(-)- Gossypol Inhibition of Musashi-Mediated Forgetting Improves Memory and Age-Dependent Memory Decline in Caenorhabditis elegans

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Musashi RNA-binding proteins (MSIs) retain a pivotal role in stem cell maintenance, tumorigenesis, and nervous system development. Recently, we showed in C. elegans that Musashi (MSI-1) actively promotes forgetting upon associative learning via a 3'UTR-dependent translational expression of the Arp2/3 actin branching complex. Here, we investigated the evolutionary conserved role of MSI proteins and the effect of their pharmacological inhibition on memory. Expression of human Musashi 1 (MSI1) and Musashi 2 (MSI2) under the endogenous Musashi promoter fully rescued the phenotype of msi-1(lf) worms. Furthermore, pharmacological inhibition of human MSI1 and MSI2 activity using (-)- gossypol resulted in improved memory retention, without causing locomotor, chemotactic, or learning deficits. No drug effect was observed in msi-1(lf) treated worms. Using Western blotting and confocal microscopy, we found no changes in MSI-1 protein abundance following (-)- gossypol treatment, suggesting that Musashi gene expression remains unaltered and that the compound exerts its inhibitory effect post-translationally. Additionally, (-)- gossypol suppressed the previously seen rescue of the msi-1(lf) phenotype in worms expressing human MSI1 specifically in the AVA neuron, indicating that (-)- gossypol can regulate the Musashi pathway in a memory-related neuronal circuit in worms. Finally, treating aged worms with (-)- gossypol reversed physiological age-dependent memory decline. Taken together, our findings indicate that pharmacological inhibition of Musashi might represent a promising approach for memory modulation.
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