Long-term Potentiation of Pain “Memory” in the Spinal Cord

At the cellular level, the formation of memories in the hippocampus relies on neuronal activity, leading to structural changes in synapses and neurons, resulting in the formation of stable, retrievable memories. This form of synaptic plasticity is a protein synthesis-dependent process and is called memory consolidation. Memory consolidation occurs at both the synaptic and systems levels. Synaptic consolidation is synonymous with long-term potentiation (LTP), relying on activation of the NMDA postsynaptic receptors by neurotransmitters and gene expression/protein synthesis. This produces a long-lasting enhancement in signal transmission between involved neurons. Consolidation stabilizes and solidifies the neuronal connections of the memory, which is “stored” for future recall. Eventually, memory becomes independent of the hippocampus in a process known as systems consolidation. During reactivation of the neurons storing the memory, protein synthesis occurs again in a process called memory reconsolidation, serving to reinforce and modify stable memories. However, the process of memory reconsolidation introduces a period of instability in the retrieved memory. This has been demonstrated experimentally through exposure of reconsolidating neurons to protein synthesis inhibitors, which induces reversal (eraser) of recalled memories by interfering with the reconsolidation process. Bonin and Koninck recently reported in “A Spinal Analog of Memory Reconsolidation Enables Reversal of Hyperalgesia” in Nature Neuroscience that pain memories encoded in the spinal cord dorsal horn undergo a process analogous to hippocampal memory reconsolidation and may effectively be erased by inhibition of protein synthesis. The authors propose that using this mechanism to modify hyperalgesia may result in a novel treatment strategy in patients suffering from chronic pain.

Using a mouse model, the authors began by injecting capsaicin into the animals’ hind paws, which induced mechanical hyperalgesia that lasted >6 hours. The protracted period of pain was necessary to induce pain pathway neurons to undergo protein synthesis–dependent changes analogous to those that occur during memory formation in the hippocampus. To reactivate the pain pathway, an identical dose of capsaicin was injected 3 hours after the initial dose. When this dose was coupled with intrathecally administered anisomysin or cyclohexamide, protein synthesis inhibitors, a significant reduction of hyperalgesia was observed. Notably, if the anisomysin was given >2 hours after the second capsaicin injection, the effect was not seen. These results were further supported by a similar experiment in which mice hind paws were injected with complete Freund adjuvant (CFA). CFA produced hyperalgesia for up to 8 days, but the hyperalgesia was reversed when a dose of capsaicin and a protein synthesis inhibitor were coadministered after the initial CFA injection. Thus, pain stimuli induced by capsaicin and CFA lasting hours to days appear to result in protein synthesis–dependent alteration in nociceptive neurons, and reactivation of these neurons by a second pain stimulus also induces protein synthesis. Inhibition of protein synthesis after the second stimulus results in decreased hyperalgesia experienced by the animal.

The transmission of pain signals that result in this protein synthesis is presumably mediated by neurotransmitters in the dorsal horn of the spinal cord. The authors tested this by determining whether blocking signal transmission between primary and secondary nociceptive neurons in the superficial dorsal horn prevents reversal of capsaicin-induced hyperalgesia by protein synthesis inhibitors. Normally, exposure of peripheral nociceptive neurons to capsaicin induces release of neurotransmitters in the dorsal horn, which activates AMPA and NMDA receptors. When this process occurs without interruption, intrathecal injection of protein synthesis inhibitors results in decreased hyperalgesia, as previously demonstrated. However, when AMPA and NMDA receptor antagonists are administered along with protein synthesis inhibitors, hyperalgesia is not reversed. This indicates that neurotransmitter-mediated signal transduction in the dorsal horn is necessary to induce protein synthesis in secondary nociceptive neurons during capsaicin-induced hyperalgesia. To provide further evidence of this, AMPA and NMDA receptor agonists were coadministered with protein synthesis inhibitors via intrathecal injection (in the absence of peripheral stimulation with capsaicin). This resulted in reversal of hyperalgesia and supports the role of neurotransmitters in the reconsolidation-like process that appears to occur in dorsal horn neurons.

Thus, a long-lasting pain stimulus relying on neurotransmitters for transmission produces protein synthesis in dorsal horn neurons of the spinal cord. This information indicates that nociceptive neurons in the dorsal horn are undergoing LTP in response to painful stimuli, analogous to the processes of memory consolidation and reconsolidation that occur in the hippocampus. To further highlight this parallel, LTP was produced in vitro in slices of superficial dorsal horn through low-frequency electric stimulation. The process was repeated 3 hours after the initial stimulation and resulted in LTP of a similar magnitude. However, when the slices were bathed in solution containing the protein synthesis inhibitor anisomysin, the neurons failed to demonstrate LTP with the second stimulation. Similar results occurred when hippocampal neurons undergoing reconsolidation were exposed to a protein synthesis inhibitor. This indicates that, in the process of pain amplification and transduction, the initial pain memory becomes susceptible to modification in a reconsolidation-like process, providing a potential cellular mechanism behind the formation of chronic pain.

The findings of these experiments are remarkable. The hippocampus and spinal cord dorsal horn, 2 seemingly disparate neuroanatomical systems, use similar physiological mechanisms to respond to stimuli. Furthermore, the nociceptive system appears to have the capacity to store information in a fashion parallel to memory storage in the hippocampus. This provides a new perspective on pain perception and a potential target for treatment of pain. Although disruption of memory reconsolidation in the hippocampus presents many ethical hurdles, the future of analgesia may rely on the erasure of painful memories.
Repurposing Mebendazole for the Treatment of Medulloblastoma

The current treatment for medulloblastoma—resection, radiation, and chemotherapy—negatively affects neurocognitive development and fails to ensure survival beyond 10 years for about 40% of children. Among the 4 molecular subtypes of this disease, the group 3 subtype has an especially poor prognosis. Recently, Bai and colleagues demonstrated compelling preclinical evidence for using the microtubule inhibitory drug mebendazole (MBZ) to treat several molecular subtypes of medulloblastoma, including group 3. As a long-standing antihelmintic drug, MBZ has the advantage of a low-toxicity profile in children compared with other microtubule inhibitors such as vincristine and paclitaxel. As a lipophilic agent with a low molecular weight, MBZ has the additional advantage of blood-brain barrier permeability. Previous studies suggest that MBZ acts as an inhibitor of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), the primary receptor mediating the effects of VEGF. This study reveals the antiangiogenic effect of MBZ in medulloblastoma preclinical mouse models and its encouraging impact on overall survival.

The authors used 3 orthotopic models of medulloblastoma: a genetic model of the sonic hedgehog (SHH) molecular subtype consisting of allografts from spontaneous medulloblastomas in patched (PTCH)1/−, p53−/− mice; a model of therapy-resistant SHH consisting of allografts from tumors resistant to the hedgehog pathway inhibitor vismodegib; and a xenograft model with human group 3 medulloblastoma cells, D425 MB, implanted into the cerebellum. Implanted cells were transduced with firefly luciferase–expressing lentivirus for in vivo bioluminescent imaging. Mice in the treatment group received daily oral gavage of MBZ (50 mg/kg) starting 5 days after tumor cell implantation. Tumor vasculature in brain tissue from treated animals was compared with that of phosphate-buffered saline–treated control animals by immunostaining for the endothelial marker CD31. The impact of MBZ on the kinase activity of VEGFR2 was assessed by Western blots for VEGFR2 autophosphorylation after VEGF stimulation of human umbilical vein endothelial cells and by a cell-free kinase assay.