A brain-to-gonad-to-embryo adrenergic signaling relay controls intergenerational transfer of temporal learning ability

Eugene L.Q. Lee, H. Robert Horvitz HHMI, Dept. Biology, MIT

Animals recognize patterns in the timing of stimuli in their environment, associate the relevant events, and when subsequent similarly timed events reoccur respond appropriately to optimize survival. How such temporal processing events are coordinated at cellular and molecular levels across tissues to produce adaptive behavior is unclear. We show that *C. elegans* is sensitive to the temporal patterning of sensory stimuli. Worms learn to associate a neutral odor stimulus with a noxious aversive light stimulus specifically when these stimuli are paired in an ordered temporal pattern in which the odor is predictive of subsequent light exposure. Notably, *C. elegans* is capable of trace-conditioning – a form of learning in which there is a delay between the presentation of a neutral (odor) stimulus and the presentation of a noxious (light) stimulus - showing that worms have the ability to detect and distinguish timing durations. We found that adrenergic signaling alters the temporal processing of the timed duration between associated stimuli. Worms defective in the synthesis of the adrenergic biogenic amines tyramine and/or octopamine (i.e., *tdc-1* and *tbh-1* mutant worms) exhibit enhanced trace-responses compared to wild-type worms and are able to associate stimuli across longer trace-delay periods. Remarkably, we discovered that trained parental worms produce progeny with enhanced sensitivity to the temporal patterns of trace-conditioning. Transmission of the experiential signal is dependent on the timed ordering of stimuli, as worms exposed to equal levels but randomly ordered patterns of learning stimuli do not exhibit such intergenerational effects. This intergenerational inheritance is flexibly coordinated by a brain-to-gonad-to-embryo communication axis that also acts through adrenergic signaling: inhibiting parental adrenergic output from either the RIM/RIC neurons or the somatic gonad abolishes inheritance of temporal sensitivities. Our results demonstrate that adrenergic signaling functions in a central inter-organ communication system for tuning temporal processing within and across generations.