Gamma-Aminobutyric Acid (GABA)-induced Growth Performance in Zebrafish Larvae via GABAA and GABAB Receptors

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Abstract

Insulin-like growth factor-1 (IGF-1) primarily increases the release of gamma-aminobutyric acid (GABA) in neurons vice versa and is also responsible for the promotion of longitudinal growth in children and adolescents. Hence, we, in this study, investigated whether exogenous GABA supplementation activates IGF-mediated growth performance. Treatment with GABA in zebrafish larvae at 3 days post fertilization (dpf) significantly increased total length from 6 to 12 dpf concomitant with the upregulation of growth-stimulating genes, including IGF-1, growth hormone-1 (GH-1), growth hormone receptor-1 (GH-R1), and cholecystokinin (CCKA). In peculiar, at 9 dpf, GABA increased growth rate from 3.60 ± 0.02 to 3.79 ± 0.03, 3.89 ± 0.02, and 3.92 ± 0.04 mm at 6.25, 12.5, and 25 mM comparable to 4 mM β-glycerophosphate (GP)-treated larvae (3.98 ± 0.02 mm). Additionally, the highest concentration of GABA (50 mM) induced 50% death in zebrafish larvae at 12 dpf. GABA also enhanced IGF-1 expression and secretion in preosteoblast MC3T3-E1 cells concomitant with high level of IGF-1 receptor (IGF-1R). In zebrafish larvae, GABA-induced growth performance remarkably decreased in the presence of an IGF-1R inhibitor, picropodophyllin (PPP), which indicates that GABA-induced IGF-1 enhances growth performance via IGF-1R. Furthermore, we investigated which GABA receptors affect growth performance along with IGF-1 activation. The inhibitors of $GABA_A$ and $GABA_B$ receptors, bicuculline and CGP 46381, considerably inhibited GABA-induced zebrafish growth rate accompanied by a marked decrease of growth-stimulating genes, including IGF-1, GH-1, GHR-1, and CCKA, but not with an inhibitor of $GABA_C$ receptor, TPMPA. Additionally, IGF-1 and IGF-1R expression was also impaired in bicuculline and CGP 46381-treated MC3TC-E1 cells, but not with TEMPA. Furthermore, treatment with bicuculline and CGP 46381 significantly downregulated GABA-induced IGF-1 release in MC3T3-E1 cells. These data indicate that GABA stimulates IGF-1 release via $GABA_A$ and $GABA_B$ receptors, leading to promotion of growth performance via IGF-1R.

Keywords: *GABA, IGF-1, GABA receptors, growth performance*

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