Effect of narcotics on membrane-bound mitochondrial processes in fish - DTU Orbit (08/11/2017)

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Around 70% of industrial chemicals are hydrophobic compounds which are assumed to elicit toxicity through narcosis by accumulating in membranes and disrupting membrane integrity and function. Although narcosis has been recognized as an important toxicity mechanism for decades, ecotoxicological research has been mostly limited to the development of quantitative structure activity relations (QSARs) to predict toxicity, resulting in insufficient understanding of the exact mechanisms involved. In this study we investigate specific aspects of the mechanism of narcosis in fish using both alternative in vivo (zebrafish embryo) and in vitro tests. We applied a passive dosing method to expose zebrafish embryos up to 5 days post fertilization to linear dilution series of a set of non-polar narcotics (phenanthrene and three chlorobenzene structure analogues). In addition to increasing mortality, we observed decreasing growth, heart rate and motility with increasing exposure concentration of all narcotics, consistent with the general assumption of reduced cardiorespiratory function. At the cellular level, the cell membrane is expected to be the first target of narcotics. Since the mitochondrial and endoplasmic reticulum membrane are known to closely interact with the cell membrane, we hypothesize that narcotics can be further partitioned into these organelle membranes where they can disrupt essential membrane-bound processes. The electron transport chain (ETC) is an example of a crucial mitochondrial membrane-bound process and is therefore a potential target. We found that in zebrafish embryos ETC activity was increased at low exposure concentrations, suggesting a compensatory response, while it decreased when exposure concentrations reached levels causing reduced motility, heart rate and eventually mortality. The effect of narcotic compounds on ETC activity was confirmed in vitro: we observed inhibition of the ETC after adding the compounds directly to a homogenate of control embryos. To further investigate effects on the energy production system, and to characterize the observed compensatory response, we are currently measuring the effect of narcotics on ATP synthase activity both in vivo and directly in vitro. Although narcosis is commonly considered a non-specific mechanism of toxicity acting by membrane disruption in general, we illustrate how we can increase our understanding of narcosis by focussing on specific membrane types and membrane-bound processes.

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