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Estrogen controls PKCepsilon-dependent mechanical hyperalgesia through direct action on nociceptive neurons

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PKC-epsilon is an important intracellular signaling molecule in primary afferent nociceptors, implicated in acute and chronic inflammatory as well as neuropathic pain. In behavioral experiments the inflammatory mediator epinephrine produces PKC-epsilon-dependent hyperalgesia only in male rats. The mechanism underlying this sexual dimorphism is unknown. We show that the hormone environment of female rats changes the nociceptive signaling in the peripheral sensory neuron. This change is maintained in culture also in the absence of a gender-simulating environment. Addition of estrogen to male-derived DRG neurons produces a switch to the female phenotype, namely abrogation of beta 2-AR-initiated activation of PKC-epsilon. Estrogen interferes downstream of the beta 2-AR with the signaling pathway leading from Epac to PKC-epsilon. The interfering action is fast indicating a transcription-independent mechanism.

As in other systems, estrogen has a dual effect. If applied minutes before beta 2-AR or Epac stimulation, estrogen abrogates the activation of PKC-epsilon. In contrast, estrogen applied alone leads to a brief translocation of PKC-epsilon. Also *in vivo* the activity of estrogen depends on the stimulation context. Intradermal injection of an Epac activator as well as estrogen alone induces mechanical hyperalgesia through a PKC-epsilon-dependent mechanism. In contrast, injection of estrogen preceeding the activation of Epac completely abrogates the Epac-induced mechanical hyperalgesia.

Our results indicate that gender differences in nociception do not reflect the use of generally different mechanisms. Instead, the contribution of a common set of signaling pathways can be modulated by hormones.