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MAPK IN THE ANTERIOR CINGULATE CORTEX CONTRIBUTES TO PAIN-RELATED AVERSION

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Pain is a multidimensional conscious experience including sensory and affective components. The former has been extensively studied, while the latter is poorly understood. Accumulating evidence from morphological, electrophysiological, neuroimaging, and behavioral studies as well as clinical observations indicate that the anterior cingulate cortex (ACC) is a key structure that contributes to pain negative affect or unpleasantness. Activation of extracellular signal-regulated kinase (ERK) leading to cAMP-response element binding protein (CREB) phosphorylation and up-regulation of Fos have been implicated in the formation of long-term memory and the pain-induced central sensitization in the spinal dorsal horn. In combination of a rat formalin-induced conditioned place avoidance (F-CPA) behavioral model and biochemical analysis, the present study demonstrated that bilateral intra-ACC microinjection of AP5 (15 nmol), a NMDA receptors antagonist, or 7-Chlorokynureate (7Cl-KYNA, 0.2, or 2 nmol), an antagonist of the glycine site of NMDA receptors, effectively eliminated induction of F-CPA. Also, inhibition of MAPK pathway by bilateral intra-ACC microinjection of PD098059 (1, and 10 nmol), a MEK inhibitor, dose-dependently blocked acquisition of F-CPA, but failed to affect formalin-induced nociceptive behavior and non-painful stimulation-induced conditioned place avoidance. Furthermore, the robust activations of ERK and CREB in the ACC were evoked by F-CPA retrieval or infusion of NMDA into ACC. Pre-administration of PD098059 in the ACC significantly suppressed NMDA- or F-CPA retrieval-induced phosphorylation of ERK and CREB, as well as Fos expression in the ACC. We therefore hypothesized that NMDA receptor activation in the ACC might trigger the intracellular ERK/CREB signal pathway leading to related target protein synthesis, which contributes to pain-related negative affect. These results indicate that activation of NMDA receptor-mediated ERK-CREB signaling pathway in the ACC might be necessary for the induction of pain-related negative emotion.

Key Words: ACC; NMDA receptor, extracellular signal-regulated protein kinase; cAMP-response element binding protein; pain affect; rat