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SIMULTANEOUS SCREENING OF ZEBRAFISH LARVA LOCOMOTOR AND CARDIAC FUNCTIONS: A MICROFLUIDIC MULTI-PHENOTYPIC APPROACH

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ABSTRACT

Zebrafish larvae offer many advantages including genetic homology to humans, optical transparency, small size and rapid development that facilitate their use for early-stage and fundamental assays. Behavioral responses of zebrafish larvae to different environmental cues are important functional readouts that should be evoked on-demand and investigated phenotypically for genetic, drug discovery and disease pathology studies. However, behavioral investigation of zebrafish larva poses important challenges in terms of applying a stimulus controllably with respect to time and space in a plate to evoke a response on-demand, while quantifying the larva's behavior such as its rapid movement phenotypically. These limitations have motivated the application of microfluidics as an ideal technology that provides accuracy, repeatability and multifunctionality to screen zebrafish and perform quantitative analyses under controllable conditions. A variety of microfluidic devices have been developed to manipulate and expose zebrafish larvae to various physical and chemical stimuli and study their neurobehavioral activities. Electrical stimulus can be considered as one of the most versatile candidates for evoking and studying locomotor behavior because it can be turned on and off quickly and manipulated on-demand in terms of magnitude, direction and time. Moreover, mild electric signals have already been shown not to affect small model organisms like C. elegans and zebrafish significantly. We recently introduced different microfluidic devices that uses a mild electrical current to stimulate tail movement in head-immobilized zebrafish larvae. This electric-induced response was modulated and quantified in terms of response duration time (RD) and tail beat frequency (TBF) as a function of electric currents in. As proof of concept in chemical and gene screening application, the effects of the neurotoxin 6-OHDA, the neuroprotective compound levodopa, and the ablation of the panx1a gene on electric locomotor behavior of zebrafish larvae was studied. We demonstrate that 6-OHDA leads to electric response impairment and levodopa treatment rescues the response. Further, we demonstrate a role of panx1a in the electric-induced movement of zebrafish larvae. Next, we integrated our microfluidic setup with an optical component (a prism) for first-time bidirectional imaging of zebrafish larvae and simultaneous monitoring of RD, TBF and heartrate (HR). Electric stimulus caused a significant increase in HR which was recovered after electric exposure cessation. We conclude that this setup has application potential for quantitative screening of locomotor and heart activity in areas like Parkinson's and related neurodegenerative diseases, or in combining advances in genome engineering with research into the biology of electric response.

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