Virus-assisted mapping of stress circuits

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Mammals exhibit instinctive reactions to danger by releasing stress hormones. Hypothalamic corticotropin releasing hormone neurons (CRHNs) control stress hormone levels, but how diverse stressors converge on CRHNs to induce stress responses is not well understood. Here, we used single cell transcriptomics to define CRHN receptors for neurotransmitters and neuromodulators and then viral tracing to localize subsets of upstream neurons expressing cognate receptor ligands. Surprisingly, one subset comprised POMC (pro-opiomelanocortin)-expressing neurons in the hypothalamic arcuate nucleus, which are linked to appetite suppression. The POMC neurons were activated by one stressor, physical restraint, but not another, a predator odor. Chemogenetic activation of POMC neurons induced a stress hormone increase and their silencing inhibited the stress hormone response to physical restraint, but not predator odor. Together, these results indicate that hypothalamic POMC neurons, which are implicated in appetite suppression, also play a major role in the stress hormone response to a specific type of stressor. We also found that two different odorants can block stress hormone responses to both physical restraint and predator odor. Both odorants activate GABAergic inhibitory neurons presynaptic to CRHNs in the hypothalamic ventromedial nucleus. Stimulation of those neurons inhibits restraint-induced stress hormone increase, mimicking a blocking odorant. Conversely, their silencing prevents odorant blocking of the response. Notably, we also observed odor blocking of stressor activation in neurons presynaptic to CRHNs in the bed nucleus of the stria terminalis. Together, these findings indicate that selected odorants can block stress responses via two routes: a direct route in which blocking odor signals directly inhibit CRHNs and an indirect route in which they inhibit stressor activation of neurons presynaptic to CRHNs and prevent them from transmitting stress signals to CRHNs.

Key words: corticotropin releasing hormone neurons (CRHNs), stress hormones, single cell transcriptomics, viral tracing, odor blocking