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Tramadol and its main metabolites: toxicological effects on zebrafish embryos and larvae

Pedro Rodrigues [1,*], Luís Oliva-Teles [1,2], António Paulo Carvalho [1,2] and Laura Guimarães [1]

[1] CIIMAR-Interdisciplinary Centre of Marine and Environmental Research, University of Porto, Terminal de Cruzeiros do Porto de Leixões, Avenida General Norton de Matos, S/N, 4450-208 Matosinhos, Portugal
[2] Faculty of Sciences – Biology Department, Rua do Campo Alegre s/n, University of Porto, 4169-007 Porto, Portugal

* Correspondence: pedromcrodrigues93@gmail.com

Abstract

Background: Tramadol (TRA) and its main metabolites are among the most detected pharmaceutical compounds in aquatic ecosystems, reaching concentrations in the µg/L range. In humans, TRA acts on different receptors of the noradrenergic, serotoninergic, dopaminergic and opioid systems. Also, it is metabolized into the active metabolite o-desmethyltramadol (OTRA) and inactive metabolite n-desmethyltramadol (NTRA). In fish, TRA was reported to have several toxic effects [1,2]. However, for OTRA and NTRA there is no information about their toxicity in fish. **Objective:** the main aims of this work were to investigate and compare the effects of TRA, OTRA and NTRA on zebrafish embryonic development; behavioural responses; expression profiles of genes related to the monoaminergic and detoxification systems and proteome, as well as develop and initial draft of an adverse outcome pathway (AOP) **Methods:** Zebrafish embryos were exposed (0.1−100µg/L) for 168hpf to TRA, OTRA and NTRA [3]. During the exposure, several developmental malformations were registered. Behaviour was evaluated through a sensorimotor assay. Gene expression for 32 target genes was obtained through qPCR, while shotgun proteomics protocols were employed for the proteome evaluation. **Results:** TRA and OTRA were found to cause significant increases in embryonic anomalies, namely in the yolk sac, spine, and otoliths, at the highest concentrations. Decreased sensorimotor responses were observed for exposure to 0.1 and 100µg/L of TRA and OTRA. Different gene expression profiles were found between TRA and the metabolites OTRA and NTRA, with a predominance of non-monotonic responses. Shotgun proteomics indicates that TRA and OTRA impact pathways linked to vital biological processes. An initial drat AOP was performed. **Conclusions:** The obtained results indicated that exposure to TRA, OTRA and NTRA can negatively impact aquatic non-target species at different levels of biological organization. These results also raise awareness for the inclusion of pharmaceutical in monitoring programmes.

Keywords: tramadol; metabolites; embryonic development; genomics; proteomics

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