Title: Exploring the Role of G Protein Coupled Receptor Kinases in Modulating Behaviors to Fluoxetine Using Caenorhabditis Elegans as an Experimental Model

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Purpose

It is currently unclear as to how protein kinases that modulate serotonin receptor activity, like the G protein coupled receptor kinases (GRKs), can influence the effects of selective serotonin reuptake inhibitors like fluoxetine. Addressing this issue may be of clinical importance because the protein expression levels of some of these kinases may vary depending on different disorders, like depression. In this study, we utilized the nematode, Caenorhabditis (C.) Elegans, with and without key G protein coupled receptor kinases to determine how C. elegans behaviors vary upon fluoxetine treatments.

Methods

C. elegans was treated with fluoxetine and egg laying and thrashing behaviors examined. For egg laying, adult C. elegans were treated for 24 hours with fluoxetine and egg laying during this period was recorded for C. elegans without GRK1, GRK2 or both GRK1 and GRK2. For thrashing, C. elegans were observed in M9 buffer with or without fluoxetine treatment for 15 minutes. One body flick was determined to be 1 thrash. Thrashing was recorded as thrashes per second and recorded for 30 seconds.

Results

C. elegans without GRK2 were found to exhibit different egg laying patterns in response to fluoxetine as well as a different thrashing behavior. Adult C. elegans without GRK2 treated with fluoxetine did not show increased egg laying compared to the wild type animal. These animals also showed reduced thrashing behaviors in the absence of fluoxetine compared to wild type (having both GRK1 and GRK2) or C. elegans without GRK1. This may suggest that these animals respond differently to serotonin and this is maybe because of an excess in the serotonin metabolite 5-HIAA, which has been reported previously to be directly associated with the loss of GRK2 activity in these animals. Thus far, fluoxetine treatment from 5-15 minutes in M9 buffer did not increase thrashing behavior of any of the strains tested.

Conclusion

In this study, we studied the effect of fluoxetine on C. elegans with or without various GRKs. This study showed that animals without GRK2 reacted differently to fluoxetine in terms of egg laying, with fluoxetine not able to increase their egg laying, unlike that with wild type and animals without GRK1. Furthermore, although our present fluoxetine treatment conditions did not change thrashing behaviors, the animals without GRK2 showed reduced levels of thrashing compared to the other animals. This suggests that animals without GRK2 may react differently to serotonin, implying that potentially neurological disorders related to low GRK2 protein expression in the brain may respond differently to selective serotonin reuptake inhibitors like fluoxetine.