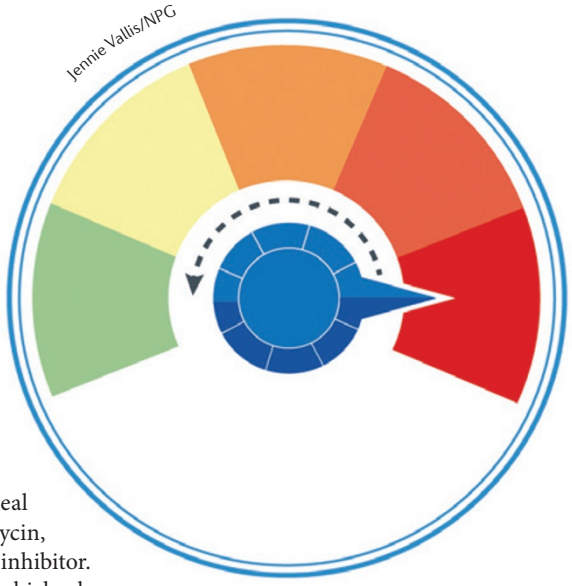

PAIN

Reversing hyperalgesia

> these results indicate that re-exposure to the sensitizing stimulus or reactivation of the sensitized pain pathways renders mechanical hyperalagesia labile

Sensitization of pain pathways in the dorsal horn of the spinal cord leads to the emergence of hyperalgesia. Bonin and De Koninck now show that reactivation of sensitized pain pathways in mice with mechanical hyperalgesia renders them labile and enables the hyperalgesia to be reversed.

Parallels have been drawn — at both the phenotypic and mechanistic levels — between memory formation in the hippocampus and the persistent changes in spinal nociceptive information processing that lead to hyperalgesia. This notion led the authors to examine whether hyperalgesia also exhibits a process akin to memory reconsolidation, in which reactivated memories become labile through a protein-synthesis-dependent process.

To test this idea, the authors induced protein-synthesis-dependent mechanical hyperalgesia in mice through hindpaw injections of capsaicin. Three hours later, each animal received a further hindpaw injection of capsaicin or vehicle and an intraperitoneal injection of anisomycin, a protein-synthesis inhibitor. Administration of vehicle plus anisomycin had no effect on the mechanical hyperalgesia (assessed by measuring hindpaw withdrawal thresholds in response to mechanical stimuli), but concurrent capsaicin and anisomycin injections markedly reduced the hyperalgesic state. Similar results were obtained when the second injection of capsaicin was replaced with optogenetic activation of nociceptors. Together, these results indicate that re-exposure to the sensitizing stimulus or reactivation of the sensitized pain pathways renders mechanical hyperalgesia labile and, indeed, reversible in the presence of protein-synthesis inhibition.

Capsaicin-induced nociceptor activation leads to the release of substance P and glutamate from C fibres, which sensitizes second-order neurons in the superficial dorsal horn (SDH). In mice with capsaicin-induced mechanical hyperalgesia, administration of certain glutamate or substance P receptor antagonists blocked the reversal of hyperalgesia caused by co-administration of capsaicin and anisomycin. Thus, activation of neurons in the SDH is crucial for the reversal of the hyperalgesic state.

Together, these findings indicate that reactivation of hyperalgesia has mechanistic parallels with memory reconsolidation. Importantly, like the latter, reactivation of hyperalgesia can be manipulated by the timely inhibition of protein synthesis, which may have important therapeutic implications for certain pathological pain conditions.

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