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Review

Modulation of defensive behavior by Transient Receptor Potential Vanilloid Type-1 (TRPV1) Channels

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ABSTRACT

The Transient Receptor Potential Vanilloid Type-1 (TRPV1) was first characterized in primary afferent fibers as a receptor for capsaicin (the pungent ingredient of chili peppers). Later on, this cation-permeable ion channel was also described in the central nervous system, where its main putative endogenous ligand is N-arachidonoyl ethanolamide (an endocannabinoid, also known as anandamide). Recent results employing genetic, pharmacological and histochemical techniques indicate that TRPV1 tonically modulate anxiety, fear and panic responses in brain regions related to defensive responses, such as the dorsal periaqueductal gray, the hippocampus and the medial prefrontal cortex. Genetic deletion or antagonism of this ion channel induces anxiolytic-like effects in several animal models. The main mechanism responsible for TRPV1-mediated effects on anxiety seems to involve facilitation of glutamatergic neurotransmission. In addition, there is evidence for interactions with other neurotransmitter systems, such as nitric oxide and endocannabinoids.

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1. The Transient Receptor Potential Type-1 (TRPV1) Channel

1.1. Structure and function

Capsaicin (8-methyl-N-vanillyl-6-nonenamide), the main pungent constituent of the native American plant *Capsicum sp*, popularly known as the hot chili pepper, was first isolated and denominated by Thresh in 1846 (Szallasi and Blumberg, 1990b). Initial studies showed that it could induce a burning pain perception (Bernstein et al., 1981; Stjarne et al., 1989) and skin hyperalgesia (Bartho et al., 1990; Baumann et al., 1991). These effects result from stimulation and depolarization of primary afferent sensory neurons (Holzer, 1991) followed by the release of pro-inflammatory mediators (Southall et al., 2003). After repeated administration, however, these capsaicin-induced responses show a rapid desensitization (Dray, 1992; Green, 1989; Hayes et al., 1984).

Biochemical and electrophysiological studies indicated that capsaicin facilitates excitability and electrical conduction in sensory unmyelinated C-fibers and neural cell bodies by increasing sodium and calcium permeability (Erdelyi et al., 1987; Marsh et al., 1987; Wood et al., 1988). Capsaicin-induced calcium influx results in exocytosis of excitatory amino acids and other neuromodulators such as substance P (Go and Yaksh, 1987; Li et al., 2004; Marinelli et al., 2002, 2003; Sasamura et al., 1998). In addition, it was initially observed that capsaicin can also bind to specific sites in the peripheral terminals of thin-myelinated Aδ fibers (Chung et al., 1985; Hiura and Sakamoto, 1987; Matsumiya et al., 1983; Szolcsanyi et al., 1988). This subset of bipolar neurons is involved in the development of chronic pain. Their cellular bodies are located in the dorsal root (DRG), nodose and trigeminal ganglion, from where they send terminals that make synapses with second-order neurons in the central nervous system (CNS; Chad et al., 1983; Holzer, 1991; Szallasi, 1995; Williams and Zieglgansberger, 1982).

It was later found that capsaicin effects were antagonized in a competitive way by a drug named capsazepine (Walpole et al., 1994). This fact, together with its biological effects, led to the proposal of an orphan "capsaicin receptor" in mammalian organisms. This receptor was indeed identified by autoradiographic studies using [3H] resiniferatoxin (RTX), a potent capsaicin analog, in tissues of several species, including humans (Acs et al., 1994; Szallasi, 1994; Szallasi and Blumberg, 1990a,b). Since capsaicin and RTX share a vanillyl group as the key structural recognition site the receptor was initially denominated "vanilloid" (Szallasi and Blumberg, 1990b). In 1997 the vanilloid receptor was cloned in rat cells from the DRG and demonstrated to be a subtype of non-selective cation channels related to the Transient Receptor Potential (TRP) family of ion channels (Caterina et al., 1997). This receptor was named by the authors as 'vanilloid receptor subtype 1' (VR1). It was later renamed by the IUPHAR Nomenclature Committee the 'Transient Receptor Potential Vanilloid Type 1' (TRPV1; Clapham et al., 2005). Structurally, it is composed by four subunits, each having six-transmembrane-spanning domains and a short hydrophobic pore between the fifth and sixth segments (Ramsey et al., 2006; Wu et al., 2010).

TRPV1 channels can be activated by several stimuli in addition to capsaicin, including noxious heat, low pH (Caterina et al., 1997; Tominaga et al., 1998) and inflammatory mediators (Moriyama et al., 2005; Tang et al., 2004; Vyklicky et al., 1998). Lipid endogenous agonists of these receptors have also been proposed and named endovanilloids. The most studied endovanilloid is, by far, anandamide (N-arachidonoyl ethanolamine), an arachidonic acid derived neuromodulator. Anandamide is primarily known as the endogenous agonist at the CB1 receptors, being the first described endocannabinoid/endovanilloid (Di Marzo et al., 2001; Smart and Jerman, 2000; Zygmunt et al., 2000). Other proposed endovanilloids are N-arachidonoyl dopamine (Huang et al., 2002; Toth et al., 2003), N-oleoyl dopamine (Chu et al., 2003) and some products of lipoxygenases, such as 12-HPETE (12-hydroperoxyeicosatetraenoic acid) and leukotriene B4 (Hwang et al., 2000). Due to their lipophilic nature, these TRPV1 agonists are able to freely cross the cell membrane and interact with the intracellular binding site of the receptor (De Petrocellis et al., 2001; Jung et al., 1999).

1.2. Brain localization

In addition to their presence in sensory neurons and some tissues such as the respiratory and urinary bladder epithelium (Szallasi et al., 1993; Ahmed et al., 2009; Watanabe et al., 2005), skin, mast cells (Stander et al., 2004) and the enteric system (Horie et al., 2005; Matsumoto et al., 2011), a large number of studies employing [3H]RTX autoradiography, immunohistochemistry, electron microscopy, electrophysiology and molecular biological (western blot, RT-PCR and in situ hybridization) techniques, as well as genetically-modified mice, indicated that TRPV1 receptors are located in several CNS regions, including the dorsal horn of the spinal cord (Acs et al., 1994; Szallasi and Blumberg, 1991), hindbrain, midbrain and forebrain areas, being present not only in neurons but also in astrocytes (Toth et al., 2005). These studies are summarized in Table 1. Some studies, however, have failed to detect the presence of TRPV1 channels in the CNS (Benninger et al., 2008; Caterina et al., 1997; Szallasi, 1995; Tominaga et al., 1998). Corroborating these latter findings, a recent study using a sophisticated genetic strategy to visualize TRPV1, complemented with the use of TRPV1 knockout mice, was also unable to detect the expression of these receptors in most of the brain areas analyzed except for a discrete expression in few regions that include areas within and adjacent to the caudal hypothalamus and rostral midbrain (Cavanaugh et al., 2011). How much these contradictory results depend on methodological issues needs to be further clarified. Only the generation of brain-specific TRPV1 deficient mouse mutants may ultimately resolve this puzzle. In addition, its cellular localization (e.g., pre- versus post-synaptic) in specific neuronal populations needs to be further investigated. Finally, further quantitative experiments need to be performed to compare TRPV1 expression across different regions of the CNS. Anyhow, as reviewed below, even if the expression of TRPV1 channels in the brain is much lower than in other areas such as the DRG (Cavanaugh et al., 2011; Sanchez et al., 2001), pharmacological, electrophysiological and behavioral studies strongly indicate that brain-located TRPV1 plays an important role on the control of emotional responses.

2. TRPV1 channels modulate defensive behavior: systemic and genetic studies

The development of pharmacological tools has been instrumental for studying the involvement of TRPV1 channels in diverse physiological processes. Among them, capsazepine (a thiourea derivate), one of the first antagonists to be discovered, was initially employed to investigate the involvement of these channels in defensive responses. This compound, however, lacks selectivity, since it can also bind to voltage-gated calcium channels and nicotinic acetylcholine receptors. The capsaicin halogenated derivate, 6-iodo-nordihydrocapsaicin, is a more selective and potent (4-fold) antagonist than capsazepine (Appendino et al., 2003). Finally, cinnamide analogs, such as SB-366791, also exhibit a very high selectivity to TRPV1 channels (for a review, see Szallasi et al., 2003).

Regarding their effects in defensive responses, an initial study employed systemic injection of capsazepine and observed