This Week in The Journal

TRPV1 Phosphorylation Produces Selective Hypersensitivity

John Joseph, Lintao Qu, Sheng Wang, Martin Kim, Daniel Bennett, et al.

(see pages 9954–9966)

Noxious heat, capsaicin, and molecules released from injured cells activate TRPV1 channels on nociceptor neurons. Calcium influx through the channels triggers the release of inflammatory mediators that feed back onto the same neurons, activating intracellular signaling pathways. These signaling pathways include kinases that phosphorylate various residues on TRPV1, increasing the responsiveness of the channel to subsequent stimulation. Thus, TRPV1 phosphorylation is a major contributor to heightened pain sensitivity (hyperalgesia) after tissue injury. Limiting TRPV1 phosphorylation might therefore reduce hyperalgesia while leaving protective pain responses intact.

This therapeutic potential motivated Chung and colleagues to investigate how phosphorylation of specific residues affects TRPV1-mediated responses under baseline and inflammatory conditions. Protein kinase C (PKC) phosphorylates mouse TRPV1 on serine 801 (S801), and previous work in cultured dorsal root ganglion (DRG) neurons showed that changing S801 to alanine (S801A) to preclude phosphorylation reduced the ability of the PKC agonist phorbol myristate acetate (PMA) to potentiate responses to capsaicin, heat, and acid. Joseph et al. replicated these effects in DRG neurons from S801A knock-in mice and went on to examine how the mutation affected behavioral responses *in vivo*.

As expected from *in vitro* studies, wild-type and knock-in mice showed similar baseline behavioral sensitivity to noxious thermal and mechanical stimuli. But injection of PMA into the paw failed to produce nocifensive responses in knock-in mice as it did in wild-type mice. In addition, the PMA-induced potentiation of nocifensive responses to capsaicin was diminished in knock-in mice. Furthermore, grimacing responses resulting from inflammation of the masseter muscle were lower in knock-in mice than in controls. Surprisingly, however, the S801A mutation did not reduce thermal hyperalgesia produced by PMA.

Moreover, the amount of mechanical and thermal hyperalgesia induced by mild thermal injury or injection of inflammatory agents into the paw were indistinguishable in wild-type and knock-in mice.

These results suggest that PKC-mediated phosphorylation of TRPV1 at S801 increases behavioral sensitivity to capsaicin and to inflammation of the masseter muscle, but does not contribute to thermal or mechanical hypersensitivity in the paw. This is reminiscent of previous studies showing modality-specific effects of phosphorylation of other TRPV1 residues, and it supports the hypothesis that targeting specific phosphorylation sites on TRPV1 may selectively reverse specific forms of hyperalgesia. See Chung et al. for details.

Delivering TMS to motor cortex during the trough or rising phase of high-power alpha oscillations produced MEPs that were larger in amplitude than those evoked during the peak or falling phase, which were not significantly different from those elicited when alpha power was low. See Bergmann et al. for details.

Mu Alpha Rhythm Increases Corticospinal Excitability

Til Ole Bergmann, Anne Lieb, Christoph Zrenner, and Ulf Ziemann

(see pages 10034–10043)

Periodic synchronous activation of cortical neurons underlies oscillations present at various frequencies in EEG recordings. Oscillations in the alpha frequency band (~10 Hz) are prominent in the resting brain, but alpha power (related to the number of synchronously activated neurons) typically decreases

during task performance. For example, alpha power over occipital cortex is greatest when the eyes are closed and decreases when eyes are opened. Furthermore, cortical excitability and the ability to detect visual stimuli decrease as occipital alpha power increases. Such findings underpin the hypothesis that alpha rhythms produce pulsed inhibition of sensory input.

Some evidence suggests that the alpha component of the mu rhythm, which occurs in sensorimotor cortex, also reflects pulsed inhibition. Motor-evoked potentials (MEPs) recorded in muscles were larger when motor cortex was stimulated during the trough of the mu alpha rhythm than when stimulation was delivered during peaks. But Bergmann et al. suggest that the mu alpha rhythm actually produces pulsed facilitation. They compared MEPs evoked by transcranial magnetic stimulation (TMS) of motor cortex at peak, trough, rising, and falling phases of strong (high-power) alpha rhythms with MEPs evoked when the alpha rhythm was virtually absent (low power). Importantly, the amplitude of MEPs evoked during the trough or rising phase of strong alpha rhythms was greater than that of MEPs evoked when alpha power was low. In contrast, MEP amplitudes evoked during alpha peaks or falling phases were similar to those evoked during low-power states. Furthermore, short-latency intracortical inhibition induced by paired-pulse TMS was similar regardless of alpha power and phase.

These results suggest that rather than producing pulsed inhibition during oscillatory peaks, the sensorimotor mu alpha rhythm produces pulsed facilitation during troughs. In addition, the difference in corticospinal excitability during rising versus falling phases of the alpha rhythm suggests that something besides absolute voltage underlies facilitation of corticospinal excitability. Importantly, the mu alpha rhythm recorded over motor cortex might actually be generated in the somatosensory cortex, which inhibits motor cortex. Therefore, future work should determine whether the mu alpha rhythm produces pulsed inhibition in somatosensory cortex and whether the apparent facilitation in motor cortex results from periodic release from inhibition from somatosensory cortex.

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