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Changes in thyroid axis responses in two ring-billed gull sub-populations differentially exposed to halogenated flame retardants

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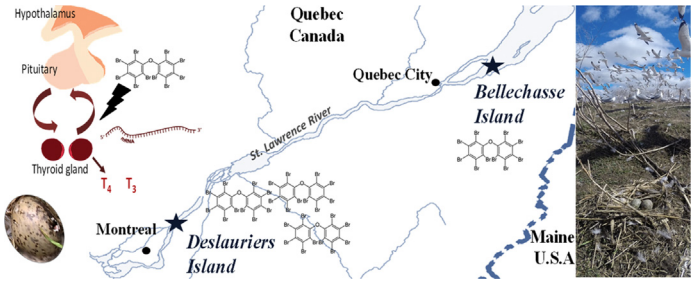
HIGHLIGHTS

- Gulls from Montreal accumulate high liver concentrations of flame retardants (FRs).
- We examined linkages between FRs and thyroid axis response in pipping gulls.
- FRs were correlated with plasma thyroid hormones (THs) in pipping gulls.
- FRs were correlated with genes involved in TH metabolism, synthesis, and feedback.
- Elevated concentrations of FRs may perturb TH homeostasis in gull embryos.

GRAPHICAL ABSTRACT



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ABSTRACT

Developing bird embryos may be affected by a number of thyroid disrupting chemicals through maternal transfer. However, thyroid disruption in developing embryos of wild birds remains largely unstudied, especially with respect to exposure to ubiquitous environmental contaminant classes including halogenated flame retardants (HFRs). The objective of the present study was to investigate responses of the hypothalamic-pituitary-thyroid (HPT) axis of developing birds that are exposed to elevated concentrations of HFRs in their environment. Ring-billed gulls (*Larus delawarensis*) were collected at the external pipping stage (i.e., just prior to hatching) from two sub-populations that are differentially exposed to HFRs in the St. Lawrence River (QC, Canada). Plasma levels of thyroid hormones (THs) and transcription levels of thyroid-related genes in three tissues (i.e., liver, thyroid gland and brain) were related to liver concentrations of HFRs in pipping gulls from these two colonies. Liver polybrominated diphenyl ether (PBDE) concentrations were negatively correlated with plasma total T_4 and total T_4/T_3 in pipping ring-billed gulls. Moreover, plasma TH levels and hepatic PBDE concentrations were correlated with the transcription of genes involved in metabolism (deiodinases type 1, 2 and 3) and synthesis (sodium iodide symporter and thyroglobulin) in the thyroid gland, negative feedback loop (thyrotropin and corticotropin releasing hormones) in the brain and the pituitary and targeted action (TH receptors) in the three tissues of gulls. The present study suggested that the alteration of TH homeostasis in developing wild birds

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through changes in the transcription of several thyroid-related genes may be related to potential PBDE-mediated effects.

1. Introduction

Wildlife species including birds are chronically exposed to a variety of chemical and natural environmental stressors that can lead to perturbations of the endocrine system. Experimental and field studies have shown that organic contaminants including polychlorinated biphenyls (PCBs) (Scanes and McNabb, 2003; Zoeller, 2007) and halogenated flame retardants (HFRs) (Fernie and Guigueno, 2017) can affect thyroid hormone (TH) homeostasis in several bird species. Thyroid disruption in birds is of great concern as THs [thyroxin (T_4) and its biologically active form, triiodothyronine (T_3)] synthesized by the thyroid gland are involved in key signaling pathways, which include embryonic development, tissue maturation and differentiation, growth, reproduction, hatching, molt, energy metabolism and thermoregulation (McNabb, 2007). In birds, as in mammals, the hypothalamic-pituitary-thyroid (HPT) axis regulates circulating THs through hypothalamic and pituitary hormones, and allows rapid physiological adaptations to environmental changes throughout all developmental stages (McNabb, 2007). The hypothalamic thyrotropin releasing hormone (TRH) and the corticotropin-releasing hormone (CRH) stimulate the anterior pituitary for synthesis/release of thyrotropin hormone (TSH) (McNabb, 2007; De Groef et al., 2006), which enhances TH synthesis/release by the thyroid gland through thyrocyte membrane receptors (Maenhaut et al., 2015). TH homeostasis is also regulated by other factors such as iodine content, availability of circulating and membrane transporters as well as metabolism in peripheral tissues by deiodinases (McNabb, 2007). Moreover, the targeted actions of THs are mediated via the binding to TH receptors (TRs), which activate the transcription of several genes by interacting with the thyroid hormone response elements (TREs) (McNabb, 2007).

The mechanisms underlying thyroid disruption in wild birds associated with exposure to environmental contaminants including the ubiquitously distributed polybrominated diphenyl ethers (PBDEs), which have structural similarities with THs, remain to be confirmed (Fernie and Guigueno, 2017). PBDEs have been added massively to consumer goods (e.g., electronic devices, construction materials, textiles, and upholstered furniture) to meet fire safety standards, and have been released into the environment since the 1970s (Abbasi et al., 2015). The three commercial mixtures of PBDEs have been listed on the Annex A of the Stockholm Convention on Persistent Organic Pollutants (Stockholm Convention, 2009, 2017) as components of these mixtures were shown to be persistent, bioaccumulative, and toxic (Abelkop et al., 2015). However, it was estimated that approximately 60% of the PBDE stocks contained in in-use products in 2014 are expected to remain in usage by 2020 (Abbasi et al., 2015), therefore, exposure to PBDEs still represents a potential health hazard for wildlife. Moreover, alternative flame retardants have been commercialised and used as replacements for PBDEs. Examples of alternative HFRs include Dechlorane Plus (DP), hexabromobenzene (HBB), 1,2-bis 2,4,6-tribromophenoxy ethane and pentabromoethylbenzene (PBEB), and most of these have already been detected in various environmental compartments and tissues of wildlife species including birds (Covaci et al., 2011).

Wild avian nestlings may be exposed *in ovo* to HFRs through maternal transfer and concentrations measured in eggs are, for most compounds, generally representative of those found in the laying female (Verreault et al., 2006; Eng et al., 2013; Zheng et al., 2014). Thyroid disruption in avian embryos or nestlings that are environmentally-exposed to HFRs is therefore of high concern as their development, metabolism and thermoregulatory capacity are, at least in part, controlled by TH action (Fernie and Guigueno, 2017). However, thyroid responses in developing birds may differ as a function of their development strategy; complete thyroid activation occurs early during the embryonic development in precocial birds (e.g., domestic chicken, *Gallus gallus domesticus*), while thyroid activity play a major role after hatching in altricial birds (e.g., ring doves, *Streptopelia capicola*) (McNabb, 2007). In addition to the inherent differences between developmental stages and species, avian thyroid responses may be affected by chemical exposure. For example, altricial female nestling American kestrels (*Falco sparverius*) exposed *in ovo* through maternal transfer to a mixture of 14 PBDE congeners (3.01, 289 and 1131 ng/g ww) showed a reduced T_4 release by the thyroid gland after a TSH challenge as well as reduced plasma total T_4 and T_3 levels (Marteinson and Fernie, 2016). An increase in plasma free T_4 was further observed in fledging altricial European starlings (*Sturnus vulgaris*) orally dosed for 20 days to BDE-99 (0, 15.8 and 174 ng BDE-99/g body weight/day) (Eng et al., 2014).

Elevated PBDE concentrations and low to moderate levels of emerging HFRs including DP isomers and other Dechlorane-related compounds have been reported in ring-billed gull (*Larus delawarensis*) eggs and liver of breeding adults collected from a colony near the metropolis of Montreal (QC, Canada)- a known hotspot for HFRs (Chen et al., 2012; Gentes et al., 2012; Técher et al., 2016). Specifically, concentrations of BDE-209 (~97% of deca-BDE mixture) in plasma of breeding ring-billed gulls were shown to be among the highest reported in birds across Canada, and were associated with the amount of time birds spent foraging in landfills (Gentes et al., 2015). A follow-up study using this same ring-billed gull colony reported significant relationships between tissue HFR (and other organohalogens) concentrations and changes in the regulation of the HPT axis (Técher et al., 2016). For example, positive correlations were observed between hepatic concentrations of PBDEs, PCBs and chlordanes, and plasma total T_4 levels. Moreover, in this same study, PBDE concentrations were significantly related to mRNA levels of several genes involved in TH metabolism, synthesis and action in the thyroid gland, and transport in the hypothalamic and pituitary regions (Técher et al., 2016). In light of these findings, it was recommended that investigation on the responses of the HPT axis in developing ring-billed gulls exposed to these elevated HFR concentrations should be prioritized.

The objective of the present study was to investigate the variations in circulating TH levels and transcription levels of several thyroid-related genes in thyroid gland, liver, and brain of pipping ring-billed gulls from two colonies in the St. Lawrence River (QC, Canada) that are differentially exposed to HFR concentrations. The external pipping stage of birds (i.e., just prior to hatching) was selected as thyroid functions at this stage of their development are highly activated in precocial (or semi-precocial) species (McNabb, 2007). A high- and a low-exposed colony of ring-billed gulls were selected within a geographically-limited region in the St. Lawrence River following reports of HFR concentrations in herring gull (*Larus*