Absence of 11-keto reduction of cortisone and 11-ketotestosterone in the model organism zebrafish

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Zebrafish are widely used as model organism. Their suitability for endocrine studies, drug screening and toxicity assessements depends on the extent of conservation of specific genes and biochemical pathways between zebrafish and human. Glucocorticoids consist of inactive 11-keto (cortisone and 11-dehydrocorticosterone) and active 11β-hydroxyl forms (cortisol and corticosterone). In mammals, two 11β-hydroxysteroid dehydrogenases (11β-HSD1 and 11β-HSD2) interconvert active and inactive glucocorticoids, allowing tissue-specific regulation of glucocorticoid action. Furthermore, 11β-HSDs are involved in the metabolism of 11-oxy androgens. As zebrafish and other teleost fish lack a direct homologue of 11β-HSD1, we investigated whether they can reduce 11-ketosteroids. We compared glucocorticoid and androgen metabolism between human and zebrafish using recombinant enzymes, microsomal preparations and zebrafish larvae. Our results provide strong evidence for the absence of 11-ketosteroid reduction in zebrafish. Neither human 11β-HSD3 nor the two zebrafish 11β-HSD3 homologues, previously hypothesized to reduce 11-ketosteroids, converted cortisone and 11-ketotestosterone (11KT) to their 11β-hydroxyl forms. Furthermore, zebrafish microsomes were unable to reduce 11-ketosteroids, and exposure of larvae to cortisone or the synthetic analogue prednisone did not affect glucocorticoid-dependent gene expression. Additionally, a dual-role of 11β-HSD2 by inactivating glucocorticoids and generating the main fish androgen 11KT was supported. Thus, due to the lack of 11-ketosteroid reduction, zebrafish and other teleost fish exhibit a limited tissue-specific regulation of glucocorticoid action, and their androgen production pathway is characterized by sustained 11KT production. These findings are of particular significance when using zebrafish as a model to study endocrine functions, stress responses and effects of pharmaceuticals.
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