Microbiome Composition and Environmental pH Modulate the Behavioral Effects of SSRIs in Larval Zebrafish (Danio rerio)

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Major depressive disorder (MDD) is a prevalent neurological disorder, affecting approximately 300 million people worldwide, and can cause severe debilitation. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed class of drugs used to treat MDD. However, despite their widespread use, the exact effects of SSRIs on the brain are unknown, and treatment efficacy varies widely between individuals. Recent studies have begun to highlight how the gut microbiome affects mental health, and it has been linked to various mental illnesses, including MDD. This investigation's objective was to study how microbiome composition influences the effect of sertraline (a common SSRI) on larval zebrafish behavior. Zebrafish embryos with reduced microbiomes were exposed to different doses of sertraline, and their larval swimming behavior in a light-dark paradigm were compared to controls. Additionally, pH was varied (7, 7.5, 8) as an environmental factor to see how it would impact swimming behavior as well as how it would interact with the microbiome status and sertraline dose. Reducing the microbiome resulted in hyperactivity, while increasing both sertraline dose and pH resulted in hypoactivity ($p < 0.001$ for all). When combined, the hypoactive effects of sertraline and high pH were magnified ($p = 0.029$) and counteracted the hyperactive effect of microbiome reduction to a large degree. The results suggest that sertraline effectiveness may rely partially on an organism's microbiome which provides a mechanism to understand individual differences in response rates to SSRIs.

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