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NEURAL CIRCUITS

Balancing threats

To stay alive, animals must respond to various danger signals — including pain, fear and hunger — that alert them to threats to their survival. However, we know little about how the brain integrates information about different threats and selects appropriate responses. Two recent papers now indicate that circuits that converge on the lateral parabrachial nucleus (PBN) encode competing danger signals and generate optimal survival responses.

Appropriate responses to pain are essential for survival; however, in some cases, other physiological needs, such as hunger, must take priority. Alhadeff et al. showed that mice that had been deprived of food for 24 hours exhibited reduced inflammatory pain-related behavioural responses to an injection of formalin to the paw. They discovered that hypothalamic agouti-related protein-expressing neurons (AGRP neurons), which are known to be activated by hunger, mediate this effect: optogenetic stimulation of AGRP neurons in control mice reduced formalin-induced inflammatory pain responses, whereas chemogenetic inhibition of their activity reduced the modulatory effects of food deprivation on inflammatory pain.

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The lateral PBN is one of several downstream targets of AGRP neurons. Alhadeff et al. found that optogenetic activation of the subpopulation of AGRP neurons that project to this region reduced inflammatory pain responses, suggesting that this region mediates the interaction between hunger and pain. Probing the molecular mechanisms involved, they identified an important role for one of the neurotransmitters released by AGRP neurons, neuropeptide Y (NPY): microinjection of NPY into the lateral PBN reduced inflammatory pain responses, whereas blocking NPY receptors in the lateral PBN abolished the inhibition of pain responses by hunger.

The findings of Campos et al. also point to a central role for the lateral PBN in integrating different threat signals. By monitoring calcium activity within a population of calcitonin gene-related peptide-expressing neurons (CGRP neurons) in the lateral PBN in vivo, they showed that these neurons are activated by pain and potential threats (such as novel food or cues that had been associated with pain through fear conditioning), as well as by visceral satiety signals. Lateral PBN CGRP neurons project to limbic brain regions and Campos et al. showed that inhibiting the CGRP neurons attenuates behavioural responses to pain and visceral satiety signals, suggesting that they may transmit affective aspects of these stimuli. Campos et al. also demonstrated that CGRP neurons are inhibited in hungry mice, an adaptive response that may inhibit satiety, fear and pain to allow increased feeding during an energy-depleted state.

The results of these two studies suggest that the lateral PBN is a key site for the integration of competing internal threat signals. It appears likely that hypothalamic ‘hunger-sensing’ AGRP neurons suppress responses to inflammatory pain signals through their projections to lateral PBN CGRP neurons; however, the additional upstream and downstream elements of these circuits remain to be established.

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ORIGINAL ARTICLES Alhadeff, A. L. et al. A neural circuit for the suppression of pain by a competing need state. *Cell* **173** 140–152 (2018)| Campos, C. A. et al. Encoding of danger by parabrachial CGRP neurons. *Nature* https://doi.org/10.1038/nature25511 (2018)