morphological and physiological irregularity (patho-physiological and patho-developmental conditions) (Figure 1) (Ahmed, 2011, 2012a, 2013 & 2014; Ahmed et al., 2014; Ahmed and El-Gareib, 2014). These can be ascribed to the diminution in the level of GH (Ahmed, 2013), the disruption of the activities of THs (Ahmed, 2012a), the synthesis and release of growth hormone-releasing hormone (GH-RH), the sensitivity of the pituitary gland to GH-RH, and the transcription of the GH gene (Osfor et al., 2013). It has also been shown that the reduction in the concentration of IGF1 was related to the variations in the activities of THs and insulin that may delay growth (Ahmed, 2013). This status might be elucidated by the depletion in leptin turnover and degradation (Houseknecht et al., 1996) or stimulation of the HPTA in response to

low TH concentrations in rats, dogs, and humans (Mazaki-Tovi et al., 2010). Especially, the loss of body weight may propose a decline in the general health level of animals (Fernandes et al., 2007), which can be vital in the explanation of thyroid effects (Ahmed et al., 2008; Ahmed, 2012a, 2013 & 2014). This is possibly due to the disorder of the hormonal homeostatic mechanisms during development. In pathological/abnormal pregnancies with either maternal or fetal THs disorders (hypo- or hyper-thyroidism), the placenta lacks the full compensatory roles essential to optimize the maternal–fetal transport of THs to achieve the normality of TH levels in the fetus (Ahmed, 2012b). This difference could be due to the experimental models, developmental period, and animal species used. Importantly, the actions of THs are highly pleiotropic, affecting many tissues at different developmental periods. Also, MCT8 insufficiency has essential metabolic consequences in the brain that could not be associated to deficiency or overload of TH supply to the brain during maturity. More recently, THTs and Ds are important regulators of intracellular T3 availability and therefore contribute to the control of TRs-dependent CNS development and early embryonic life (Ahmed, 2015). As a result, their effects on proliferation and differentiation are extremely heterogeneous depending on the cell type, the cellular context, and the developmental or transformation condition. During brain development, iodine deficit, maternal thyroid dysfunction, interruption of the maternal transfer of T4 and neonatal thyroid distortion together with the genetic factors contribute to neurodevelopmental deficits. This leads to irreversible variations and harm to the fetal CNS (i.e. abnormal corticogenesis). Interestingly, even mild to moderate maternal hypothyroxinemia may result in suboptimal neurodevelopment (Morreale de Escobar et al., 2007) and may affect the neuropsychological development of the child (Gärtner, 2009). Maternal subclinical hypothyroidism had major negative impact on neurodevelopment (Zhang et al., 2014). In addition, maternal thyroid dysfunction, hyper- and hypothyroidism, would increase the risk of seizure in the child via slight alter in brain structure (Andersen et al., 2013). Both hypothyroid and hyperthyroid diseases (resulting from genetic and acquired aetiologies) can lead to characteristic neurological diseases, with cognitive delay, extrapyramidal movement disorders, neuropsychiatric indications, and neuromuscular demonstrations (Kurian et al., 2014). As well, defects in fetal Ds or THTs may have more impact on fetal brain since they can result in intracellular T3 deficiency despite sufficient maternal TH supply (Ahmed, 2015). These deficiencies can adversely affect neurodevelopment. These results imply that the disturbance in the maternofetal THs, Ds, THTs or TRs may impair the fetal neuroendocrine system and delay the development (Figure 2).

Finally, all these abnormalities can be prevented (1) by maternal thyroxine therapy; and (2) when a normal iodine supply is provided to the mother before and during pregnancy and to the neonate and young infant during the vital period of brain development. Inadequate iodine intake in the mother can cause low T4 in gestation and also insufficient production of T4 in breast-fed infants when enough T4 is crucial for normal brain development. It therefore follows that mothers should be screened for hypothyroidism and treated before or as early as probable during gestation. An sufficient serum concentration of T4 is essential for developing brain. A better understanding of these mechanisms would also allow us to refine any deviations or polymorphisms in elements of the pathway of TH action, e.g., T3/rT3 ratio, deiodinase or transporter polymorphisms which predict the emotional reaction to TH or associate with other potentially TH related effects. I hope that new insights into the complex actions by THs and their receptors control cell proliferation and differentiation will be provided in the near future.

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Figure legends

Figure 1: Thyroid disruptors affecting the maternal-fetal thyroid alterations.

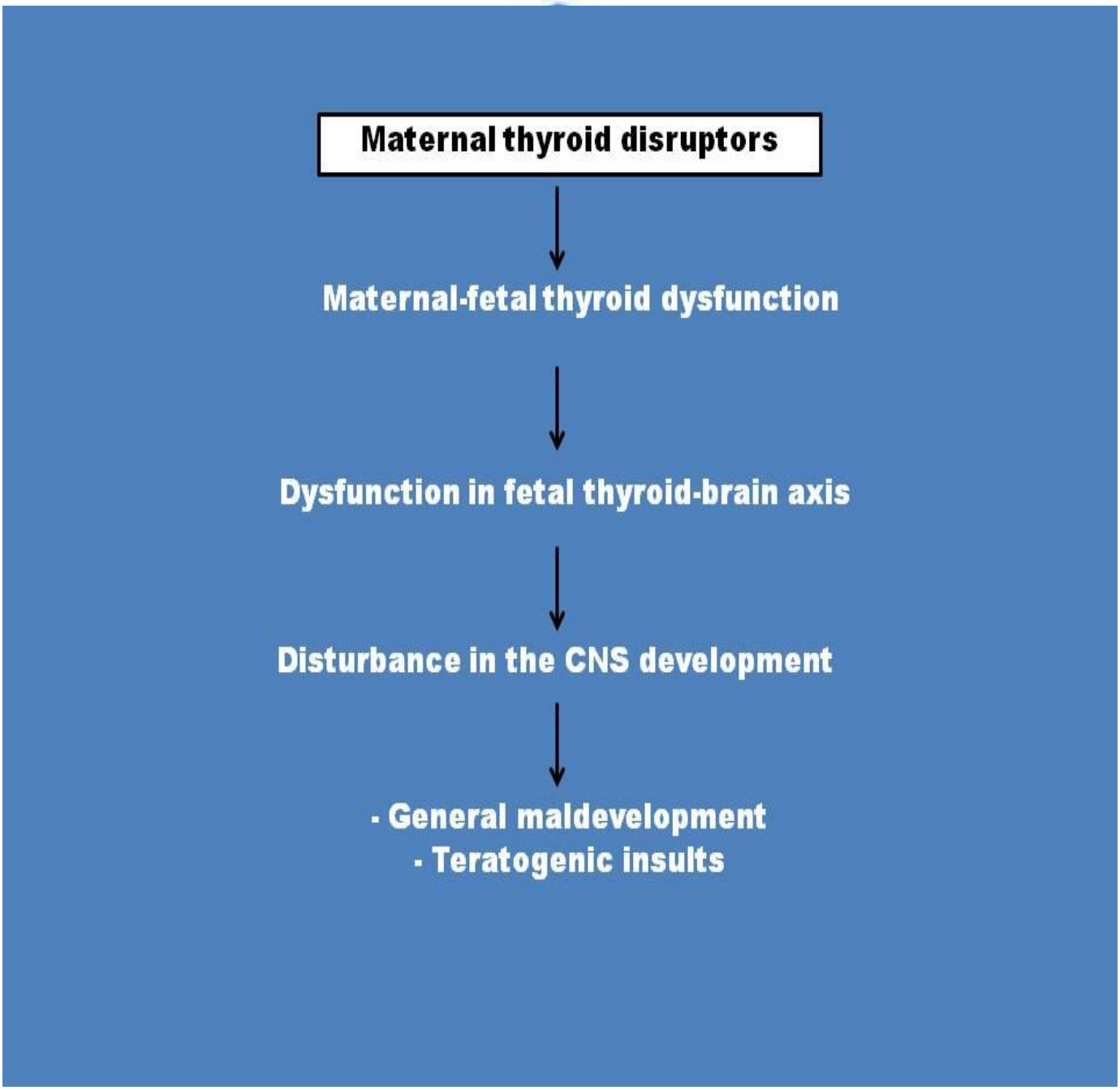

Figure 2: Schematic diagram of the maternofetal thyroid axis and the developmental neuroendocrine homeostasis.