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Exposure to graphene oxide at environmental concentrations induces thyroid endocrine disruption and lipid metabolic disturbance in *Xenopus laevis*

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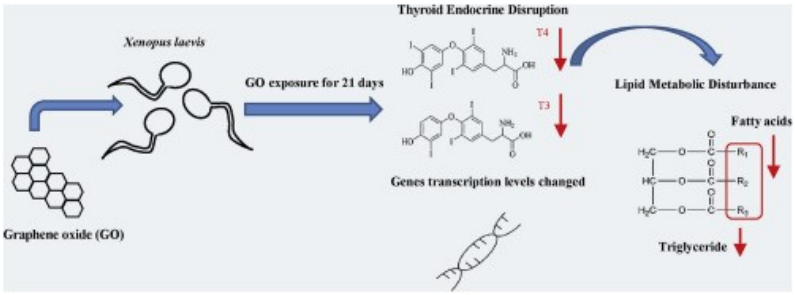
Highlights

- The potential toxic effects of GO to amphibians were studied.
- GO showed obvious developmental toxicity in tadpoles.
- GO exposure exhibited thyroid endocrine disruption to tadpoles.
- GO obviously disturbed lipid synthesis and metabolism in tadpoles.

Abstract

Graphene oxide (GO) has become a topic of increasing concern for its environmental and health risks. However, the potential toxic effects of GO on wildlife remain limited. The present study chose the *Xenopus laevis* tadpole as a model to assess the thyroid endocrine disruption as well as the lipid metabolic disturbance of GO. Tadpoles at the 51 stage were exposed to GO (0, 0.01, 0.1, and 1 mg/L) for 21 days, when tadpoles were undergoing an extremely complicated phase of morphological changes and growth. GO treatment showed obvious developmental toxicity, such as shortened snout-to-vent length (SVL) and hind limb length (HLL), decreased body weight, and delayed developmental stage. Exposure to GO also induced obvious decreases in whole-body triiodothyronine (T3) and thyroxin (T4) concentrations. The mRNA expression of genes related to the hypothalamic–pituitary–thyroid (HPT) axis also changed significantly. Furthermore, we observed significant decline in the fatty acids and triglycerides (TGs) concomitantly with changes in the expression of genes involved in the synthesis and metabolism of lipids in GO exposure groups. In contrast, high-density lipoprotein (HDL) and total bile acid levels increased remarkably, but cholesterol and low-density lipoprotein (LDH) levels showed no obvious changes. Taken together, the results revealed for the first time that GO could induce thyroid endocrine disruption and produce obvious disturbance effect on lipid synthesis and metabolism.

Graphical abstract



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Introduction

Graphene oxide (GO), which has attracted a substantial amount of attention due to its unique properties (Pastrana-Martínez et al., 2015), shows great potential application in areas including agriculture, biology, and environmental protection (Li et al., 2017; Abraham et al., 2017). Recent studies have reported that the market of GO was expected to reach $675 million by 2020 (Ahmed and Rodrigues, 2013). With the increasing production and application of GO, it has been inevitably introduced into the aqueous environments, which could be enhanced when graphene-based materials are exposed to ultraviolet (UV) radiation (Bernard et al., 2011; Goodwin et al., 2018; Du et al., 2017). A previous study also demonstrated that carbon nanotubes and GO had a similar fate: more than 80% of manufactured GO could be introduced into aqueous environments (Lanphere et al., 2014). Additionally, GO contains numerous oxygen-containing groups, which makes it more soluble in water, and it may be transported by food chains or physical processes (Chowdhury et al., 2013). Thus, in an aqueous ecosystem, the environmental concentration of GO was expected to reach as high as 1000 μg/L (Zhang et al., 2017). Therefore, it is imperative to understand the potential ecological risk and health threats of GO by evaluating its potential toxicity.

An increasing number of studies has indicated that GO resulted in adverse effects (e.g., oxidative stress, genotoxicity, and reproductive toxicity) on cells, mammals and aquatic animals, including zebrafish and *Xenopus laevis* (Hu et al., 2014, 2017; El-Yamanya et al., 2017; Zhang et al., 2017; Zou et al., 2018; Saria et al., 2014; Evariste et al., 2019). For instance, in *in vivo* experiments with zebrafish, GO induced immunotoxicity, neurotoxicity, and developmental toxicity. In addition, GO could translocate to the brain of zebrafish and lead to mitochondrial damages, DNA methylation changes, and metabolic disturbance (Yang et al., 2018; Chen et al., 2016). Moreover, there was evidence suggesting that exposure to low concentrations of GO induced oxidative stress and genotoxicity in *Xenopus laevis* tadpoles (Evariste et al., 2019). Although these studies have demonstrated some potential toxicity of GO to the aquatic organism, the toxic effects of GO on the thyroid endocrine system is still relatively poorly investigated. Therefore, in the present study we aimed to quantify the potential thyroid endocrine disruption effect of GO.

Amphibian metamorphosis serves as an excellent model to study thyroid system function in vertebrates due to

its total dependence on thyroid hormones (Tamura et al., 2015). Alarmingly, incomplete metamorphosis may lead to a complete loss of one generation of frogs in a pond, finally inducing a significant decrease of population (Kloas and Lutz, 2006). Thus, we used *Xenopus laevis* tadpole as an ecological model to assess the thyroid endocrine disruption of GO. Thyroid hormones (THs) have prominent effects on growth and metamorphic development and could regulate the metabolism of fatty acid and cholesterol (Sinha et al., 2018). Therefore, the following points were investigated: a) the developmental toxicity of GO in tadpoles; b) the effect of GO on the thyroid endocrine system of tadpoles; c) the effect of GO on the synthesis and metabolism of lipids. Taken together, our work will contribute to better characterizations of the environmental risk of GO in amphibians.

Section snippets

Chemical

GO with a purity and single layer ratio of greater than 99% (GO; CAS: 7440-44-0) was purchased from Nanjing XFNANO Materials Tech Co., Ltd (Nanjing, China). According to the manufacturer, the thickness of GO was 0.8–1.2 nm, and the diameter was 50–200 nm.…

Characterization of GO

The characterization of GO was verified in our previous study (Li et al., 2019). Briefly, the elemental composition of GO was determined by a Quantax 400 (Bruker, Germany) energy-dispersive X-ray spectrometer. The average diameter and zeta…

Characterization of GO

The characterization of GO was verified in our previous study (Li et al., 2019). According to the AFM images, the thickness of the GO nanosheets was 3.12 ± 0.25 nm. The GO compositions were 63.46% C, 35.61% O, 0.75% S, and 0.18% K in EDX image (Li et al., 2019). The hydrodynamic diameter and zeta potential of GO in the GO exposure solution were 183.63 nm and−22.53 mV, respectively (Li et al., 2019).…

GO identification in tadpoles

The transmission electron microscopy (TEM) image revealed the uptake of GO in tadpoles, and the…

Discussion

In the present study, we assessed the toxic effects of GO on the thyroid endocrine system, TH-dependent metamorphic development, and the metabolism of lipids of *Xenopus laevis* tadpoles. The results demonstrated that GO suppressed the metamorphic development and showed the thyroid endocrine disruption effect on tadpoles. In addition, we found that GO induced obvious perturbation in the synthesis and metabolism of fatty acids of tadpoles.

The TEM images in our results indicate the uptake of GO by…

Notes

The authors declare no competing financial interest.…

Acknowledgments

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2023, Science of the Total Environment

> *Citation Excerpt :*
> ...In amphibian, previous studies highlighted that the growth of Xenopus laevis tadpoles was altered by exposure to GBMs (Mottier et al., 2016), including GO (Lagier et al., 2017). It was also highlighted that the tadpole growth inhibition was independent from a disruption of the thyroid pathway (Evariste et al., 2021b), while it was associated to a decrease of the fatty acids and triglyceride metabolism (Li et al., 2019). Intestinal accumulation of the nanomaterials favors direct contact with the gut microbiota which may be modulated by the nanomaterials and lead to host physiological alterations (Bantun et al., 2022)....

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2021, Chemosphere

Citation Excerpt :

...These changes were associated to gill resorption, limb outgrowth and brain remodeling (Heimeier and Shi, 2010). In addition, exposure to GBMs in absence of T3 hormone in the water did not influence either the morphological parameters measured (ANOVA, $p > 0.05$) or the weight of the larvae (ANOVA, $p = 0.100$), indicating that GBMs alone did not exert a T3-like action, in agreement with the work of Li et al. (2019). In the case of co-exposure to GO and T3, the response to the T3 hormone improved significantly, leading to more marked T3-induced biometrical changes in presence of GO....

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