A Zebrafish Genetic Screen Identifies Neuromedin U as a Regulator of Sleep/Wake States

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Author(s) Chiu, Cindy N.; Rihel, Jason; Lee, Daniel A.; Singh, Chanpreet; Mosser, Eric A.; Chen, Shijia; Sapin, Viveca; Pham, Uyen; Engle, Jae; Niles, Brett J.; Montz, Christin J.; Chakravarthy, Sridhara; Zimmerman, Steven; Salehi-Ashtiani, Kourosh; Vidal, Marc; Schier, Alexander F.; Prober, David A.
Author(s) at UniBasel Schier, Alexander ;
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Neuromodulation of arousal states ensures that an animal appropriately responds to its environment and engages in behaviors necessary for survival. However, the molecular and circuit properties underlying neuromodulation of arousal states such as sleep and wakefulness remain unclear. To tackle this challenge in a systematic and unbiased manner, we performed a genetic overexpression screen to identify genes that affect larval zebrafish arousal. We found that the neuropeptide neuromedin U (Nmu) promotes hyperactivity and inhibits sleep in zebrafish larvae, whereas nmu mutant animals are hypoactive. We show that Nmu-induced arousal requires Nmu receptor 2 and signaling via corticotropin releasing hormone (Crh) receptor 1. In contrast to previously proposed models, we find that Nmu does not promote arousal via the hypothalamic-pituitary-adrenal axis, but rather probably acts via brainstem crh-expressing neurons. These results reveal an unexpected functional and anatomical interface between the Nmu system and brainstem arousal systems that represents a novel wake-promoting pathway.
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