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Review

Role of TRPV1 receptors in descending modulation of pain

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Abstract

Transient receptor potential vanilloid type 1 (TRPV1) receptor is a ligand-gated non-selective cation channel activated by heat (>43 °C), low pH and endogenous lipid molecules such as anandamide, *N*-arachidonoyl-dopamine, *N*-acyl-dopamines and products of lipoxygenases (12- and 15-(*S*)-HPETE) termed endovanilloids. Apart from peripheral primary afferent neurons and dorsal root ganglia, TRPV1 receptor is expressed throughout the brain. Recent evidence shows that TRPV1 receptor stimulation by endocannabinoids or by capsaicin within the periaqueductal grey (PAG) leads to analgesia and this effect is associated with glutamate increase and the activation of OFF cell population in the rostral ventromedial medulla (RVM). Activation of the antinociceptive descending pathway via TPRV1 receptor stimulation in the PAG may be a novel strategy for producing analgesia. This review will summarize the more recent insights into the role of TRPV1 receptor within the antinociceptive descending pathway and its possible exploitation as a target for novel pain-killer agents.

Keywords: Endocannabinoids; Transient receptor potential vanilloid type 1; Periaqueductal grey; Rostral ventromedial medulla; ON and OFF cells; Pain

Contents

1. Introduction

Periaqueductal grey (PAG)–rostral ventromedial medulla (RVM)–dorsal horn circuitry is the best-characterized nociceptive modulatory system through which pain is endogenously inhibited. In particular, PAG plays a key role in the descending modulation of nociception (Behbehani, 1995; Fields, 2000), although this region has limited direct projections to the spinal cord (Sandkuhler and Gebhart, 1984), uses the RVM, as an intermediate relay station (Basbaum and Fields, 1984; Fields et al., 1995), which in turn projects directly to the spinal cord dorsal horn.

Transient receptor vanilloid type-1 (TRPV1), formerly known as the vanilloid receptor (VR1), is a ligand-gated non-selective cation channel that is considered to be an important pain integrator. It can be activated not only by exogenous agents such as capsaicin (the pungent ingredient of hot pepper) or

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resiniferatoxin (isolated from cactus-like plant) but also by many endogenous stimuli, including heat (>43 °C), low pH and endovanilloids (Caterina et al., 1997; Chuang et al., 2001; De Petrocellis et al., 2004b; Ferreira et al., 2004; Premkumar and Ahern, 2000; Tominaga et al., 1999; Szallasi and Blumberg, 1999; Starowicz et al., 2007a). The role of TRPV1 receptor in pain-related behavior has been definitely demonstrated using TRPV1 receptor gene knockout mice, which showed impairment in detecting thermal painful stimuli without altered mechanical noxious responses (Caterina et al., 2000). Most research on the TRPV1 receptor's role in pain facilitation and pain transmission has been carried out at peripheral and spinal level (Nagy et al., 2004; Sasamura and Kuraishi, 1999). Nevertheless, data on the role of the TRPV1 receptor in the supraspinal control of pain is still scant, despite the fact that increasing evidence confirms the expression of TRPV1 receptors throughout the brain (Cristino et al., 2006; Liapi and Wood, 2005; Maione et al., 2006; Mezey et al., 2000; Roberts et al., 2004; Sanchez et al., 2001; Toth et al., 2005). Increasing evidence demonstrates the presence of TRPV1 receptors throughout the PAG (Cristino et al., 2006; Maione et al., 2007; McGaraughty et al., 2003; Starowicz et al., 2007a,b). Stimulation of TRPV1 receptors in the PAG has been proven to inhibit pain by either acting on the downstream rostral ventromedial neurons that mediate analgesia or by desensitizing the activity of other neurons involved in inducing hyperalgesia (McGaraughty et al., 2003; Palazzo et al., 2002; Starowicz et al., 2007b). In this review we highlight studies that report supraspinal TRPV1 receptor involvement in pain modulation with particular emphasis on the descending antinociceptive pathway areas such as the PAG and RVM.

2. Endogenous ligands of TRPV1 receptors

Endogenous ligands using TRPV1 receptors for inter- and intra-cellular signaling have been termed endovannilloids (Di Marzo et al., 2001; Starowicz et al., 2007a). First endovanilloid to be identified has been anandamide (Ross, 2003; Smart et al., 2000; Zygmunt et al., 1999). Later on the chemical similarity between anandamide and capsaicin, and in particular between *N*-acylvanyllamide ligands and AM404, the inhibitor of anandamide membrane transporter, led to multiplicity of studies testing the activity of endocannabinoids on TRPV1 receptors and vice versa. *N*-acyldopamine (Huang et al., 2002; De Petrocellis et al., 2004a) and *N*-arachidonoyl-dopamine (NADA) (Hwang et al., 2000) were found to activate TRPV1 receptors as well as several products of lypoxygenases, among these 12-(*S*)-hydroperoxyeicosatetraenoic acid [12-(*S*)HPETE], 15-(*S*)-hydroperoxyeicosatetraenoic acid [15-(*S*)HPETE] and leukotriene B_4 (LTB_4) showed the highest efficacy (Hwang et al., 2000).

3. Expression of TRPV1 in the brain

In the brain TRPV1 receptors have been identified in various regions known for their role in pain transmission or modulation (Mezey et al., 2000; Roberts et al., 2004; Szabo et al., 2002). These regions include RVM, PAG, amygdala, solitary tract nucleus, somatosensory cortex, anterior cingulated cortex and insula (Millan, 1999, 2002). The TRPV1 receptor is localized in neuron cell bodies and dendrites, astrocytes and perivascular structures within the brain (Liapi and Wood, 2005; Mezey et al., 2000; Roberts et al., 2004; Sasamura et al., 1998). At subcellular level TRPV1 receptors are mainly expressed on postsynaptic spines (Toth et al., 2005). Capsaicin evokes glutamate release from slices of hypothalamus and lumbar dorsal horn, but not cerebellum. Such capsaicin action has shown to be Ca^{2+}-dependent and inhibited by the TRPV1 receptor antagonist, capsazepine, thus suggesting that TRPV1 receptor may be expressed on glutamatergic neurons in the hypothalamus (Sasamura et al., 1998).

4. The role of brain TRPV1 receptors in pain

Early work by Bodnar et al. (1982, 1983) demonstrated that intracerebroventricular (ICV) capsaicin injection decreased nociceptive threshold and reduced morphine- and stress-induced analgesia. ICV administration of capsazepine or ruthenium red (both TRPV1 receptor antagonists) attenuated nocifensive behavior induced by an intradermal injection of capsaicin or formalin in mice (Santos and Calixto, 1997). Furthermore, nociceptive thresholds were increased by the ICV infusion of two novel TRPV1 receptor antagonists, A-425619 and A-784168. A-425619 dose-dependently delayed the tail flick response to noxious thermal stimulation (McGaraughty, unpublished observation), while A-784168 reduced CFA-induced thermal hyperalgesia and the hind limb weight-bearing difference in a model of osteoarthritic pain. The locus coeruleus (LC) is activated by painful stimuli and its stimulation produces antinociception. Systemic capsaicin increased LC firing activity even after sensory nerve fiber destruction, confirming a central effect of capsaicin (Hajós et al., 1986, 1987). In accordance with this evidence, TRPV1 receptor activation with capsaicin increased glutamatergic miniature excitatory postsynaptic currents in LC (Marinelli et al., 2002). TRPV1 receptor stimulation by capsaicin application into the ventral tegmental area enhanced dopaminergic output to the nucleus accumbens, following peripheral noxious stimulation, suggesting a novel role for TRPV1 channels in the mesencephalon (Marinelli et al., 2005).

5. The role of TRPV1 receptors in periaqueductal grey

Capsaicin (6 nmol/rat) injection into the dorsolateral (DL) PAG increased the latency of nociceptive responses, showing that stimulation of TRPV1 receptor within the descending antinociceptive pathway elicits analgesia. This effect requires glutamate release and subsequent activation of group I metabotropic glutamate (mGlu) and *N*-methyl-D-aspartate (NMDA) receptors. Indeed, riluzole, a voltage-dependent Na^+ channel blocker which inhibits the release of glutamate, mGlu subtypes 1 and 5 ($mGlu_1$ and $mGlu_5$) and NMDA receptor antagonists blocked the analgesic effect of capsaicin. These data support the idea that intra-PAG capsaicin may generate analgesia by increasing the release of glutamate which activates the