AOP ID and Title:

SNAPSHOT

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AOP 8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals

Short Title: Nuclear receptor induced TH Catabolism and Developmental Hearing Loss

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Status

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Abstract

Data from rodent studies demonstrate that thyroid hormone disruption during cochlear development culminates in ototoxicity. Developmental exposure of rats to polychlorinated biphenyls (PCBs) results in a low-frequency hearing loss in adult offspring (Goldey et al., 1995a; Herr et al., 1996; 2001; Crofton and Rice, 1999; Laskey et al., 2002). A body of work now supports the hypothesis that this ototoxicity results from PCB-induced hypothyroxinemia during a critical period of auditory development. Evidence for this hypothesis includes: a correlation between the severity of functional auditory impairment and the degree of thyroid hormone depletion (Goldey et al., 1995a; 1995b; Goldey and Crofton, 1998; Crofton, 2004), a cross-fostering study demonstrating that the critical exposure period is postnatal (Crofton et al., 2000a), and amelioration of the hearing loss following postnatal thyroxine replacement (Goldey and Crofton, 1998). Below an adverse outcome pathway is described for chemicals that activate xenobiotic nuclear receptors, including AhR, CAR, and PXR, leading to thyroid hormone disruption during cochlear development and resulting in permanent auditory loss.

This AOP is a revision and update of the original started on the Chemical Mode of Action wiki sponsored by WHO/IPCS. This MOA was described and published by Crofton and Zoeller 2005).

Summary of the AOP

Molecular Initiating Event

Title	Short name
Activation, Pregnane-X receptor, NR1I2 (https://aopwiki.org/events/239)	Activation, Pregnane-X receptor, NR1I2

239: Activation, Pregnane-X receptor, NR1I2 (https://aopwiki.org/events/239)

Short Name: Activation, Pregnane-X receptor, NR1I2

AOPs Including This Key Event

AOP ID and Name	Event Type
8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	MolecularInitiatingEvent

Biological Organization

Level of Biological Organization
Molecular

Evidence Supporting Applicability of this Event

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Rattus norvegicus	Rattus norvegicus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)
Mus musculus	Mus musculus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
Homo sapiens	Homo sapiens	Moderate	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)

Key Events

Title	Short name
Decrease of thyroxine (T4) in neuronal tissue (https://aopwiki.org/events/280)	T4 in neuronal tissue, Decreased
Decrease of thyroxine (T4) in serum (https://aopwiki.org/events/281)	T4 in serum, Decreased
Induction, Upregulation of glucuronyltransferase activity (https://aopwiki.org/events/295)	Induction, Upregulation of glucuronyltransferase activity
Increase, Biliary excretion TH glucuronide (https://aopwiki.org/events/401)	Increase, Biliary excretion TH glucuronide
Hippocampal anatomy, Altered (https://aopwiki.org/events/757)	Hippocampal anatomy, Altered
Hippocampal Physiology, Altered (https://aopwiki.org/events/758)	Hippocampal Physiology, Altered
Hippocampal gene expression, Altered (https://aopwiki.org/events/756)	Hippocampal gene expression, Altered

280: Decrease of thyroxine (T4) in neuronal tissue (https://aopwiki.org/events/280)

Short Name: T4 in neuronal tissue, Decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
42: Inhibition of Thyroperoxidase and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/42)	KeyEvent
54: Inhibition of Na+/I- symporter (NIS) leads to learning and memory impairment (https://aopwiki.org/aops/54)	KeyEvent
8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	KeyEvent
65: XX Inhibition of Sodium Iodide Symporter and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/65)	KeyEvent
134: Sodium Iodide Symporter (NIS) Inhibition and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/134)	KeyEvent
152: Interference with thyroid serum binding protein transthyretin and subsequent adverse human neurodevelopmental toxicity (https://aopwiki.org/aops/152)	KeyEvent

Stressors

Name
Methimazole
Propylthiouracil

Biological Organization

Level of Biological Organization
Organ

Evidence Supporting Applicability of this Event

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
human	Homo sapiens	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
rat	Rattus norvegicus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)
chicken	Gallus gallus	Weak	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9031)

Life Stage Applicability

Life Stage	Evidence
During brain development	Strong

Sex Applicability

Sex	Evidence
Female	Strong
Male	Strong

THs are critical for normal brain development in most vertebrates, primarily documented empirically in mammalian species (Bernal, 2013). However, there is compelling data that demonstrates the need for TH in brain development for many other taxa, including: birds, fish and frogs (Van Herck et al., 2013; Denver, 1998; Power et al., 2001). The most well known non-mammalian action of TH is to induce metamorphosis in amphibians and some fish species. However, there is a fundamental difference in the mechanisms by which T3 affects amphibian metamorphosis vs its role in mammalian brain development (Galton, 1983). In the rat, brain development proceeds, even if defective, despite the absence of TH. By contrast, TH administration to tadpoles induces early metamorphosis, whereas in its absence, tadpoles grow to extremely large size, but the metamorphosis program is never activated (Galton, 1983).

How this Key Event Works

Thyroid hormones (TH) are present in brain tissue of most vertebrate species, and thyroxine (T4) is converted to triiodothyronine locally in this tissue. The amount of THs in brain is known to vary during development and to differ among brain regions (Calvo et al., 1990; Kester et al., 2004; Tu et al., 1999). In human cerebral cortex, T3 increases steadily from 13-weeks, reaching adult levels by 20 weeks post conception. This occurs despite very low and unchanging levels in fetal serum T3, when fetal serum T4 increases 3-fold over the same period. This indicates that T3 in fetal brain is locally generated from serum-derived T4 via the activity of deiodinases, primarily DIO2. DIO2 serves to convert T4 to T3. During this time in fetal development DIO3 activity, which converts T3 to the inactive reverse T3 (rT3), remains very low in cortex. In contrast, in other brain regions including hippocampus and cerebellum, T3 remains low throughout early and mid-gestation and corresponds with high activity of DIO3 in these brain regions. In late gestation and after birth, DIO3 levels drop in hippocampus and cerebellum with a corresponding increase in T3 concentrations (Kester et al., 2004).

A similar spatial and temporal profile of deiodinase activity and corresponding brain hormone concentrations has been observed in rodent brain (Calvo et al., 1990; Tu et al., 1999). In the rat, either whole brain or cortex have been preferentially assessed as due to the low levels of hormones present and the small tissue volumes make quantitification difficult. Brain T3 and T4 rise in parallel from gestational day 10 to gestational day 20 in rat. They are typically both quite low until gestational 17 with steep increases between GD18 and GD20 corresponding to the onset of fetal

thyroid function (Calvo et al., 1990; Ruiz de Ono et al., 1988; Obergon et al., 1981). Just before birth, brain T3 and T4 concentrations are about one-third to one-half that of adult brain. Brain development in the early postnatal period in rat is roughly equivalent to the 3rd trimester in humans such that adult levels of T3 and T4 in brain are not reached in rodents until the 2nd-3rd postnatal week.

For THs to gain access to brain tissue they need to cross the blood brain barrier (BBB) which regulates the active transport of TH into neurons. Many transporter proteins have been identified, and the monocarboxylate transporters (Mct8, Mct10) and anion-transporting polypeptide (OATP1c1) show the highest degree of affinity towards TH and are prevalent in brain (Jansen et al., 2007; Mayer et al., 2014). Transporters express a distinct distribution pattern that varies by tissue and age (Friesema et al., 2005; Henneman et al., 2001; Visser et al., 2007; Heuer et al., 2005; Muller and Heuer, 2007). Although several transporters have been identified, current knowledge of cell specific profile of transporters is limited.

Most of the hormone transported across the blood brain barrier is in the form of T4, primarily though the cellular membrane transporters (e.g., OATP1c1 transporter) into the astrocyte (Visser and Visser, 2012; Sugiyama et al., 2003; Tohyama et al., 2004). Within the astrocyte, T4 is converted into T3 via the local activity of deiodinase 2 (DIO2) (Guadano-Ferraz et al., 1997). A small amount of T3 may cross the blood brain barrier directly via the T3-specific transporter, MCT8 (Heuer et al., 2005). Although in mature brain T3 derives partially from the circulation and from the deiodination of T4, in the fetal brain T3 is exclusively a product of T4 deiodination (Calvo et al., 1990; Grijota-Martinez et al., 2011). In both cases, only the required amount of T3 is utilized in neurons and the excess is degraded by the neuron-specific deiodinase DIO3 (Tu et al., 1999; St. Germain et al., 2009; Hernandez et al., 2010).

Both deiodinase and transporter expression in brain peak in different brain regions at different times in fetal and neonatal life (Kester et al., 2004; Bates et al., 1999; Muller and Heuer, 2014; Heuer, 2007). Collectively, these spatial and temporal patterns of transporter expression and deiodinase activity provide exquisite control of brain T3 available for nuclear receptor activation and regulated gene expression.

How it is Measured or Detected

Radioimmunoassays (RIAs) are commonly used to detect TH in the brain (e.g., Obregon et al., 1982; Calvo et al., 1990; Morse et al., 1996; Bansal et al., 2005; Gilbert et al., 2013). The method (and minor variants) is well established in the published literature. However, it is not available in a simple 'kit' and requires technical knowledge of RIAs, thus has not been used in most routine toxicology studies. Evaluations in neuronal tissue are complicated by the difficulty of the fatty matrix, heterogeneity of regions within the brain, and low tissue concentrations and small tissue amounts especially in immature brain. Two analytical techniques, LC- and HPLC-inductively coupled plasma–mass spectrometry have recently been used to measure brain concentrations of TH. These techniques have proven capable of measuring very low levels in whole-body homogenates of frog tadpoles at different developmental stages (e.g., Simon et al., 2002; Tietge et al., 2010). The assay detects I–, MIT, DIT, T4, T3, and rT3. More recently, Wang and Stapleton (2010) and Donzelli et al. (2016) used liquid chromatography-tandem mass spectrometry for the simultaneous analysis of five THs including thyroxine (T4), 3,3′,5-triidothyronine (T3), 3,3′,5′-triiodothyronine (rT3; reverse T3), 3,3′-diiodothyronine (3,3′-T2), and 3,5-diiodothyronine (3,5-T2) in serum and a variety of tissues including brain. These analytical methods require expensive equipment and technical expertise and as such are not routinely used.

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281: Decrease of thyroxine (T4) in serum (https://aopwiki.org/events/281)

Short Name: T4 in serum, Decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
42: Inhibition of Thyroperoxidase and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/42)	KeyEvent
54: Inhibition of Na+/I- symporter (NIS) leads to learning and memory impairment (https://aopwiki.org/aops/54)	KeyEvent
8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	KeyEvent

AOP ID and Name	Event Type
65: XX Inhibition of Sodium Iodide Symporter and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/65)	KeyEvent
134: Sodium Iodide Symporter (NIS) Inhibition and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/134)	KeyEvent
152: Interference with thyroid serum binding protein transthyretin and subsequent adverse human neurodevelopmental toxicity (https://aopwiki.org/aops/152)	KeyEvent
159: Thyroperoxidase inhibition leading to reduced young of year survival via anterior swim bladder inflation (https://aopwiki.org/aops/159)	KeyEvent
175: Thyroperoxidase inhibition leading to altered amphibian metamorphosis (https://aopwiki.org/aops/175)	KeyEvent
176: Sodium Iodide Symporter (NIS) Inhibition leading to altered amphibian metamorphosis (https://aopwiki.org/aops/176)	KeyEvent
194: Hepatic nuclear receptor activation leading to altered amphibian metamorphosis (https://aopwiki.org/aops/194)	KeyEvent

Stressors

Name
Propylthiouracil
Methimazole

Propylthiouracil

6-n-propylthouracil is a classic positive control for inhibition of TPO

Methimazole

Classic positive control

Biological Organization

Level of Biological Organization
Tissue

Evidence Supporting Applicability of this Event

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
human	Homo sapiens	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
rat	Rattus norvegicus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)
mouse	Mus musculus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
chicken	Gallus gallus	Moderate	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9031)
Xenopus laevis	Xenopus laevis	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=8355)

Term	Scientific Term	Evidence	Links
Pig	Pig	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=0)
zebra fish	Danio rerio	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=7955)

Life Stage Applicability

Life Stage	Evidence
During brain development	Strong
All life stages	Strong
During brain development, adulthood and aging	Strong

Sex Applicability

Sex	Evidence
Female	Strong
Male	Strong

The overall evidence supporting taxonomic applicability is strong. THs are evolutionarily conserved molecules present in all vertebrate species (Hulbert, 2000; Yen, 2001). Moreover, their crucial role in zebra fish (Thienpont et al., 2011), amphibian and lamprey metamorphoses is well established (Manzon and Youson, 1997; Yaoita and Brown, 1990; Furlow and Neff, 2006). Their existence and importance has also been described in many different animal and plant kingdoms (Eales, 1997; Heyland and Moroz, 2005), while their role as environmental messenger via exogenous routes in echinoderms confirms the hypothesis that these molecules are widely distributed among the living organisms (Heyland and Hodin, 2004). However, the role of TH in the different species depends on the expression and function of specific proteins (e.g receptors or enzymes) under TH control and may vary across species and tissues. As such extrapolation regarding TH action across species should be done with caution.

With few exceptions, vertebrate species have circulating T4 (and T3) that are bound to transport proteins in blood. Clear species differences exist in serum transport proteins (Dohler et al., 1979; Yamauchi and Isihara, 2009). There are three major transport proteins in mammals; thyroid binding globulin (TBG), transthyretin (TTR), and albumin. In adult humans, the percent bound to these proteins is about 75, 15 and 10 percent, respectively (Schussler 2000). In contrast, in adult rats the majority of THs are bound to TTR. Thyroid binding proteins are developmentally regulated in rats. TBG is expressed in rats until approximately postnatal day (PND) 60, with peak expression occurring during weaning (Savu et al., 1989). Although low levels of TBG persist into adult ages in rats and can be experimentally induced by hypothyroidism, malnutrition, or caloric restriction (Rouaze-Romet et al., 1992). While these species differences impact TH half-life (Capen, 1997) and possibly regulatory feedback mechanisms, there is little information on quantitative dose-response relationships of binding proteins and serum hormones during development across different species. Serum THs are still regarded as the most robust measurable key event causally linked to downstream adverse outcomes.

There is some uncertainty in the literature about the role of thyroid stimulating hormone (TSH) in thyroid hormone based adverse outcome pathways and the relevance of rodent data for humans. It is well accepted that TSH is a key event in the AOP for rat thyroid follicular tumors (McCain, 1995; Hill et al., 1998) and this pathway is not deemed relevant to humans (Axelrad et al., 2005). However, it is critically important to note that the current AOP does not contain TSH as a KE. This is because TSH may play a role in feedback-driven compensatory processes to maintain peripheral hormone level, it is not directly involved in brain development. Thus, TSH may be used as a supporting biomarker for alterations in circulating THs, however, it is not a perfect surrogate. There are also numerous examples of pharmaceutical and industrial chemicals that alter circulating THs in rats without any measurable change in TSH (NTP, 1990; O'Connor et al., 1998 2000; Liu et al., 1994; Zoeller et al., 2005; Morse et al., 1996; Goldey et al., 1995; Lau et al 2003; Schneider et al., 2011). In the absence of TSH changes, some of these chemicals do result in adverse neurological outcomes (e.g., Goldey and Crofton, 1998; Crofton, 2004; Zoeller et al., 2005; Cope et al., 2015). Therefore, stressor-induced changes in thyroid hormones, not in TSH, are responsible for adverse neurological outcomes.

How this Key Event Works

All iodothyronines are derived from the modification of tyrosine molecules (Taurog, 2000). There are two biologically active thyroid hormones (THs) in serum, triiodothyronine (T3) and T4, and a few inactive iodothyronines (rT3, 3,5-T2). T4 is the predominant TH in circulation, comprising approximately 80% of the TH excreted from the thyroid gland and is the pool from which the majority of T3 in serum is generated (Zoeller et al., 2007). As such, serum T4 changes usually precede changes in other serum THs. Decreased thyroxine (T4) in serum results result from one or more MIEs upstream and is considered a key biomarker of altered TH homeostasis (DeVito et al., 1999).

Serum T4 is used as a biomarker of TH status because the circulatory system serves as the major transport and delivery system for TH delivery to tissues. The majority of THs in the blood are bound to transport proteins (Bartalena and Robbins, 1993). In serum, it is the unbound, or 'free' form of the hormone that thought to be available for transport into tissues. Free hormones are approximately 0.03 and 0.3 percent for T4 and T3,

respectively. There are major species differences in the predominant binding proteins and their affinities for THs (see below). However, there is broad agreement that changes in serum concentrations of THs is diagnostic of thyroid disease or chemical-induced disruption of thyroid homeostasis (DeVito et al., 1999; Miller et al., 2009; Zoeller et al., 2007).

Normal serum T4 reference ranges can be species and lifestage specific. In rodents, serum THs are low in the fetal circulation, increasing as the fetal thyroid gland becomes functional on gestational day 17, just a few days prior to birth. After birth serum hormones increase steadily, peaking at two weeks, and falling slightly to adult levels by postnatal day 21 (Walker et al., 1980; Harris et al., 1978; Goldely et al., 1995; Lau et al., 2003). Similarly, in humans, adult reference ranges for THs do not reflect the normal ranges for children at different developmental stages, with TH concentrations highest in infants, still increased in childhood, prior to a decline to adult levels coincident with pubertal development (Corcoran et al. 1977; Kapelari et al., 2008). In some frog species, there is an analogous peak in thyroid hormones in tadpoles that starts around NF stage 56, peaks at Stage 62 and the declines to lower levels by Stage 56 (Sternberg et al., 2011; Leloup and Buscaglia, 1977).

How it is Measured or Detected

Serum T3 and T4 can be measured as free (unbound) or total (bound + unbound). Free hormone concentrations are clinically considered more direct indicators of T4 and T3 activities in the body, but in animal studies, total T3 and T4 are typically measured. Historically, the most widely used method in toxicology is radioimmunoassay (RIA). The method is routinely used in rodent endocrine and toxicity studies. The ELISA method is a commonly used as a human clinical test method. Least common is analytical determination of iodothyronines (T3, T4, rT3, T2) and their conjugates, though methods employing HLPC and mass spectrometry exist (Hornung et al., 2015; DeVito et al., 1999; Spencer, 2013).

Any of these measurements should be evaluated for the relationship to the actual endpoint of interest, repeatability, reproducibility, and lower limits of quantification using a fit-for-purpose approach (i.e., different regulatory needs will require different levels of confidence in the AOP). All three of the methods summarized above would be fit-for-purpose, depending on the number of samples to be evaluated and the associated costs of each method. Both RIA and ELISA measure THs by an indirect methodology, whereas analytical determination is the most direct measurement available. All these methods, particularly RIA, are repeatable and reproducible.

Thyroxine-immunofluorescence quantitative disruption test (TIQDT) was designed to provide a simple, rapid, alternative bioassay for assessing the potential of chemical pollutants and drugs to disrupt thyroid gland function. Thyroid gland functionality was evaluated by measuring IT4C in 4768 120 hpf zebrafish eleutheroembryos, following the TIQDT protocol (Thienpont et al., 2011).This study demonstrated that zebrafish eleutheroembryos provided a suitable vertebrate model, not only for screening the potential thyroid disrupting effect of molecules, but also for estimating the potential hazards associated with exposure to chemicals directly impairing thyroxine (T4) synthesis. Amitrole, potassium perchlorate, potassium thiocyanate, methimazole (MMI), phloroglucinol, 6-propyl-2-thiouracil, ethylenethiourea, benzophenone-2, resorcinol, pyrazole, sulfamethoxazole, sodium bromide, mancozeb, and genistein were classified as thyroid gland function disruptors. Concordance between TIQDT on zebrafish and mammalian published data was very high. TIQDT performed on zebrafish eleutheroembryos is an alternative whole-organism screening assay that provides relevant information for environmental and human risk assessments.

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295: Induction, Upregulation of glucuronyltransferase activity (https://aopwiki.org/events/295)

Short Name: Induction, Upregulation of glucuronyltransferase activity

AOPs Including This Key Event

AOP ID and Name	Event Type
8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	KeyEvent
194: Hepatic nuclear receptor activation leading to altered amphibian metamorphosis (https://aopwiki.org/aops/194)	KeyEvent

Biological Organization

Level of Biological Organization
Molecular

401: Increase, Biliary excretion TH glucuronide (https://aopwiki.org/events/401)

Short Name: Increase, Biliary excretion TH glucuronide

AOPs Including This Key Event

AOP ID and Name	Event Type
8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	KeyEvent
194: Hepatic nuclear receptor activation leading to altered amphibian metamorphosis (https://aopwiki.org/aops/194)	KeyEvent

Biological Organization

Level of Biological Organization
Organ

757: Hippocampal anatomy, Altered (https://aopwiki.org/events/757)

Short Name: Hippocampal anatomy, Altered

AOPs Including This Key Event

AOP ID and Name	Event Type
42: Inhibition of Thyroperoxidase and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/42)	KeyEvent
8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	KeyEvent
134: Sodium Iodide Symporter (NIS) Inhibition and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/134)	KeyEvent

AOP ID and Name	Event Type
152: Interference with thyroid serum binding protein transthyretin and subsequent adverse human neurodevelopmental toxicity (https://aopwiki.org/aops/152)	KeyEvent

Stressors

Name
Propylthiouracil
Methimazole

Biological Organization

Level of Biological Organization
Tissue

Evidence Supporting Applicability of this Event

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
mouse	Mus musculus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
rat	Rattus norvegicus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)
human	Homo sapiens	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)

Life Stage Applicability

Life Stage	Evidence
During brain development	Strong

Sex Applicability

Sex	Evidence
Male	Strong
Female	Strong

The hippocampus is generally similar in structure function across most mammalian species (West, 1990). The vast majority of information on the structure of the hippocampus is from mice, rats and primates including humans.

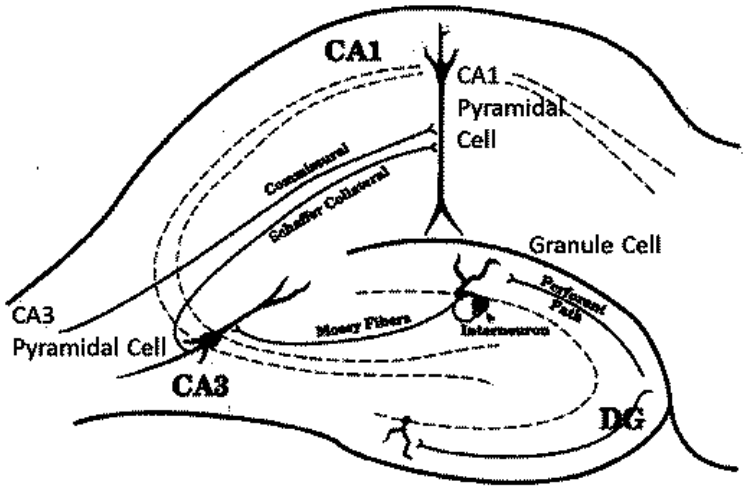
How this Key Event Works

The hippocampus is a major brain region located in the medial temporal lobe in humans and other mammals (West, 1990). Developmentally it is derived from neuronal and glial cells in the neural tube and differentiates in the proencephalon and telencephalon. The hippocampus is a cortical structure, but only contains 3-layers, distinct from the 6-layered neocortical structures. For this reason, it is known as archicortex or paleocortex meaning old cortex. Within humans, the structure is identified as early as fetal week 13 and matures rapidly until 2 to 3 years of age (Kier et al 1997), with continuing slow growth thereafter until adult ages (Utsunomiya et al., 1999). In rodents, the hippocampus begins to form in midgestation, with the CA fields forming in advance of the dentate gyrus. Dentate gyrus forms in late gestation with most of it development occurring in the first 2-3 postnatal weeks (Altman and Bayer, 1990a; 1990b).

The structure of the hippocampus has been divided into regions that include CA1 through CA4 and the dentate gyrus. The principal cell bodies of the CA field are pyramidal neurons, those of the dentate gyrus are granule cells. The dentate gyrus forms later in development than the CA fields of the hippocampus. These regions are generally found in all mammalian hippocampi.

The major input pathway to the hippocampus is from the layer 2 neurons of the entorhinal cortex to the dentate gyrus via the perforant path forming the first connection of the trisynaptic loop of the hippocampal circuit. Direct afferents from the dentate gyrus (mossy fibers) then synapse on CA3 pyramidal cells which in turn send their axons (Schaeffer Collaterals) to CA1 neurons to complete the trisynaptic circuit (Figure 1). From the CA fields information then passes through the subiculum entering the fiber pathways of the alveus, fimbria, and fornix and it routed to other areas of the brain (Amaral and Lavenex, 2006). Through the interconnectivity within the hippocampus and its connections to amygdala, septum and cortex, the hippocampus plays a pivotal role in several learning and memory processes, including spatial behaviors. The primary input pathway to the CA regions of the hippocampus is from the septum by way of the fornix and direct input from the amygdala. Reciprocal outputs from the hippocampus back to these regions and beyond also exist.

Trisynaptic Hippocampal Circuitry



How it is Measured or Detected

Data in support of this key event have been collected using a wide variety of standard biochemical, histological and anatomical methods (e.g., morphometrics, immunohistochemical staining, in situ hybridization and imaging procedures). Many of methods applied to reveal anatomical abnormalities are routine neurohistopathology procedures similar to those recommended in EPA and OECD developmental neurotoxicity guidelines (US EPA, 1998; OCED, 2007). Subtle cytoarchitectural features depend on more specialized birth dating procedures and staining techniques. It is essential to consider the timing of events during development for detection to occur, as well as the timing for detection (Hevner, 2007; Garman et al., 2001; Zgraggen et al., 2012). Similar techniques used in rodent stydies have been applied to postmortem tissue in humans.

In humans, structural neuroimaging techniques are used to assess hippocampal volume with an analysis technique known as voxel-based morphometry (VBM). Volume of brain regions is measured by drawing regions of interest (ROIs) on images from brain scans obtained from magnetic resonance imaging (MRI) or positron emission tomography (PET) scans and calculating the volume enclosed. (Mechelli et al., 2005). Similar imaging techniques can be applied in rodent models (Powell et al., 2009; Hasegawa et al., 2010; Pirko et al., 2005; Pirko and Johnson, 2008).

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758: Hippocampal Physiology, Altered (https://aopwiki.org/events/758)

Short Name: Hippocampal Physiology, Altered

AOPs Including This Key Event

AOP ID and Name	Event Type
42: Inhibition of Thyroperoxidase and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/42)	KeyEvent
8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	KeyEvent
134: Sodium Iodide Symporter (NIS) Inhibition and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/134)	KeyEvent
152: Interference with thyroid serum binding protein transthyretin and subsequent adverse human neurodevelopmental toxicity (https://aopwiki.org/aops/152)	KeyEvent

Stressors

Name
Propylthiouracil
Iodine deficiency
Methimazole

Biological Organization

Level of Biological Organization
Tissue

Evidence Supporting Applicability of this Event

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
human	Homo sapiens	Moderate	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
rat	Rattus norvegicus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)
mouse	Mus musculus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)

Life Stage Applicability

Life Stage	Evidence
During brain development	Strong

Sex Applicability

Sex	Evidence
Female	Strong
Male	Strong

The majority of evidence for this key event come from work in rodent species (i.e., rat, mouse). There is a moderate amount of evidence from other species, including humans (Clapp et al., 2012).

How this Key Event Works

The hippocampus functions as a highly integrated and organized communication and information processing network with millions of interconnections among its constitutive neurons. Neurons in the hippocampus and throughout the brain transmit and receive information largely through chemical transmission across the synaptic cleft, the space where the specialized ending of the presynaptic axon terminus of the transmitting neuron meets the specialized postsynaptic region of the neuron that is receiving that information (Kandell et al., 2012).

During development (see KE: Hippocampal anatomy, Altered), as neurons reach their final destination and extend axonal processes, early patterns of electrical synaptic activity emerge in the hippocampus. These are large fields of axonal innervation of broad synaptic target sites that are replaced by more elaborate but highly targeted and refined axonal projections brought about by activity-dependent synaptic pruning and synapse elimination. This is a classic case of the interaction between physiological and anatomical development, where anatomy develops first, and can be ‘reshaped’ by physiological function (Kutsarova et al., 2017).

Excitatory processes are fully mature in area CA1 of hippocampus within 2 weeks of birth with inhibitory processes lagging begin by several weeks (Muller et al., 1989; Michelson and Lothman, 1988; Harris and Teyler, 1984). In hippocampal slices, inhibitory function in areaCA1s is first seen on postnatal day 5 and increases in strength at postnatal day 12 through 15. In vivo studies fail to detect inhibition until postnatal day 18 with steady increase thereafter to adult levels by postnatal day 28. Synaptic plasticity in the form of long-term potentiation (LTP) is absent in the very young animal, only emerging about postnatal day 14, appearing to require the stability of both excitatory and inhibitory function to be established (Muller et al., 1989; Bekenstein and Lothman, 1991). These features of the maturation of hippocampal physiology are paralleled in dentate gyrus, but as with anatomical indices, the development of these physiological parameters lag behind the CA1 by about 1 week.

How it is Measured or Detected

In animals, synaptic function in the hippocampus has been examined with imaging techniques, but more routinely, electrical field potentials recorded in two subregions of the hippocampus, area CA1 and dentate gyrus, have been assessed in vivo or in vitro from slices taken from naive or exposed animals. Field potentials reflect the summed synaptic response of a population of neurons following direct stimulation of input pathways across a monosynaptic connection. Changes in response amplitude due to chemical perturbations and other stressors is evidence of altered synaptic function. This can be measured in vitro, in vivo, or in hippocampal slices taken from treated animals (Gilbert and Burdette, 1995). The most common physiological measurements used to assess function of the hippocampus are excitatory synaptic transmission, inhibitory synaptic transmission, and synaptic plasticity in the form of long-term potentiation (LTP).

Excitatory Synaptic Transmission: Two measures, the excitatory postsynaptic potential (EPSP) and the population spike are derived from the compound field potential at increasing stimulus strengths. The function described by the relationship of current strength (input, I) and evoked response (output, O), the I-O curve is the measure of excitatory synaptic transmission (Gilbert and Burdette, 1995).

Inhibitory Synaptic Transmission: Pairs of stimulus pulses delivered in close temporal proximity is used to probe the integrity of inhibitory synaptic transmission. The response evoked by the second pulse of the pair at brief intervals (<30 msec) arrives during the activation of feedback inhibitory loops in the hippocampus. An alteration in the degree of suppression to the 2nd pulse of the pair reflects altered inhibitory synaptic function (Gilbert and Burdette, 1995).

Long Term Potentiation (LTP): LTP is widely accepted to be a major component of the cellular processes that underlie learning and memory (Malenka and Bear, 2004; Bramham and Messaoudi, 2005). LTP represents, at the synapse and molecular level, the coincident firing of large numbers of neurons that are engaged during a learning event. The persistence of LTP emulates the duration of the memory. Synaptic plasticity in the form of LTP is assessed by delivering trains of high frequency stimulation to induce a prolonged augmentation of synaptic response. Probe stimuli at midrange stimulus strengths are delivered before and after application of LTP-inducing trains. The degree of increase in EPSP and PS amplitude to the probe stimulus after train application, and the duration of the induced synaptic enhancement are metrics of LTP. Additionally, contrasting I-O functions of excitatory synaptic transmission before and after (hours to days) LTP is induced is also a common measure of LTP maintanence (Bramham and Messaoudi, 2005; Kandell et al., 2012; Malenka and Bear, 2004).

Synaptic function in the human hippocampus has been assessed using electroencephalography (EEG) and functional neuroimaging techniques (Clapp et al., 2012). EEG is a measure of electrical activity over many brain regions but primarily from the cortex using small flat metal discs (electrodes) placed over the surface of the skull. It is a readily available test that provides evidence of how the brain functions over time. Functional magnetic resonance imaging or functional MRI (fMRI) uses MRI technology to measure brain activity by detecting associated changes in blood flow. This technique relies on the fact that cerebral blood flow and neuronal activation are coupled. Positron emission tomography (PET) is a functional imaging technique that detects pairs of gamma rays emitted indirectly by a radionuclide (tracer) injected into the body (Tietze, 2012; McCarthy, 1995). Like fMRI, PET scans indirectly measure blood flow to different parts of the brain – the higher the blood flow, the greater the activation (McCarthy, 1995). These techniques have been widely applied in clinical and research settings to assess learning and memory in humans and can provide information targeted to hippocampal functionality (McCarthy, 1995; Smith and Jonides, 1997; Willoughby et al., 2014; Wheeler et al., 2015; Gilbert et al., 1998).

Assays of this type are fit for purpose, have been well accepted in the literature, and are reproducible across laboratories. The assay directly measures the key event of altered neurophysiological function.

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756: Hippocampal gene expression, Altered (https://aopwiki.org/events/756)

Short Name: Hippocampal gene expression, Altered

AOPs Including This Key Event

AOP ID and Name	Event Type
42: Inhibition of Thyroperoxidase and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/42)	KeyEvent
8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	KeyEvent
134: Sodium Iodide Symporter (NIS) Inhibition and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/134)	KeyEvent
152: Interference with thyroid serum binding protein transthyretin and subsequent adverse human neurodevelopmental toxicity (https://aopwiki.org/aops/152)	KeyEvent

Stressors

Name
Methimazole
Propylthiouracil

Biological Organization

Level of Biological Organization
Tissue

Evidence Supporting Applicability of this Event

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
mouse	Mus musculus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
rats	Rattus norvegicus	Strong	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)
human	Homo sapiens	Moderate	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)

Life Stage Applicability

Life Stage	Evidence
During brain development	Strong

Sex Applicability

Sex	Evidence
Female	Strong
Male	Strong

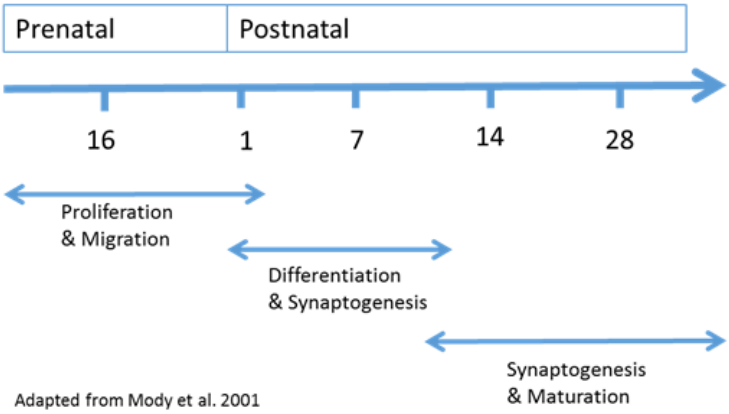
Gene expression in the developing brain in general is analogous across most mammalian species. Most of the empirical data on gene expression in hippocampus is from rat, mouse and human studies.

How this Key Event Works

Gene expression profiles have been published for the developing human and rodent hippocampus (Zhang et al., 2002; Mody et al., 2001). In both

humans and rodents, the hippocampus undergoes typical stages of neurodevelopment found in most brain regions, including: cell proliferation, migration, differentiation, synapse formation, and the maturation of synaptic function. In the rodent, peak windows during pre- and post-natal periods have been identified during which major cellular and physiological events occur (see Figure 1). Each window expresses distinct patterns of gene transcription and clusters of genes increase their expression corresponding to the progression of events of hippocampal ontogeny (see Mody et al., 2001). Tables of gene clusters associated with these phasescan be found in Supplementary Tables of Mody et al. (2001).

Figure 1. Mouse Hippocampal Developmental Stages Controlled by Gene Expression



During the very early prenatal period, genes corresponding to general cellular function are prominent (Mody et al., 2001). These are followed in time by genes regulating neuronal differentiation and migration in the mid to late gestational period. From late gestation (gestational day 15) until birth almost all the cells in the CA fields switch from a highly active proliferation state to a postmitotic state, and undergo differentiation and migration. Expression of proliferative genes involved in cell cycle progression are highly expressed at gestational day 16, then subsequently are silent immediately after birth when genes directing neuronal growth switch on. The pyramidal neurons of the CA fields in the hippocampus proper develop in advance of the granule cells that comprise the principal cells of the dentate gyrus. As such, the genes controlling the distinct phases of neurodevelopment are expressed at different times in these two hippocampal subregions (Altman and Bayer, 1990a; b). In both subregions, however, many phenotypic changes within the hippocampal neuron occur in the period immediately after birth (postnatal day 1 to 7). Almost all neurons show extensive growth and differentiation during the first postnatal week. These cellular changes are marked by rapid cytoskeletal changes, production of cell adhesion molecules, and extracellular matrix formation. The gene families involved in these processes include actins, tubulins, and chaperonin proteins essential for promoting correct protein folding of cytoskeletal components. Cell adhesion and extracellular matrix proteins are also upregulated during this period as these genes are critical for differentiation and synaptogenesis.

During late postnatal hippocampal development (postnatal day 16-30), hippocampal circuits become more active and exhibit increased synaptic plasticity. Many genes upregulated during this phase of development are involved in synaptic function and include genes regulating vesicle associated proteins and calcium-mediated transmitter release, neurotrophins, and neurotransmitter receptors. Efficient energy utilization is essential during this period of increased synaptic activity, events mirrored by an upregulation of enzymes involved in glucose and oxidative metabolism.

How it is Measured or Detected

Measurement of genomic profiles in developing brain use methods that are well established and accepted in the published literature. Microarray studies with expression profile analyses have been conducted in cortex and hippocampus of humans (Zhang et al., 2002), non-human primates, and rodent brains of various ages (Mody et al., 2001; Royland et al., 2008; Dong et al., 2015). More commonly, quantitative rtPCR or in situ hybridization have been used to probe individual gene transcripts (Dowling et al., 2000, Morte et al., 2010) or their protein products (Alvarez-Dolado et al., 1994; Gilbert et al., 2007). Recently RNA-Seq technology was applied to T3-treated primary mouse cortical cells and gene targets enriched in astrocytes and neurons to identify TH-responsive genes (Gil-Ibanez et al, 2015).

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Adverse Outcomes

Title	Short name
Loss, Cochlear function (https://aopwiki.org/events/319)	Loss, Cochlear function

319: Loss, Cochlear function (https://aopwiki.org/events/319)

Short Name: Loss, Cochlear function

AOPs Including This Key Event

AOP ID and Name	Event Type
8: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	AdverseOutcome

Biological Organization

Level of Biological Organization
Organ

Scientific evidence supporting the linkages in the AOP

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
Decrease, Tissue thyroid hormone concentration	indirectly leads to	Decrease, TR-regulated cochlear proteins	Weak	
Decrease, TR-regulated cochlear proteins	directly leads to	Damage, Structure of the cochlea	Weak	
Damage, Structure of the cochlea	directly leads to	Loss, Cochlear function	Moderate	
Activation, Pregnane-X receptor, NR1I2	directly leads to	Up Regulation, Hepatic transporter gene expression	Moderate	

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
Up Regulation, Hepatic transporter gene expression	indirectly leads to	Increase, Hepatic transport of parent T4	Moderate	
Decrease, Serum thyroxine (T4)	directly leads to	Decrease, Tissue thyroid hormone concentration	Moderate	Weak
Activation, Pregnane-X receptor, NR1I2	directly leads to	Induction, Upregulation of glucuronyltransferase activity	Strong	Weak
Activation, Constitutive androstane receptor, NR1I3	directly leads to	Induction, Upregulation of glucuronyltransferase activity	Moderate	Weak
Induction, Upregulation of glucuronyltransferase activity	indirectly leads to	Decrease, Serum thyroxine (T4)	Strong	Weak
Increase, Biliary excretion TH glucuronide	directly leads to	Decrease, Serum thyroxine (T4)	Moderate	Weak
Induction, Upregulation of glucuronyltransferase activity	directly leads to	Increase, Biliary excretion TH glucuronide	Moderate	

Decrease, Tissue thyroid hormone concentration leads to Decrease, TR-regulated cochlear proteins (https://aopwiki.org/relationships/313)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**indirectly leads to**	**Weak**	

Decrease, TR-regulated cochlear proteins leads to Damage, Structure of the cochlea (https://aopwiki.org/relationships/314)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**directly leads to**	**Weak**	

Damage, Structure of the cochlea leads to Loss, Cochlear function (https://aopwiki.org/relationships/297)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**directly leads to**	**Moderate**	

Activation, Pregnane-X receptor, NR1I2 leads to Up Regulation, Hepatic transporter gene expression (https://aopwiki.org/relationships/264)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**directly leads to**	**Moderate**	

Up Regulation, Hepatic transporter gene expression leads to Increase, Hepatic transport of parent T4 (https://aopwiki.org/relationships/149)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**indirectly leads to**	**Moderate**	

Decrease, Serum thyroxine (T4) leads to Decrease, Tissue thyroid hormone concentration (https://aopwiki.org/relationships/285)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**directly leads to**	**Moderate**	**Weak**

Activation, Pregnane-X receptor, NR1I2 leads to Induction, Upregulation of glucuronyltransferase activity (https://aopwiki.org/relationships/265)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**directly leads to**	**Strong**	**Weak**

Activation, Constitutive androstane receptor, NR1I3 leads to Induction, Upregulation of glucuronyltransferase activity (https://aopwiki.org/relationships/85)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**directly leads to**	**Moderate**	**Weak**

Induction, Upregulation of glucuronyltransferase activity leads to Decrease, Serum thyroxine (T4) (https://aopwiki.org/relationships/381)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**indirectly leads to**	**Strong**	**Weak**

Increase, Biliary excretion TH glucuronide leads to Decrease, Serum thyroxine (T4) (https://aopwiki.org/relationships/382)

AOPs Referencing Relationship

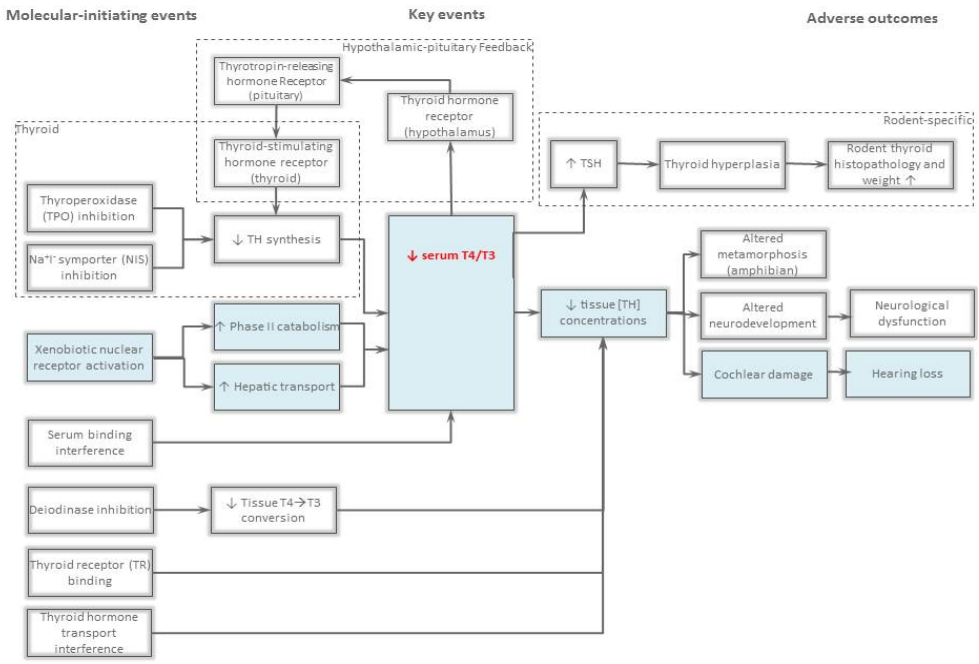
AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**directly leads to**	**Moderate**	**Weak**

Induction, Upregulation of glucuronyltransferase activity leads to Increase, Biliary excretion TH glucuronide (https://aopwiki.org/relationships/1060)

AOPs Referencing Relationship

AOP Name	Directness	Weight of Evidence	Quantitative Understanding
Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals (https://aopwiki.org/aops/8)	**directly leads to**	**Moderate**	

Graphical Representation



Overall Assessment of the AOP

Domain of Applicability

Life Stage Applicability

Life Stage	Evidence
Fetal to Parturition	Moderate
Nursing Child	Moderate

Weight of Evidence Summary

Summary Table

Provide an overall summary of the weight of evidence based on the evaluations of the individual linkages from the Key Event Relationship pages.

Concordance of dose-response relationships

Multiple studies provide limited (2-3 doses) dose-response data for many of the key events. These studies demonstrate similar magnitudes of effect on circulating hormones for doses of PCBs that are within an order of magnitude (3-25 mg/kg/day for Aroclor 1254) (e.g.,Morse et al., 1996; Goldey et al., 1998). Very limited data are available correlating any of the key events. One exception is the relationship between circulating serum T4 concentrations during development and the magnitude of hearing loss (Crofton, 2004). There is a very good correlation between total serum T4 concentrations on postnatal day (PND) 14 and hearing loss assessed in adult offspring of PCB exposed dams (Figure 2). All of these events occur within a 2-3 fold dose range.

Temporal concordance among the key events and the adverse outcome Strength, consistency, and specificity of association of adverse effect and initiating event Biological plausibility, coherence, and consistency of the experimental evidence Alternative mechanism(s) or MIE(s) that logically present themselves and the extent to which they may detract from the AOP Uncertainties, inconsistencies, and data gaps

References