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Cross-Species C. Elegans Model of Opioid-Induced Behavior Identifies Gao and a Multi-Layered RGS Profile Mediating Opioid Receptor Signaling

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We previously pioneered a cross-species transgenic model of mu-opioid receptor signaling (tgMOR) using C. elegans. In the tgMOR model, mammalian MOR is expressed in the C. elegans nervous system imbuing the animal with robust opioid-responsive behaviors. Previous unbiased, forward genetic studies with the tgMOR model revealed novel, conserved regulators of MOR signaling that influence opioid responses from C. elegans through rodents. At present, we know little about how tgMOR engages endogenous neuronal signaling components to generate opioid-responsive behaviors. Here, we investigate how G-protein signaling and RGS proteins influence opioid sensitivity. Forward genetics identified tgMOR; goa-1 mutants as opioid hypersensitive. GOA-1 is the sole conserved G□o protein in C. elegans. CRISPR engineered null and deletion mutants for tgMOR; goa-1 displayed impaired behavioral responses to fentanyl. To further investigate tgMOR signaling, we CRISPR engineered early stop cassettes into two evolutionarily conserved RGS proteins, eat-16 (mammalian RGS9) and egl-10 (RGS6/7). Our results demonstrate both tgMOR; eat-16 and tgMOR; egl-10 mutants are hypersensitive to fentanyl. Our findings further indicate RSBP-1 (R7BP) and Gq signaling influence opioid sensitivity. Overall, our observations support two key conclusions: 1) G□o is potentially an ancient evolutionarily conserved mediator of MOR signaling. 2) Engineered MOR signaling in C. elegans creates a multi-layered RGS regulatory profile that restricts tgMOR/GOA-1 signaling with EGL-10 being a primary inhibitor and EAT-16 playing a secondary inhibitory role. Ongoing large-scale genetic studies with the tgMOR C. elegans model are now poised to reveal further genetic targets for potentially managing opioid substance use disorder.