Zebrafish as a model for systems medicine R&D: rethinking the metabolic effects of carrier solvents and culture buffers determined by 1H NMR metabolomics

ABSTRACT

Zebrafish is a frequently employed model organism in systems medicine and biomarker discovery. A crosscutting fundamental question, and one that has been overlooked in the field, is the ñsystem-wideò (omics) effects induced in zebrafish by metabolic solvents and culture buffers. Indeed, any bioactivity or toxicity test requires that the target compounds are dissolved in an appropriate nonpolar solvent or aqueous media. It is important to know whether the solvent or the buffer itself has an effect on the zebrafish model organism. We evaluated the effects of two organic carrier solvents used in research with zebrafish, as well as in drug screening: dimethyl sulfoxide (DMSO) and ethanol, and two commonly used aqueous buffers (egg water and Hank's balanced salt solution). The effects of three concentrations (0.01, 0.1, and 1%) of DMSO and ethanol were tested in the 5-day-old zebrafish embryo using proton nuclear magnetic resonance (1H NMR) based metabolomics. DMSO (1% and 0.1%, but not 0.01%) exposure significantly decreased the levels of adenosine triphosphate (ATP), betaine, alanine, histidine, lactate, acetate, and creatine ($p < 0.05$). By contrast, ethanol exposure did not alter the embryos' metabolome at any concentration tested. The two different aqueous media noted above impacted the zebrafish embryo metabolome as evidenced by changes in valine, alanine, lactate, acetate, betaine, glycine, glutamate, adenosine triphosphate, and histidine. These results show that DMSO has greater effects on the embryo metabolome than ethanol, and thus is used with caution as a carrier solvent in zebrafish biomarker research and oral medicine. Moreover, the DMSO concentration should not be higher than 0.01%. Careful attention is also warranted for the use of the buffers egg water and Hank's balanced salt solution in zebrafish. In conclusion, as zebrafish is widely used as a model organism in life sciences, metabolome changes induced by solvents and culture buffers warrant further attention for robust systems science, and precision biomarkers that will stand the test of time.

Keyword: Zebrafish; 1H NMR; Buffers; Solvents; Dimethyl sulfoxide; Ethanol; Metabolome