ACUTE DOPAMINE TRANSPORTER INHIBITION MODULATES BEHAVIORAL CHANGES AND BRAIN OXIDATIVE STATUS IN ADULT ZEBRAFISH

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INTRODUCTION: Alterations in dopamine levels, such as dysfunctions in the dopamine transporter (DAT), may trigger dopaminergic neurotoxicity. In experimental research, the inhibition of DAT induces behavioral changes, including hyperactivity, impulsivity, cognitive deficits, compulsive-like behaviors, and motivation/reward deficits. Thus, developing novel animal models that mimic conditions related to dopamine-induced toxicity by pharmacological modulation the dopaminergic signaling is a valuable approach. The zebrafish (*Danio rerio*) has been considered a suitable vertebrate system for modeling responses associated with dopaminergic toxicology, due to the well-characterized behavioral responses and physiological and evolutionary conservation of the dopaminergic system of this species. OBJECTIVE: Here, we investigate whether GBR 12909 administration causes dopaminergic toxicity across different neurobehavioral domains in zebrafish, similar to those observed in other models of dopaminergic dysfunction. MATERIAL AND METHODS: Behaviors were recorded after a single intraperitoneal (*i.p.*) administration of GBR 12909 at different doses (3.75, 7.5, 15 and 30 mg/kg). Locomotion, anxiety-like behavior, social preference, aggression, despair-like behavior, and oxidative stress-related biomarkers in the brain, including SOD, CAT and GR activity, SH and NPSH content, TBARS, and protein carbonylation were measured 30 min post administration. RESULTS AND CONCLUSION: GBR 12909 elicited hyperlocomotion, anxiety-like behavior, decreased social preference, increased aggression, and induced depressive-like behavior in a behavioral despair task. Moreover, GBR 12909 reduced SOD activity and TBARS levels, as well as increased GR activity

and NPSH content, demonstrating an influence of the DAT inhibitor on redox homeostasis. Notably, the effects of GBR 12909 on different behaviors were found to be dose-dependent. Collectively, our novel findings demonstrate that a single GBR 12909 administration evokes neurobehavioral alterations that recapitulate dopaminergic toxicity observed in experimental dopamine studies, supporting the use of zebrafish models to explore dopaminergic responses in translational neuroscience research. Finally, our novel data reinforce the applicability of zebrafish to assess how GBR 12909 simultaneously affects multiple behavioral domains in a simple- and cost-effective manner, as well as to investigate future neuroprotective strategies in preclinical neuropharmacological studies.

Keywords: GBR 12909, neurobehavioral changes, zebrafish