Interference of Environmental Exposure Mixtures with Thyroid Hormone Regulation

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INTRODUCTION AND AIM

Endocrine disruption through steroid hormones is relatively well described, while not much information is available regarding interference of pollutants and namely environmental exposure mixtures with thyroid hormone regulation.

AIMs

- Prioritization of most relevant Molecular Initiating Events.
- Development and optimization of assays for relevant exposure mixtures.
- Identification of contributing compounds.

STEP 1: development and optimization of assay for sodium/iodide cotransporter (NIS) inhibition. NIS mediated uptake of iodide into follicular cells of the thyroid gland is the first step in the synthesis of thyroid hormone.

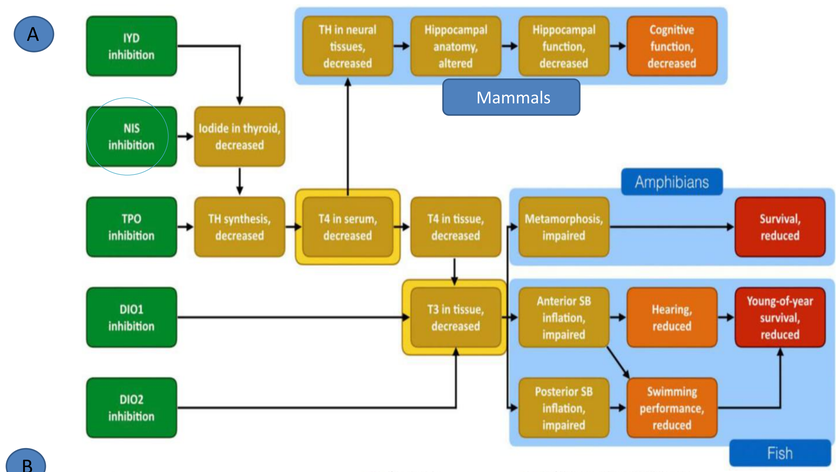

Fig 1: (A) AOP network demonstrating thyroid hormone disruption highlighting NIS as molecular initiating event (MIE); (B) Alignment of protein sequence of NIS using SeqAPASS tool (% similarity in mammals, amphibians and fishes)

METHODOLOGY

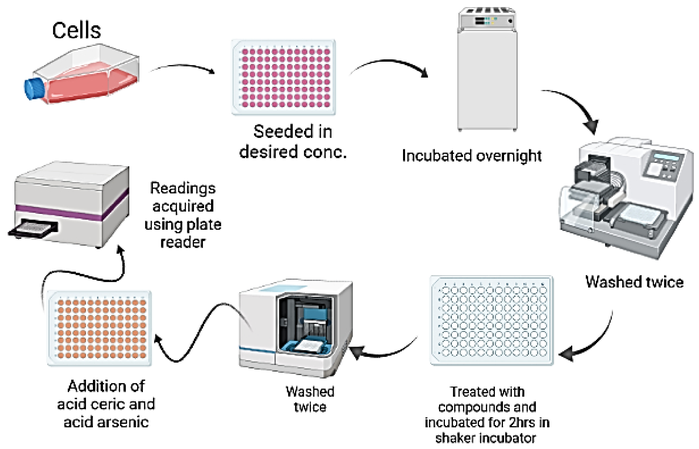

Fig 2: Pictorial representation of NIS assay, responsible to mediate the active uptake of Iodide as NIS plays a crucial role in the synthesis of thyroid hormones.

CONCLUSION

We are developing novel bioassay focusing on prioritized endpoints in thyroid hormone disruption. The assay for the assessment of iodide uptake by thyroid cells mediated by Na^+/I^- symporter (NIS) is based on stably transfected human cell line overexpressing NIS and the detection of uptaken iodide levels by the cells used a non-radioactive assay based on Sandell-Kolthoff reaction

The results demonstrate the utility of the newly developed bioassay for high-throughput screening of chemicals as well as environmentally relevant complex pollutant mixtures for the characterization of their thyroid hormone-disrupting potential.

FUTURE RESEARCH

1. Assessment of real exposure mixtures from field studies.
2. Prioritization of most relevant:
   a) MIEs (Molecular Initiating Events).
   b) Compounds contributing to the effects.
3. Assessment of predictability of in vivo effects using Zebrafish model by in vitro assays.

REFERENCES

1. Dong, H., Atlas, E. and Wade, M. G. (2019) 'Development of a non-radioactive screening assay to detect chemicals disrupting the human sodium iodide symporter activity', *Toxicology in Vitro*. Elsevier, 57(January), pp. 39–47. doi: 10.1016/j.tiv.2019.01.021.

RESULTS

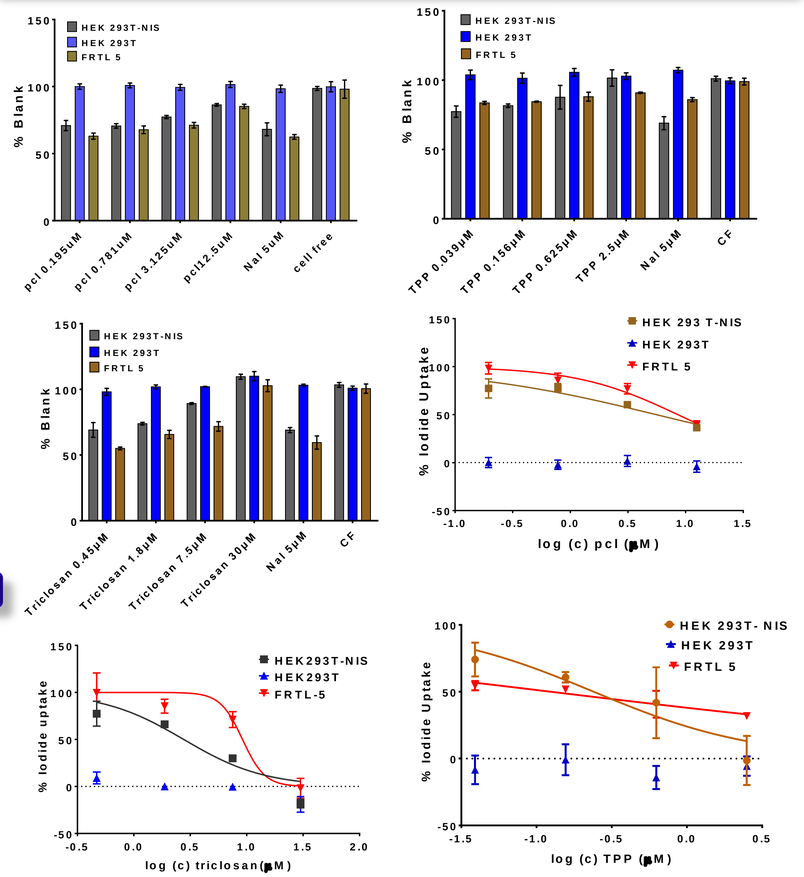

Fig 3: Inhibition of iodide uptake by perchlorate (PCL), triclosan and triphenyl phosphate (TPP) in novel cell model transfected with human NIS (HEK293T-NIS), non-transfected cells (HEK293T) and Rat FRTL-5 cell line with intrisic NIS activity.

These transfected models were prepared as sensitive in vitro models are not available for this MIE; HEK293T is used as the negative control whereas FRTL5 is used as the positive control. %Blank in bar graphs is 100% (corresponds to CF=cell free variant) in case there is no iodide uptake, smaller bars mean greater iodide uptake. The exposure chemicals decreased the uptake in comparison to NaI treatment alone, which shows the maximal uptake.

NIS Inhibition IC50 (µM)	HEK293T-NIS	HEK293T	FRTL-5
Triclosan	2.77	n.q.	9.18
Perchlorate	5.55	n.q.	8.56
Triphenyl Phosphate	0.24	n.q.	0.12

Table 1: IC50 levels of triclosan, perchlorate and triphenyl phosphate on NIS-mediated uptake of iodide in novel cell model transfected with human NIS (HEK293T-NIS), non-transfected cells (HEK293T) and rat FRTL-5 cell line with intrisic NIS activity; n.q. –non quantifiable

Disclosures : The authors have nothing to disclose