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Atypical soluble guanylyl cyclases in Drosophila as neutral oxygen sensors and their involvement in gestation

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In addition to the conventional, NO-stimulated soluble guanylyl cyclases (sGCs), recent evidence has identified another class of sGCs that are insensitive or poorly activated by NO, named atypical sGCs. We have been studying the function and regulation of atypical sGCs using the fruit fly, *Drosophila melanogaster* as a model. The *Drosophila* genome contains 5 genes that code for sGC subunits. Two of these, Gycα-99B and Gycβ-100B form a conventional sGC and the remaining 3 genes code for atypical subunits Gyc-88E, Gyc-89Da and Gyc-89Db. When expressed in heterologous cells, Gyc-88E forms active homodimers, whereas Gyc-89Da and Gyc-89Db are only active when co-expressed with Gyc-88E. We cannot detect any biochemical differences between Gyc-89Da and Gyc-89Db. The atypical sGCs are only stimulated 2–4 fold by NO donors, whereas Gycα-99B/Gycβ-100B is stimulated up to 100 fold. The atypical sGCs, by contrast, are potently activated when incubated in an oxygen-free environment. This activation is graded over 0-21% oxygen and can be detected within 1 minute when cells expressing the subunits are exposed to 100% nitrogen. The sGC inhibitor ODQ inhibits the activation. These biochemical properties are consistent with a role as molecular oxygen sensors and are also supported by studies in *C. elegans* that show that loss of an atypical sGC subunit leads to defects in oxygen sensing (Gray et al., 2004).

Using *in situ* hybridization and promoter: GFP transformed flies, we have mapped the expression patterns of the atypical subunits to a partially overlapping population of sensory and central neurons. Some of the sensory neurons have previously been described as responding to chemosensory modalities and others are of unknown function. To determine the functions of these neurons we are using the GAL4/UAS system to express tetanus toxin (TNT) and block neuronal function in the cells that express Gyc-89Da. These larvae are defective in their ability to show a hypoxia escape response. Larvae expressing TNT required almost 5 minutes for 50% of the larvae to withdraw from food when exposed to 100% nitrogen, whereas control larvae exited from food within several seconds. The TNT expressing larvae also showed deficits in taste preference and larval foraging behavior, while locomotion and olfactory responses were unaffected. We also have a fly line that has a transposable element within the Gyc-89Da gene. These flies have no detectable levels of Gyc-89Da, but normal levels of Gyc-89Db expression. Larvae show a normal hypoxia escape response, but as Gyc-89Da and Gyc-89Db are co-expressed in the cells most likely to detect low oxygen levels the lack of a phenotype might represent redundancy between these subunits. However, adult Gyc-89Da-/- flies do show a reduced preference for fructose solutions in taste preference assays.

References

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