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Genomic Actions of Thyroid Hormones during Development

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RAPID COMMUNICATIONS

Thyroid hormones (THs) exhibit crucial activities during the development (El-bakry et al., 2010; Ahmed, 2011, 2012a,b, 2013, 2014, 2015a-c, 2016a-d, 2017a-u & 2018a-c; Ahmed et al., 2008, 2010, 2012, 2013a,b, 2014; 2015a,b& 2018a,b; Ahmed and **Ahmed,** 2012; Ahmed and Incerpi, 2013;Van Herck**et al., 2013; Ahmed and** El-Gareib, 2014,Incerpi et al., 2014; Can delotti et al., 2015; De Vito et al., 2015; El-Ghareeb et al., 2016; Ahmed and El-Gareib, 2017) via the nuclear and extra nuclear actions (De Vito et al., 2015).THs are released by the thyroid gland to the circulation where they are carried bound to proteins such as thyroxin binding globulin (TBG), transthyretin (TTR) or serum albumin (Shi et al., 2002). The level of albumin, which has the lowest thyroxine (T4) affinity and enables a fast release of T4 (Schussler, 2002), gradually decreases during pregnancy (Larsson et al., 2008). TBG is an active carrier and has a possibility to switch between the high-affinity and the low-affinity form (Zhou et al., 2006). TBG levels are the highest in the second and third trimester of pregnancy (Glinoer et al., 1990; Glinoer, 1997; Ahmed, 2012a) and the same holds true for TH-binding ratio (Lee et al., 2009) and thyroid-binding capacity (Kurioka et al., 2005), which decreases as soon as 3-4 days after delivery.

On the other hand, genomic actions of THs have been found inside the nucleus (Ahmed, 2012b). THs (3,5,3'-triiodothyronine (T3) and T4) arrive to the cell via transporter such as the organic anion transporter family (OATPs) and monocarboxylate transporter 8 (MCT8). Then, deiodinases (DI, and II) convert T4 (inactive form) to T3 (active form) (Ahmed et al., 2008; De Vito et al., 2011). At that point, T3 binds to thyroid receptors (TRs; TRα and TRβ), that stimulate transcription by binding, generally as heterodimers with the retinoid X receptor (RXR) (Bassett et al., 2003), to TH response elements (TREs) situated in regulatory regions of target genes (Chen et al., 2011). Its activity is controlled by an exchange of corepressor (CoR) and co activator (CoA) complexes. Negative TREs (nTRE) can facilitate ligand-dependent transcriptional repression (Contreras-Jurado et al., 2011). TRs can also adjust the actions of genes that do not comprise a TRE via cross-talk with other transcription factors (TF) that modulate target gene expression (Blair et al., 1999; Sirakov et al., 2011). Both co-regulators and receptors are goals for phosphorylation by signal transduction pathways motivated by hormones and growth factors (Chen et al., 2011; Contreras-Jurado et al., 2011).The nuclear actions of T3 are sensitive to inhibitors of transcription and translation and have a latency of hours to days (Yen, 2001; Ahmed, 2012a).Thus, the genomic action of THs can show significant roles during the cellular proliferations and differentiations. A better understanding of these mechanisms would also permit us to refine the timing and dosage of the increase in levothyroxine (L-T4) therapy in hypothyroid pregnant women and to establish whether T4 on its own is indeed the best form of TH replacement in pregnancy. Further studies are required to recognize the crosstalk between THs, their genomic actions and growth factors during the development.

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