Behavioral and molecular correlates of zebrafish brain pathogenesis

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The zebrafish (Danio rerio) is rapidly becoming a popular model species in experimental neuroscience research. Zebrafish behavior is robustly and bidirectionally affected by various environmental challenges and pharmacological manipulations. These alterations can be examined using exploration-based paradigms, and paralleled by analysis of endocrine (cortisol) stress responses in these fish. As humans, zebrafish use cortisol as their main stress hormone, making them an excellent model to study molecular mechanisms of zebrafish stress. Here we will describe several different applications of zebrafish-based models to study brain disorders, including anxiety, drug dependence, epilepsy and withdrawal. As in humans and rodent models, discontinuation of psychotropic drug exposure in zebrafish evokes withdrawal symptoms characterized by increased anxiety. Our examination of the effects of withdrawal from chronic ethanol, morphine, chlordiazepoxide, and diazepam demonstrated the relationship between anxiogenic-like behavioral phenotypes, identified using the novel tank diving test, and an increase in circulating cortisol levels, quantified via ELISA assay. These findings suggest the existence of readily-identifiable endophenotypes of drug withdrawal in zebrafish. Our research on epilepsy (using caffeine, RDX, picrotoxin and pentylenetetrazole) showed the utility of zebrafish in modeling drug-evoked seizures, paralleled by markedly elevated cortisol levels. Hallucinogenic drugs, such as LSD and MDMA, evoke prominent behavioral activation in zebrafish (detected in 3 different behavioral models), accompanied by elevated cortisol levels. Taken together, these findings further validate the utility of zebrafish-based animal model in translational research of brain pathogenesis.