REGULATION OF ONSET OF SEXUAL MATURATION BY MELANOCORTIN RECEPTOR 4 POLYMORPHISMS IN *XIPHOPHORUS*

Schartl M.[1], Schories S.[1], Schmidt C.[1], Fischer P.[1], Lampert K.[2], Volff J.-N.[3], C. Hoffmann C.[4] and Lohse M.[4]

[1]Physiological Chemistry I, Biocenter, University of Wuerzburg, Germany, Fax: +49-931-3184150 email: phch1@biozentrum.uni-wuerzburg.de
[2]Evolutionary Ecology and Biodiversity of Animals, University of Bochum, Germany, Fax: +49-234-32-14114 email: kathrin.lampert@ruhr-uni-bochum.de
[3]Institut de Génomique Fonctionnelle de Lyon, Ecole Normale Supérieure de Lyon, France, Fax: +33-472-728992 email: Jean-Nicolas.Volff@ens-lyon.fr
[4]Pharmacology and Toxicology, University of Wuerzburg, Germany, Fax: +49-931-201-48539 email C.Hoffmann@toxi.uni-wuerzburg.de, and Fax: +49-931-201-48411 email: lohse@toxi.uni-wuerzburg.de

Introduction:

The onset of sexual maturation marks an important point in the reproductive life of a fish. Moreover, precocious or delayed puberty can have profound negative effects in fish farming and broodstock management. Our knowledge about the molecular processes involved in regulation of puberty in fish are still fragmentary. To identify still unknown components of puberty regulation, experimental model systems that exhibit genetic defects or genetic polymorphisms affecting the onset of sexual maturity provide useful tools for further analyses. A prominent example is the polymorphism in adult male body size in some species of platyfish and swordtails of the genus *Xiphophorus*. A single Mendelian locus (*P*) was shown to be responsible for the observed polymorphism. *P* determines the onset of sexual maturity of males and results, due to the fact that males stop to grow after reaching puberty, in a marked size polymorphism. Strikingly the different male size classes show pronounced differences in behavior and females prefer large over small males.

Results:

We show that a polymorphism of the melanocortin receptor 4 (mc4r) comprising functional and non-signal transducing versions and the copy number variation of *mc4r* genes on the Y-chromosome underlie the polymorphism of the *P*-locus. Non-functional copies of *mc4r* that are only present in some males act as dominant negative mutations and delay the onset of puberty leading to the large phenotype. The co-expression of dominant –negative receptor versions with wildtype mc4r leads to a reduction of cAMP production and decreased expression of mc4r effector genes. Copy number variation, as a regulating mechanism, makes the system extremely flexible and is responsible for the large variety of phenotypes.

Conclusion:

Our analysis shows that a gene polymorphism of mc4r is linked to size differences of adult males and explains the molecular mechanisms maintaining phenotypic variation. As mc4r is a critical component of the hypothalamus-pituitary axis involved in regulation of body weight and appetite, a novel link between the physiological system controlling energy balance and the regulation of reproduction becomes apparent.