

Modulation of Ca²⁺ channel current by μ opioid receptors in prefrontal cortex pyramidal neurons in rats

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Our work assesses the effects of μ opioid receptor activation on high-threshold Ca²⁺/Ba²⁺ currents in freshly dispersed pyramidal neurons of the medial prefrontal cortex in rats. Application of the specific μ receptor agonist (D-Ala², N-Me-Phe⁴, Gly⁵-ol)-enkephalin (DAMGO) at 1 μ M decreased Ca²⁺ current amplitudes from 0.72 to 0.49 nA. The effect was abolished by naloxone and ω -Conotoxin GVIA. Inhibition was not abolished by strong depolarisation of the cell membrane. In addition, a macroscopic Ba²⁺ current recorded in cell-attached configuration was inhibited when DAMGO was applied outside the patch pipette. An adenylyl cyclase inhibitor (SQ 22536) and a protein kinase A inhibitor (H-89) decreased Ca²⁺ current amplitude. Moreover, the inhibitory effect of μ opioid receptors on Ca²⁺ currents required the activation of protein kinase A. We conclude that activation of μ opioid receptors in medial prefrontal cortex pyramidal neurons inhibits N type Ca²⁺ channel currents, and that protein kinase A is involved in this transduction pathway.

Key words: prefrontal cortex, pyramidal neurons, Ca²⁺ currents, Ba²⁺ currents, μ opioid receptors, PKA

INTRODUCTION

The prelimbic and infralimbic areas of the medial prefrontal cortex (mPFC), which receive dense dopaminergic input from the midbrain (Carr et al. 1999, Carr and Sesack 2000), are crucial for working memory in mammals (Williams and Castner 2006). It has been suggested that these areas are involved in higher cognitive processes, and that damage to them leads to devastating pathologies, including schizophrenia (Manoach 2003) and dementia (Rosen et al. 2005).

μ opioid receptors are widely distributed in the neocortex (Mansour et al. 1995), including the prefrontal cortex in humans (Schmidt et al. 2001, 2003). Recent neuroimaging studies in humans have indicated that μ opioid cortical transmission in the prefrontal cortex is tonically active (Zubieta et al. 2002), and participates in the organism's adaptation to pain and negative emotional states (Ribeiro et al. 2005). Moreover, cortical opioid transmission is involved in the regulation of

mood. In particular, sadness states have been associated with a decrease in cortical cingulate μ opioid transmission (Zubieta et al. 2003).

Ca²⁺ ions are important second messengers which control numerous cellular effectors and influence the shape and activity pattern of action potentials (Carafoli 2002). One of the routes of Ca²⁺ entry into the intracellular compartment is *via* voltage-gated Ca²⁺ channels. Voltage-gated Ca²⁺ channels are negatively coupled to μ opioid receptors. For example, it was demonstrated that N-type (Rhim and Miller 1994, Wilding et al. 1995, Kim et al. 1997, Soldo and Moises 1997, Connor et al. 1999, Chieng and Bekkers 2001, Lee et al. 2004), and P- or Q-type Ca²⁺ currents (Rusin and Moises 1995) could be inhibited during activation of μ opioid receptors. Pyramidal neurons are the principal output cortical cells. Some pyramidal neurons of the prefrontal cortex express μ opioid receptors (Schmidt et al. 2001, 2003). Moreover, these neurons express N, L, P, Q and R high-threshold, voltage-dependent Ca²⁺ currents (Ishibashi et al. 1997, Day et al. 2002) and never or rarely display prominent low-threshold voltage-dependent Ca²⁺ currents (Lorenzon and Foehring 1995, Stewart et al. 1999, Day et al. 2002). Therefore, the

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