
EFFECTS OF DOPAMINE BETA HYDROXYLASE LEVELS IN A MOUSE MODEL OF FD

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Familial dysautonomia is a severe, recessive disease that devastates the peripheral nervous system, culminating in death of most patients by age 40. The most debilitating feature of familial dysautonomia is the severe autonomic crises that occur. These crises, which can sometimes last for days, cause extreme vomiting and nausea, among other symptoms. The crises have been shown to coincide with an increased level of circulating dopamine following stress. The current hypothesis suggests that elevated levels of tyrosine hydroxylase cause an overproduction of dopamine. The chromaffin cells cannot convert this dopamine into norepinephrine quickly enough; therefore, this dopamine is released into the blood stream. We propose an alternate hypothesis in which the levels of dopamine beta hydroxylase are instead reduced. Reduction of dopamine beta hydroxylase, the enzyme that converts dopamine to norepinephrine, would result in a larger amount of dopamine being released from chromaffin cells during the response to stress. This reduction in enzyme levels is also seen in dopamine beta hydroxylase deficiency, a disease that shares many of the same symptoms of familial dysautonomia. In support of this hypothesis, we have shown through quantitative RT-PCR that dopamine beta hydroxylase transcript levels are decreased in *Wnt1-Cre; IkbkapLoxP/LoxP* conditional knockout (CKO) embryos in which *Ikbkap* is ablated in the adrenal gland. Further analysis of the CKO using immunohistochemistry indicates that DBH protein levels may also be diminished as well as mis-localized within the cell.