Volume 13

Washington University
Undergraduate Research Digest

Spring 2018

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Native opioid signaling is clinically important. It has been implicated in sleep/arousal, temperature regulation, and the endocrine system. Exogenous opiate administration can have a profound effect on these systems. Although opiates are primarily used medicinally for pain relief, there are a host of negative side effects including a high abuse potential that has contributed to the opioid epidemic of the past two decades. There are three families of endogenous opioid peptides: dynorphin, a ligand of kappa opioid receptor (KOR); enkephalin, a ligand of delta and mu opioid receptors (MOR); and beta-endorphin, which preferentially binds to MOR. The neurocircuitry and sources of endogenous opioids that mediate native regulation of the sleep/arousal, temperature regulation, and endocrine systems remain poorly understood.

To identify the neurons that are the source of endogenous opioids in the preoptic area of the hypothalamus (POA), we used novel retrograde viral tools to selectively label neurons based on projection to the POA and genetic identity (expression of opioid peptide or receptor). We identified that dynorphinergic neurons in the supramammillary nucleus (SuM), a region implicated in arousal and stress, enkephalinergic neurons in the premammillary nucleus (PM), a region associated with reproductive control, and both dynorphinergic and enkephalinergic cells in the parabrachial nucleus (PBN), a region implicated in temperature sensation/regulation, nociception, and arousal, all present to the POA.

We identified glutamatergic neuronal populations in the SuM, PM, and PBN that project to the POA as well, suggesting that glutamate may be the fast neurotransmitter released from the opioidergic cells. We also identified limited local populations of dynorphin and enkephalin in the POA. Our research focused on the PBN inputs to POA, suspecting that the dynorphinergic and enkephalinergic PBN populations may project to the ventral medial preoptic area (VMPO) specifically and may be activated by changes in ambient temperature. Anterograde viral tracing experiments revealed that both populations project to the VMPO. As identified by cFos staining following temperature exposures, 72% and 45% of cold-activated PBN cells were dynorphinergic and enkephalinergic respectively, while 83% and 58% of warm-activated PBN cells were dynorphinergic and enkephalinergic respectively. Excitation of KOR-positive neurons in the VMPO lead to a 3°C drop in body temperature, and along with data showing overlap between these cells and warm-activated cFos cells, this suggests that KOR-positive cells in the VMPO are potentially warm-activated. Moving forward, we plan to use optogenetic techniques to elucidate the functional significance of the identified PBN to VMPO pathways in the context of thermoregulation.