CHARACTERIZATION OF DEFECTS IN CARDIAC REGULATION IN MACHO AND BANDONEON MUTANT ZEBRAFISH

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An Abstract of a Thesis Submitted to the Graduate

Faculty of Rensselaer Polytechnic Institute

in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: BIOLOGY

The original of the complete thesis is on file
in the Rensselaer Polytechnic Institute Library

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December 2008
(For Graduation December 2008)

ABSTRACT

Surveys show that one in three American adults have a cardiovascular disease and cardiovascular diseases are the number one cause of death in the United States. Abnormalities in autonomic cardiac regulation are thought to play major roles in the progression of various cardiovascular diseases and it is therefore of critical importance that we gain a precise understanding of how the heart is autonomically regulated. The autonomic nervous system is highly conserved in vertebrates, both functionally and anatomically. It is divided into sympathetic and parasympathetic (vagal) nervous systems, which act to counterbalance each other. Through this sympathovagal balance, the heart is precisely regulated. This regulation is very complex and input to nervous cardiovascular regulation is derived from a multitude of anatomical sites and is affected by a plethora of physiological, environmental, and genetic factors. We have examined the effects of two genes on cardiac regulation in zebrafish: *macho*, a gene encoding a yet-unknown protein, and *bandoneon*, a gene encoding the glycine receptor beta-2 subunit. We have found that mutations in either of these genes deleteriously effects sympathovagal balance. *macho* mutants suffer from an overactive parasympathetic system which can be partially rescued by the muscarinic antagonist atropine. *bandoneon* mutants exhibited an adaptive phenotype which was phenocopied by mediosagittal lesion of commissural neurons in the hindbrain in a non-additive manner, indicating the importance of these neurons in glycinergic heart regulation. Lastly, we have shown distinct similarities in the *beo* cardiac phenotype to the phenotype elicited by long-term stress, suggesting a possible parallel in the mechanism of action as well as implicating glycine signaling in stress-induced cardioregulatory changes.