This Week in The Journal

Growth Hormone Contribution to Neonatal Pain Sensation

Adam J. Dourson, Zachary K. Ford, Kathryn J. Green, Carolyn E. McCrossan, Megan C. Hofmann, et al.

(see pages 4410–4427)

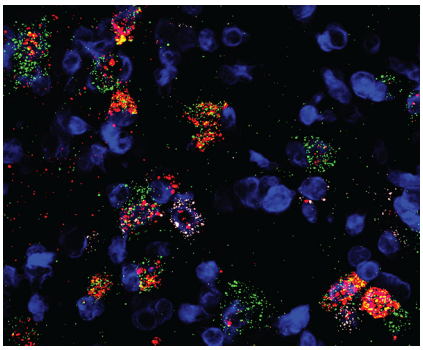
The development of human somatosensory circuits occurs perinatally and can be influenced by early sensory experience. This can be problematic, especially for preterm infants, who often require multiple invasive medical procedures. The resulting modification of nociceptive circuits is thought to cause nociceptive priming, which leads to prolonged pain after surgeries later in life. Experiments in rodents have shown that minimizing pain processing after neonatal injury reduces later hypersensitivity. But such studies have also shown that pain processing differs in neonates and adults. Enumerating these differences will be necessary to develop treatments for neonatal pain.

One factor that influences pain processing in neonatal animals is growth hormone. Previous work in mouse pups showed that an inflammatory molecule not only increased mechanical and thermal sensitivity in a paw, but also reduced local levels of growth hormone. Importantly, administering growth hormone before inducing inflammation lessened hypersensitivity. Conversely, reducing growth hormone levels increased sensitivity to somatosensory stimuli.

Dourson et al. report that incision of a paw muscle also caused local reductions in growth hormone while increasing pain-related behaviors and lowering response thresholds of sensory neurons in young ($\leq$14-d-old) mice. These effects were prevented by pretreatment with growth hormone. Moreover, growth hormone pretreatment prevented nociceptive priming, thus preventing the prolonged hypersensitivity that otherwise appeared after a repeat incision at 7 weeks. Notably, paw incision did not affect growth hormone levels in previously uninjured 7-week-old mice, and pretreating these mice with growth hormone had no effect on pain-related behaviors.

The incision-induced reduction in growth hormone levels in pups may have resulted from hormone internalization by macrophages. Indeed, knocking out the growth hormone receptor in macrophages decreased pain-related behaviors and muscle hypersensitivity after incision. Additional experiments identified upregulation of serum response factor (SRF) as a contributor to neonatal hypersensitivity. Growth hormone treatment prevented SRF upregulation, and knocking down SRF reduced pain-related behavior after incision.

These results suggest that macrophage-dependent reduction in local growth hormone levels contributes to hypersensitivity in neonatal mice by altering gene expression profiles and excitability of dorsal root ganglion neurons. These effects contribute to nociceptive priming that results in prolonged pain after subsequent injury. Therefore, growth hormone supplementation might be beneficial in reducing immediate and future pain in newborns undergoing surgical procedures.



GABAergic (GAD1$^+$) neurons (green) and glutamatergic (vGlut2$^+$) neurons (white) in the ventral pallidum. Nuclei are blue. A subset of GAD1-expressing neurons also express mCherry (red). These neurons promote reward seeking when costs are present. See Farrell et al. for details.

GABAergic Ventral Pallidal Neuron Role in Difficult Choices

Mitchell R. Farrell, Jeanine Sandra D. Esteban, Lauren Faget, Stan B. Floresco, Thomas S. Hnasko, et al.

(see pages 4500–4513)

Most of our decisions require cost–benefit analyses. When deciding whether to dine in or out, for example, one might consider relative food quality, effort, cost, and safety, as well as one's current hunger level. Many parts of the brain are involved in making such decisions, including the ventral pallidum. Recent work has shown that distinct subpopulations of ventral pallidal neurons have opposite roles in pursuing rewards and avoiding costs. Specifically, glutamatergic neurons restrain pursuit of rewards when costs are high, whereas GABAergic neurons promote reward seeking despite costs (Stephenson-Jones et al., 2020, Neuron 105:921). Farrell et al. have further elucidated the roles of ventral pallidal GABAergic neurons in aversive and appetitive behaviors in rats.

The authors used a chemogenetic strategy to inhibit ventral pallidal GABAergic neurons during various tasks. Normally, rats given a choice between two rewards of different sizes nearly always choose the larger reward. If the larger reward is sometimes paired with an electric shock, however, rats become less likely to choose that reward as the probability of shock increases. Inhibiting GABAergic ventral pallidal neurons did not affect the likelihood that rats would choose larger rewards in the absence of shock, but it increased the probability that no reward would be chosen during such trials. Moreover, when GABAergic neurons were inhibited, rats were less likely to choose the larger reward when shock probability was moderate and took longer to make a choice when shock probability was high. Inhibiting GABAergic neurons also reduced the number of times rats would press a lever to obtain a treat, but it did not affect consumption of easily obtained treats. Finally, when rats were trained to press a lever to avoid getting a shock, inhibiting GABAergic neurons increased the latency for lever pressing without reducing the number of trials on which the lever was pressed.

These results suggest that GABAergic neurons in the ventral pallidum promote reward seeking in the face of effort or danger. They may play a similar role in promoting effort to avoid discomfort. Thus, proper regulation of these neurons may be necessary to help one achieve difficult goals without engaging in excessively risky behaviors.

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