"A zebrafish model of the schizophrenia-drug addiction association"

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Dysregulation of N-methyl-D-aspartate receptor (NMDAR) signaling and opioid use both increase the vulnerability for schizophrenia. However, it remains unclear whether schizophrenia is caused by opioid-regulated brain circuitry, or stemming from congenital defects in the NMDA pathway, or both. Here we use larval zebrafish as the animal model to compare the extent of the sensorimotor deficits under pharmacological manipulations with MK801 (a non-competitive NMDAR antagonist) and morphine. Tap stimuli generated using a solenoid programmed at preset intervals were used to induce startle activity in the larvae separately held in the two types of drug solutions. Our results showed that both MK801 and morphine caused a deficiency in the habituation response compared to the control. The extent of the deficiency, however, was less prominent in the larvae subjected to morphine, suggesting that defects in the opioid pathway play a less critical role in the manifestation of the disease. Such changes in the sensorimotor functions could associate with the modulation in the formation of dopaminergic signaling network, as a noticeable increase was recorded in the number of dopaminergic cells in the forebrain of the larvae subjected to both the short-term (3-day) and the long-term (10- day) treatments with the two drugs. To determine whether the NMDAR antagonist and opioid also led to changes in the functional network activity, extracellular recordings were performed using dissociated cortical cultures growing on multi- electrode arrays (MEAs) – two-dimensional arrays of electrodes on glass or silicone substrates. Our analysis revealed attenuation in the array-wide spike detection rate and the burst rate in the cultures subjected to MK801 treatment, but not in the cultures treated with morphine. Such results reinforced a stronger association between dysregulation of the NMDAR pathway and manifestation of cognitive deficits in schizophrenia, compared to the opioid circuitry.

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